OPTICAL ACTIVITY DUE TO ISOTOPIC SUBSTITUTION

W. C. M. C. KOKKE

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Aan mijn Moeder

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CHAPTER ONE

INTRODUCTION

Historical remarks.

Optical activity of organic molecules was discovered early in the 19th century[1]. Already in the eighties of that century, the beginning of the flourishing-time of the chemistry of the monoterpenes, optical activity was used for the characterisation of organic compounds.
When more monochromatic light sources became available the dependence of the angle of rotation on the wavelength could be investigated and anomalous rotatory dispersion curves were discovered. Cotton[2] in 1895 was the first who measured a circular dichroism curve. From measurements on potassium chromium tartrate and other coloured substances he concluded that an anomalous rotatory dispersion curve is associated with a CD curve.
A satisfactory theoretical evaluation of Cotton effects had to wait until the advent of quantum mechanics. In 1928 Rosenfeld gave a quantummechanical theory[3] on optical activity. In various formulations this theory has served as a basis for the explanation of observed effects in CD and ORD.

Study of optical activity due to isotopic substitution became possible when deuterium was discovered in 1932. In 1948 the first example of such a compound of which the specific rotation could be measured, was reported[4] (2,3-dideutero-p.-menthane).
Many optically active deuterium compounds have been synthesized ever since, either for the study of (biochemical) reaction mechanisms or because their synthesis was a challenge to a synthetic chemist[5]. Some examples of optical activity due to ^{18}O-substitution have also been reported[6].
Measurements of the optical activity of these compounds have never been used as a basis for theoretical work[7], possibly because no complete Cotton effect has been reported of this kind of optically active compounds before this work was started.

Scope of this thesis.

One might expect that CD of compounds with optical activity due to isotopic substitution is especially of interest to theoreticians since the mass difference which underlies the optical activity constitutes a small perturbation of a symmetric situation and is therefore an attractive

problem for mathematical analysis.

On the other hand in obtaining suitable compounds one is faced with a number of synthetic problems, which have to be solved first. The present thesis is concerned with the synthetic part of the program.

Selection of compounds.

The angles of rotation due to hydrogen-deuterium asymmetry[5] are a factor 500 smaller than for example the corresponding effects due to replacing a hydrogen atom by a methyl group. One may expect a similar reduction in the magnitude of known effects in CD if optical activity is due to isotopic substitution only.

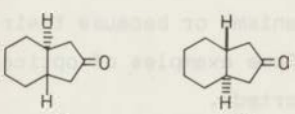
This has consequences for the choice of compounds to be synthesized with the purpose of obtaining CD data:

1/ The absorption bands to be studied should have low molar extinction coefficients (e.g. electrically forbidden transitions, $n \rightarrow \Pi^*$ transitions) so that concentrated solutions can be used. In order to obtain observable CD values the magnetic transition moment should be high.

2/ The optical as well as the isotopical purity[8] should be as high as possible.

Requirement 1/ is fullfilled by carbonyl compounds.

Through the work of Deen[9] and Emeis[10] on trans-β-hydrindanone (fig. 1-1)



1 2

Figure 1-1

a great deal of experience with (mainly) the theoretical features of the carbonyl group has been accumulated in the Department of Theoretical Organic Chemistry in Leiden. One of the features of the carbonyl absorption at about 300nm is the fine-structure (which is especially pronounced when the ketone has a two-fold axis) due to a progression of the carbonyl stretching mode in the excited state. This progression is expected to change on ^{18}O-substitution as will be made clear in the next example.

Consider a "simplified" optically active ketone and suppose that only transitions to one vibrational level (and its harmonic overtones) of the excited state are possible, and assume this particular mode to be a group vibration of the carbonyl group. Then this ketone should have a very simple CD spectrum: on a frequency scale it should consist of equally

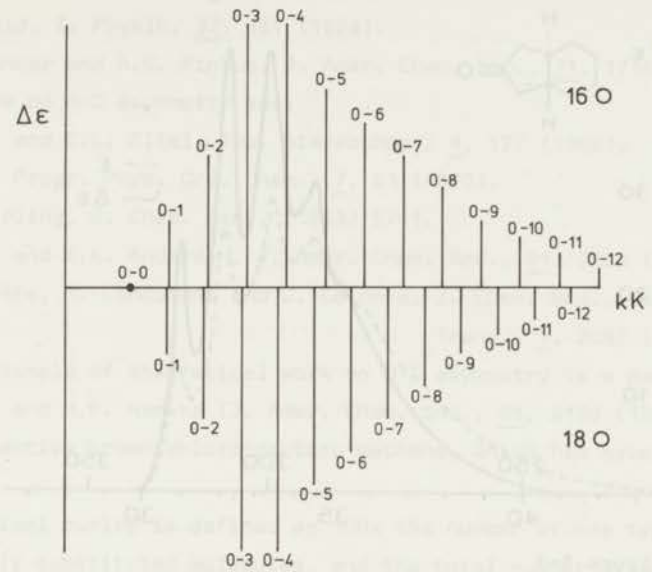


Figure 1-2

spaced peaks. Fig 1-2 gives a sketch of this CD spectrum together with that of the antipode where ^{16}O has been replaced by ^{18}O. That the progression of the active mode in the latter compound is smaller (factor $\sqrt{(16/18)}$) follows from the solution of the harmonic oscillator. Thus an equimolar mixture of these antipodes, one antipode 100% ^{18}O, the other 100% ^{16}O, should give rise to an observable CD as the difference of two CD bands with different contours.

The CD spectrum of an actual ketone, hydrindanone, is depicted in fig. 1-3. Here also substitution of ^{16}O by ^{18}O would change the progression of the carbonyl stretch vibration, thus an equimolar mixture of compound 1 (fig. 1-1) and its antipode 2 where ^{16}O has been replaced by ^{18}O should give rise to an observable effect in CD.

In practice it would be very difficult to obtain both antipodes of a ketone of the same opical purity, and to label one antipode with 100% ^{18}O. For this reason we directed our attention to the synthesis of dicarbonyl compound with a plane of symmetry in the case both oxygen atoms had equal mass, but would lose symmetry if one of the oxygens was replaced by ^{18}O (see fig. 7-1 for examples). Our first choice was the synthesis of an α-diketone because of the presence of two absorption bands which are both accessible to accurate CD measurements.

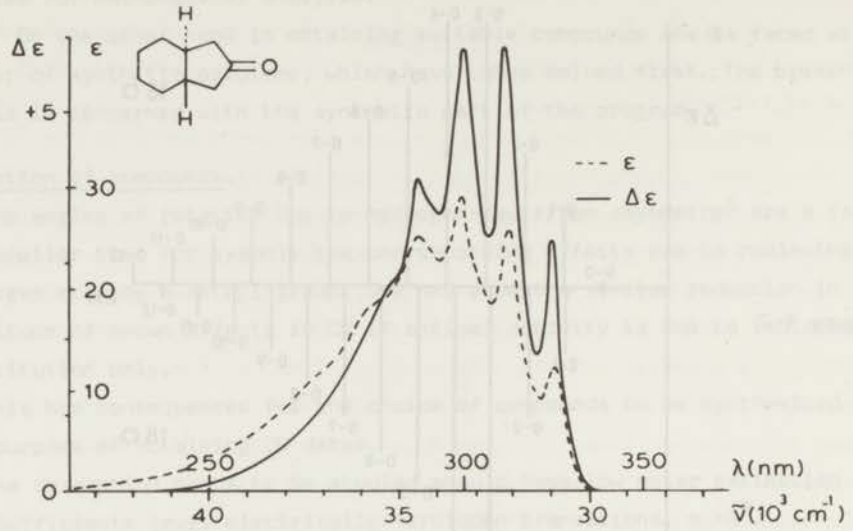


Figure 1-3

General remarks.

1/ The situation illustrated in fig. 1-2 is indeed very simplified. The shift of the frequency of vibrational transitions is not the only cause of an isotopically created CD. There are other origins of such an effect that will have to be considered in a refined theory such as the differences in amplitudes of vibrations due to different masses of the isotopes, and the influence of anharmonicity of the potentials governing molecular vibrations. The difference in equilibrium bond length between C-H and C-D as a consequence of anharmonicity, amounts to 0.004Å only[11], but should nevertheless not be neglected.

2/ When we mentioned a plane of symmetry in a dicarbonyl compound with identical isotopes we included in this term planes of symmetry that are only present as time-averages, e.g. in the case of rapidly interconverting conformers. Introduction of an isotope (deuterium in cyclopentanone e.g. [12])) may shift the equilibrium sufficiently to give rise to a measureable optical activity

References.

[1]) Biot, Bull. Soc. Philomat., (1815) 190.
This reference and the next one is taken from: T. Martin Lowry, Optical Rotatory Power, Dover Publications Inc., (1964).

2) Cotton, Ann. Chim., {VII} 8, 347 (1896).

3) L. Rosenfeld, Z. Physik, 32, 161 (1928).

4) E.R. Alexander and A.G. Pinkus, J. Amer. Chem. Soc., 71, 1786 (1949).

5) For reviews on H-D asymmetry see:
D. Arigoni and E.L. Eliel, Top. Stereochem., 4, 127 (1969).
L. Verbit, Progr. Phys. Org. Chem., 7, 51 (1970).

6) C.J.M. Stirling, J. Chem. Soc., (1963) 5741.
M.A. Sabol and K.K. Andersen, J. Amer. Chem. Soc., 91, 3603 (1968).
R. Annunziata, M. Cinquinni and C. Colonna, J. Chem. Soc., Perkin Trans., 1, 2057 (1972).

7) The best example of theoretical work on H-D asymmetry is a paper by N.V. Cohan and H.F. Hameka (J. Amer. Chem. Soc., 88, 2136 (1966)) on optically active bromo-chloro-deutero-methane, which has never been prepared.

8) The isotopical purity is defined as 100x the number of one type of isotopically substituted molecules, and the total number of molecules in the mixture (both isotopically substituted and unsubstituted).

9) R. Deen, Thesis Leiden (1961).

10) C.A. Emeis, Thesis Leiden (1968).
Figure 1-3 is taken from this thesis.

11) Such differences in bond lengths follow from microwave spectroscopical studies. Cf. J.E. Wollrab, Rotational Spectra and Molecular Structure, Academic Press, (1967), p 110.

12) 3-Deuterocyclopentanone is an example. This compound has been prepared but no Cotton effect has been detected (C. Djerassi and B. Tursch, J. Amer. Chem. Soc., 83, 4609 (1961)). We recommend reinvestigation of the optical activity of this compound but with a more sensitive apparatus. Of course, 3,4-dideuterocyclopentanone would be a better choice.

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CHAPTER TWO

(^{16}O, ^{18}O)-α-FENCHOCAMPHORONEQUINONE

OPTICAL ACTIVITY DUE TO ISOTOPIC SUBSTITUTION. CIRCULAR DICHROISM OF (1R)-2-^{18}O-α-FENCHOCAMPHORONEQUINONE[1].

Sir:

During the last twenty-five years many substances have been synthesized which derive optical activity from deuterium substitution[2]. Only a few examples of optical activity due to other isotopic substitution have been reported, viz. some (^{16}O, ^{18}O)-sulphones[3 4 5] and (^{16}O, ^{18}O)-sulphonate esters[4]. No Cotton effect has been measured in any of these compounds, neither in CD nor in ORD. Two ORD curves only show the first half of a Cotton effect[6].

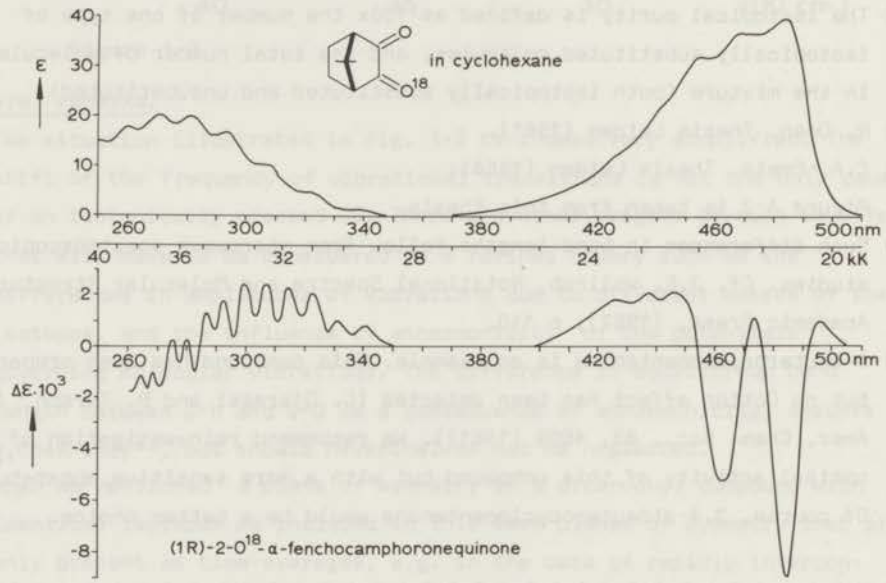

Fig. 2-1 [7]

We have started the synthesis of a number of diketones which derive optical activity from substitution of one ^{16}O by ^{18}O. The first compound which is reported here is an α-diketone: (1R)-2-^{18}O-α-fenchocamphoronequinone (I). The CD-curve between 250 and 520nm has been measured with a very sensitive instrument built by Mr. Dekkers in this department.

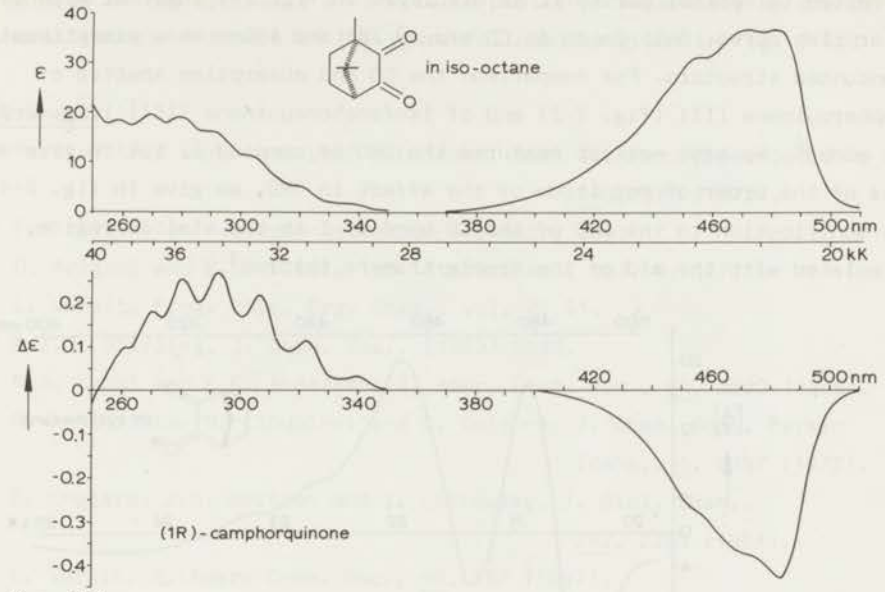
ε
in iso-octane
260
300
340
380
420
460
500nm
40
36
32
28
24
20kK
Δε
(1R)-camphorquinone

Fig. 2-2

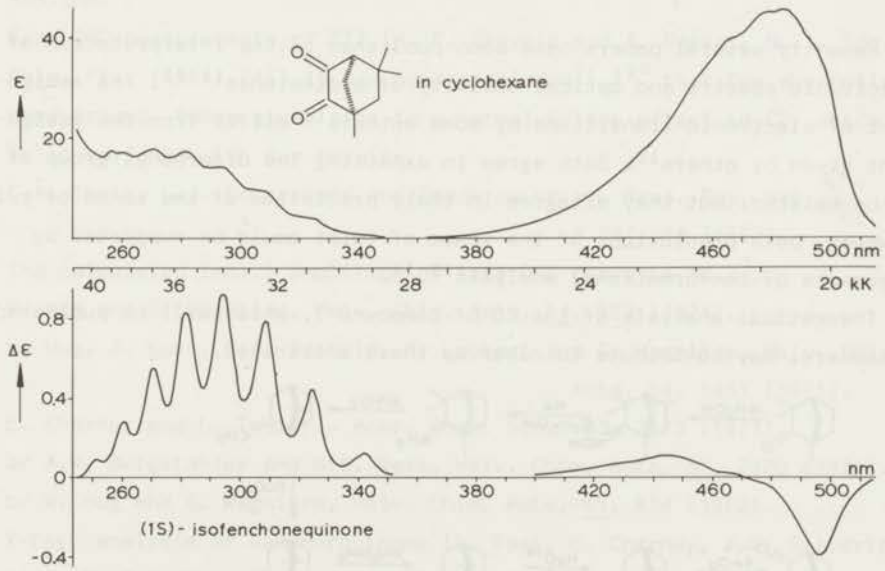
ε
in cyclohexane
260
300
340
380
420
460
500 nm
40
36
32
28
24
20 kK
Δε
nm
(1S)-isofenchonequinone

Fig. 2-3

Corrected to optical purity it is displayed in fig. 2-1 together with the absorption curve. Both bands in CD around 280 and 480nm show exceptionally pronounced structure. For comparison the CD and absorption spectra of camphorquinone (II) (fig. 2-2) and of isofenchonequinone (III) (fig. 2-3) are added[8]. We have not yet measured the ORD of compoud I, but to give an idea of the order of magnitude of the effect in ORD, we give in fig. 2-4 the contribution to the ORD of the CD band of I in the visible region, calculated with the aid of the Kronig-Kramers theorem[9].

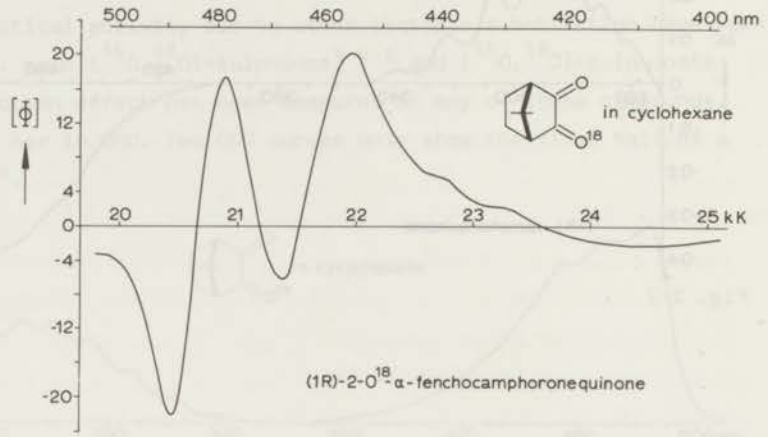

Fig. 2-4 [10])

Recently several papers have been published on the interpretation of electronic spectra and optical activity of α-diketones[11] [12]. The assignment of electronic transitions by some authors[11] differ from the assignment given by others[12]. Both agree in expecting the dicarbonyl group of II to be twisted, but they disagree in their prediction of the sense of twist. However, both predictions of the sense of twist could be supported by arguments of conformational analysis[13] [14].

Theoretical analysis of the CD of compound I, which will be published elsewhere, may contribute to clear up these antitheses.

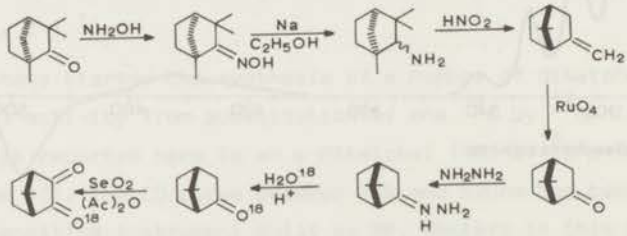

Fig. 2-5 The synthesis of compound I from (+)-(1S)-fenchone.

Details of the synthesis of I will be published separately by one of the authors (Kokke). A scheme of the route followed is given in fig. 2-5.

References.

[1] Part of this work has been published. See: J. Amer. Chem. Soc., 94, 7583 (1972).

[2] For reviews on hydrogen-deuterium asymmetry see:
D. Arigoni and E.L. Eliel, Top. Stereochem., vol. 4, 127.
L. Verbit, Prog. Phys. Org. Chem., vol. 7, 51.

[3] C.J.M. Stirling, J. Chem. Soc., (1963) 5741.

[4] M.A. Sabol and K.K. Andersen, J. Amer. Chem. Soc., 91, 3603 (1968).

[5] R. Annunziata, M. Cinquinni and C. Colonna, J. Chem. Soc., Perkin Trans., 1, 2057 (1972).

[6] S. Englard, J.S. Britten and I. Listowsky, J. Biol. Chem., 242, 2255 (1967).
L. Verbit, J. Amer. Chem. Soc., 89, 167 (1967).

[7] Data of this CD-curve. UV band: $\Delta\varepsilon_{max}=2.4\cdot10^{-3}$; peaks at 264.5 , 268.3 275.0 , 279.8 , 286.7 , 292.3 , 299.3 , 306.6 , 314.2 , 322.5 , 331.0 and 340.7nm ; visible band: $\Delta\varepsilon_{min}=-9.05\cdot10^{-3}$; peaks at 462.5 and 484.5nm.

[8] From ORD-measurements of III (H.-P. Gervais and A. Rassat, Bull. Soc. Chim. Fr., (1961) 745) it has been concluded[11 13a] that the absorption band around 480nm gives rise to a normal Cotton effect in CD, which is at variance with our results.

[9] C.A. Emeis, L.J. Oosterhoff and Gonda de Vries, Proc. Roy. Soc., A 297, 54 (1967).

[10] The calculated (max.) amplitude of this ORD-curve is 42.2^{o}.

[11] W. Hug and G. Wagnière, Helv. Chim. Acta, 54, 663 (1971).
W. Hug, J. Kuhn, K.J. Seibold, H. Labhart and G. Wagnière, Helv. Chim. Acta, 54, 1451 (1971).

[12] E. Charney and L. Tsai, J. Amer. Chem. Soc., 93, 7123 (1971).

[13] a/ A.W. Burgstahler and N.C. Naik, Helv. Chim. Acta, 54, 2920 (1971).
b/ W. Hug and G. Wagnière, Helv. Chim. Acta, 55, 634 (1972).

[14] X-ray analysis of camphorquinone (L. Tsai, E. Charney, J.V. Silverton and W.M. Bright, to be published) proved the sense of twist predicted in [12] to be correct (fig. 2-6). However, this does not mean that the assignment of electronic transitions, given in [12], is also correct

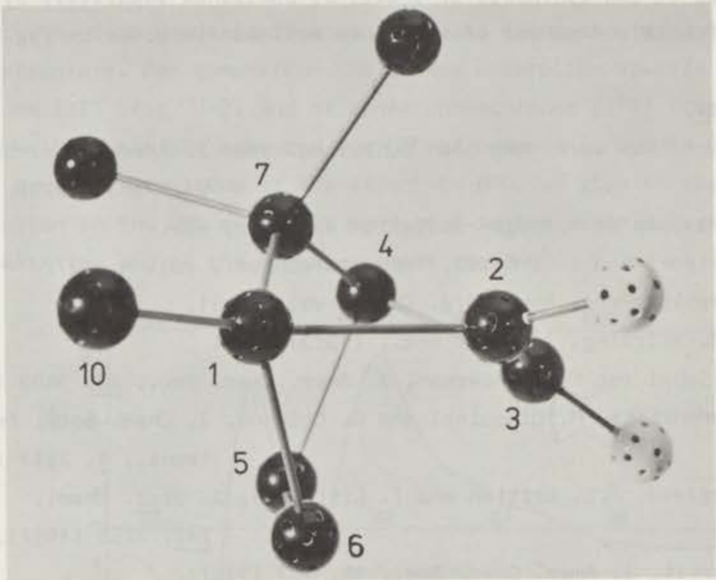

Fig. 2-6 A model of (-)-(1R)-camphorquinone (II) showing the the sense of twist as found by X-ray analysis[14].

(cf. chapter 4).

15) One of the authors (Kokke) is indebted to the Netherlands Organization for the Advancement of Pure Research (Z.W.O.) for the sponsoring of this work. A NATO grant for the purchase of ^{18}O is gratefully acknowledged.

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THE SYNTHESIS OF (1R)-2-^{18}O-α-FENCHOCAMPHORONEQUINONE: SPECIFIC LABELING OF ONE CARBONYL GROUP IN A NORBORNANE-2,3-DIONE.

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Summary.

A method has been devised for the preparation of a norbornane-2,3-dione with one of the carbonyl groups enriched specifically in ^{18}O, viz., oxidation of a labeled ketone with selenium dioxide in acetic anhydride. This method has been applied to the oxidation of labeled, optically active α-fenchocamphorone giving specifically labeled α-fenchocamphoronequinone. This diketone, whose optical activity is due only to ^{18}O-substitution, showed a small but measureable effect in the CD of both low intensity absorption bands in the region 250-520nm.

Introduction.

Compounds which derive optical activity from isotopic substitution offer interesting possibilities for studying the origin of vibronic absorption bands if these bands are accessible to CD-measurements. Up to now much work has been done to synthesize compounds whose optical activity stems from deuterium substitution[16]. In addition a few examples have been reported where optical activity is due to oxygen isotopes, viz. some ^{16}O-^{18}O-sulphones[17 18 19] and ^{16}O-^{18}O-sulphonate esters[18]. Measurement of the optical activity of these compounds has usually resulted in plain ORD-curves[20].

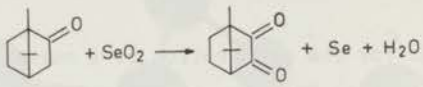
In view of this situation it seemed worth while to start a program for the synthesis of ketones and diketones with optical activity due to isotopic substitution. α-Diketones were particularly inviting because two low intensity absorption bands in the region 250-520nm can be studied by CD provided the effect is large enough.

One of our efforts was directed towards the synthesis of a specifically labeled ^{16}O-^{18}O-α-diketone starting from optically active norcamphor or α-fenchocamphorone (5). Because of the availability and the price of starting materials ($H_2{}^{18}O$ e.g.) it was decided to try out the various steps in the synthesis with cheaper materials. This resulted in a number of interesting observations which will be discussed first.

Model experiments.

Initially the synthesis of specifically labeled camphorquinone was attempted from camphor. Water, enriched in ^{18}O (2.095 at.% ^{18}O [21]) was used for labeling the reagents, since an ^{18}O-label of 2% is sufficient high to detect the possible exchange of oxygen between the reagents and the reaction medium by mass spectroscopy.

Figure 2-7



An α-diketone is most conveniently prepared by oxidation of a ketone with selenium dioxide[22]. Because the water formed in this reaction (fig. 2-7) reacts with selenium dioxide to form selenious acid, which might catalyse in unfavourable conditions exchange of oxygen between the carbonyl group and water[23], a solvent was required in which either selenious acid was insoluble, or the water formed could be removed.

In a first experiment labeled camphor was oxidized with selenium dioxide in acetic anhydride[24] (molar ratio of camphor, selenium dioxide and acetic anhydride = 0.33 : 0.54 : 0.53), the intention being to bind the water formed with acetic anhydride. This first experiment was a faillure: the camphorquinone prepared from labeled camphor (2.26% ^{18}O) had too low a label (1.52% ^{18}O; retention is 2.45% ^{18}O).

Various possible reasons for this loss of label were systematically investigated. First it was verified that labeled camphor does not lose label[25] when boiled with acetic anhydride for four hours[26 27]. Similarly no loss of label occurred when 0.3g of water was added to a boiling solution of 2.5g of labeled camphor in 2.5ml of acetic anhydride[28] (molar ratio of camphor, water and acetic anhydride = 0.33 : 0.33 : 0.53). Apparently under these conditions the reaction between water and acetic anhydride is much faster than the acetic acid-catalyzed exchange reaction between water and camphor.

Reconsidering in the light of these results the oxidation experiment in which loss of label did occur, it was realized that both ketone and solvent[29] were oxidized by selenium dioxide so that toward the end of the reaction hardly any acetic anhydride was left. The lifetime of a water molecule then became long enough to permit oxygen exchange with the carbonyl group.

Indeed it was found that loss of ^{18}O in the oxidation of labeled camphor

can be prevented by sufficiently reducing the quantity of selenium dioxide with respect to camphor and acetic anhydride. Although the mass spectra of camphorquinone clearly showed retention of label[25] and that selective label incorporation had been achieved[30], the possibility of interchange of the two oxygen atoms within one diketone molecule could not be excluded on the basis of these results[31]. On the other hand this process seemed to be very improbable so that continuation of the synthesis with highly labeled materials seemed justified.

Meanwhile two other routes to the desired compounds had been explored. It appeared that the oxidation of labeled camphor with selenium dioxide in toluene[32] proceeds with retention of label. although in poor yield. In this case water is probably removed by the excess of unreacted selenium dioxide. Finally it was tried to devise an oxidation reaction for the preparation of camphorquinone where water could not possibly be a reaction product, so that troubles due to exchange with water could not occur. The oxidation of camphor-enol-benzoate was attempted with selenium dioxide in benzene. Camphorquinone and benzoic acid were formed in good yield. However, when labeled selenium dioxide[33] was employed, randomly labeled camphorquinone was obtained.

Experiments with high label incorporation.

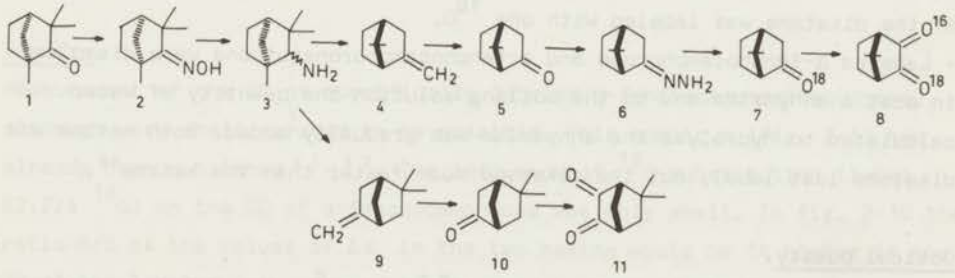


Fig. 2-8 The synthesis of the title compound (8) from (+)-(1S)-fenchone. (Absolute configurations are depicted[34].)

The route followed to (1R)-2-^{18}O-α-fenchocamphoronequinone (8) is indicated in fig. 2-8.

The required α-fenchocamphorone (5) was prepared via α-fenchene (4) from fenchone (1); this route was chosen because it was judged to be the one by which α-fenchene (4) of the highest chemical purity could be obtained[35 36]. The α-fenchocamphorone (5) thus obtained did not contain

the most likely impurity β-fenchocamphorone (10), because after selenium dioxide oxidation the diketone obtained was optically inactive (no effect in CD), i.e. the diketone did not contain a measureable quantity of β-fenchocamphoronequinone (11) as an impurity[38].

α-Fenchocamphorone (5) was labeled by regeneration from the hydrazone (6) with water enriched in ^{18}O. This labeled ketone contained 62.72% ^{18}O. After the oxidation with selenium dioxide in acetic anhydride some unreacted ketone was recovered with a label of 60.19% ^{18}O; of the diketone prepared 48.05% was specifically labeled with ^{18}O, and 0.08% was doubly labeled. Completely specific labeling had been achieved[39].

Much less label is missing from the ketone recovered than from the diketone formed. One might suppose that oxygen exchange of the diketone with water formed during the selenium dioxide oxidation is faster than oxygen exchange of the starting mono-ketone. The results of two exchange experiments confirmed this hypothesis.

- A homogeneous solution of α-fenchocamphorone (0.5754g), α-fenchocamphoronequinone (0.5363g), labeled water (1.1210g, 12.062 at.% ^{18}O [21]) and 0.20N acetic acid in dioxane (1.1230g) was left at room temperature for 96 hours. After working-up it was shown that the ketone had hardly exchanged oxygen (label 0.38% ^{18}O; no label is 0.2% ^{18}O), whereas 14.90% of the diketone was labeled with one ^{18}O.
- Labeled α-fenchocamphorone and α-fenchocamphoronequinone were dissolved in acetic anhydride and to the boiling solution the quantity of water calculated to hydrolyse the anhydride was gradually added. Both ketone and diketone lost label, but the diketone much faster than the ketone[40].

Optical purity.

Our starting fenchone-oxime (2) had $[\alpha]_D$+41.19° (abs. EtOH); comparison with a reliable value of $[\alpha]_D$+46.5° (EtOH)[46] indicates an optical purity of 88.6%.

The physical constants recorded by Rassat[47] for (1S)-α-fenchocamphorone: $[\alpha]_D$-60° (EtOH), $\Delta\varepsilon_{max}$-1.60 (cyclohexane), are not consistent with our best data: $[\alpha]_D$+67.05° (MeOH)[48], $\Delta\varepsilon_{max}$+2.3 (cyclohexane). Mattinen[35c] recorded $[\alpha]_D$+73.94° (EtOH); if this is taken as the correct value, then our α-fenchocamphorone has an optical purity of 90.7%.

A discussion of the optical purity of the ^{16}O-^{18}O-diketone prepared

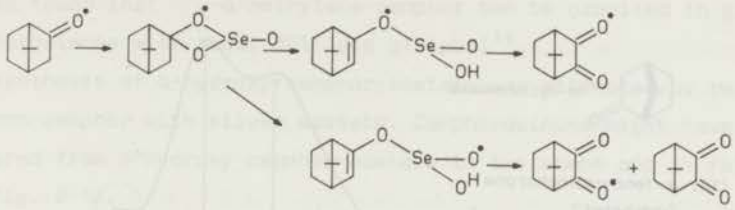


Fig. 2-9 A mechanism which gives rise to specifically labeled diketone, but with partial racemisation.

according to fig. 2-8 must involve the mechanism of the oxidation reaction with selenium dioxide. Corey and Schaefer[49] have postulated a selenite-enol-ester as a reaction intermediate. If such a species is formed via a cyclo-addition of selenium dioxide to the ketone, then one would expect (fig. 2-9) in our case 66.67% racemisation and 25% loss of label. This mechanism seems unlikely because labeled camphor can be oxidized with retention of label[25] and our exchange experiments suggest, that during the oxidation of α-fenchocamphorone loss of label is due to exchange with water.

If we assume that oxidation of labeled α-fenchocamphorone with selenium dioxide gives rise to no racemisation because of the mechanism of the oxidation reaction[50], then (1R)-2-^{18}O-α-fenchocamphoronequinone (8) has an optical purity of 90.7%.

Spectra.

Measurement of the CD of specifically labeled α-fenchocamphoronequinone, although very small, proved to be possible. This spectrum (fig. 2-1) has already been published[51 52]. The influence of ^{18}O-substitution (label 62.72% ^{18}O) on the CD of α-fenchocamphrone was only small. In fig. 2-10 the ratio A/B of the values of $\Delta\varepsilon$ in the two maxima would be 1% higher if the CD of the labeled ketone was depicted here instead of the CD of the unlabeled ketone. The dotted line in fig. 2-10 encloses a part of the graph which is different in the case of the labeled ketone. In fig. 2-11 this detail of the CD curves of both labeled and unlabeled ketone is enlarged. The influence of ^{18}O-substitution on the absorption spectra of ketone (7) and diketone (8) could not be detected with a Cary-14 or a Cary-15.

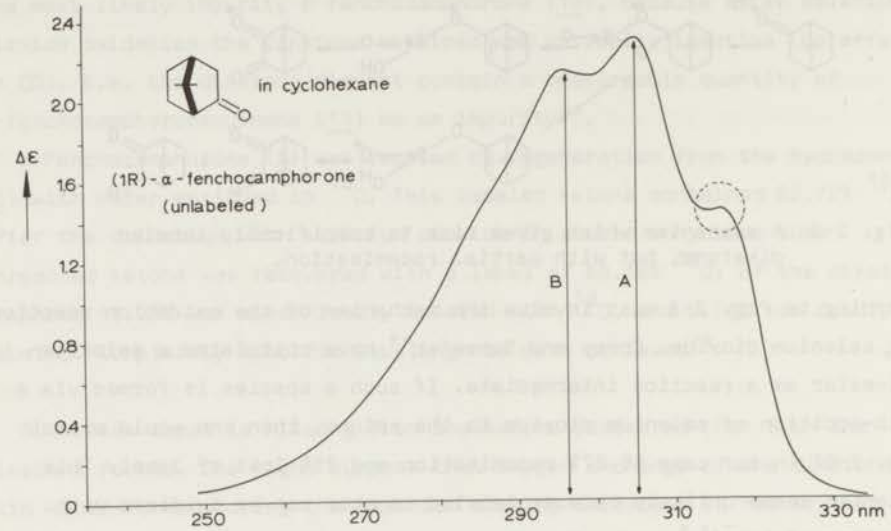


Figure 2-10 CD of compound 5.

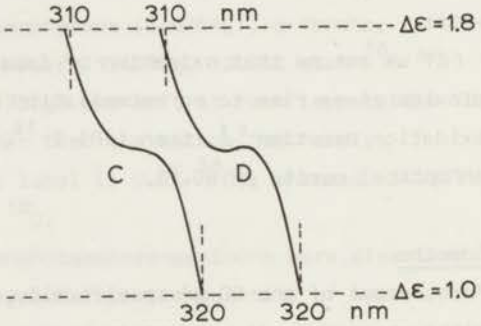


Figure 2-11 Detail of the CD of labeled (C) and unlabeled (D) α-fenchocamphorone (in cyclohexane)

Model experiments not involving use of selenium dioxide.

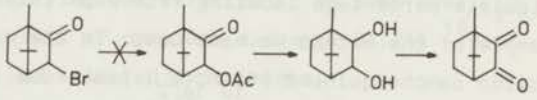
Simultaneously with the oxidation of a ketone and an enol-ester with selenium dioxide, some other reactions which might led to specifically labeled diketones were investigated as well. These model experiments, not involving use of selenium dioxide, are described in this section.

1/ Ruthenium tetroxide is a vigorous oxidizing agent which reacts with carbon-carbon double bonds to give carbonyl functions. It is used in analytical chemistry to determine the number of double bonds in steroids [53]. We found that ruthenium tetroxide reacts with α-methylene-camphor to give camphorquinone. However, we have not investigated whether oxidation of ^{18}O-α-methylene-camphor with this oxidizing agent proceeds with retention of label[55].

2/ It was found that ^{18}O-α-methylene-camphor can be ozonised to give camphorquinone with about 30% loss of label[56].

3/ The synthesis of α-hydroxy-camphor-acetate was attempted by reacting α-bromo-camphor with silver acetate. Camphorquinone might have been prepared from α-hydroxy-camphor-acetate in two steps and in fair yield, cf. fig. 2-12.

Figure 2-12



But siver acetate abstracted hydrogen bromide from α-bromo-camphor and a reaction product $C_{10}H_{14}O$ was formed. We have not investigated the structure of this product[57 58]. Because 2-hydroxy-3-bromo-camphane is reported not to be stable[60] we have not tried to react this compound with silver acetate.

4/ One of the methods for the methylation of amines is heating the amine with formalin and acid (the Leuckart reaction)[61]. However, when α-amino-camphor-hydrochloride is treated with formalin, the expected N-methylated product is not isolated, but camphorquinone instead[62 63]. We have examined the possible utility of the Leuckart reaction for our purpose by heating in a sealed tube α-amino-camphor-hydrochloride, labeled water and 1,3-dioxolane. In this manner in situ labeled formaldehyde could be generated, because it is known, that on hydrolysis of an acetal the oxygen of the carbonyl group formed is provided by the water[64]. After the reaction it appeared , that the liquid from which camphorquinone was filtered, was acid and accordingly the camphorquinone isolated had to high a label because exchange had occurred between the reaction product and the excess of labeled water.
We have obtained except for camphorquinone a colourless compound $C_{11}H_{16}O_2$ in this reaction. The structure of this compound has not been elucidated.

5/ One of the latest developments in the organic chemistry of thallium is the discovery[65] that oximes can be hydrolysed by $Tl(NO_3)_3 \cdot 3H_2O$ in benzene. It was hoped that isonitrosocamphor (=camphorquinone-3-oxime), labeled by exchange, might be converted in specifically labeled camphorquinone. However, reaction of thallium trinitrate with isonitrosocamphor gave rise to a range of products, each in low yield.

Experimental.

Melting points are not corrected. Angles of rotation were determined with a Bendix-NPL photoelectric polarimeter at room temperature.

Mass spectra. Labels were calculated from peak intensities in spectra obtained with a MS-9 mass spectrometer. Because of the various methods to calculate percentage labeling from peak intensities, we give a numerical example of the method we have used. In the mass spectrum of a sample of labeled camphorquinone ($C_{10}H_{14}O_2$) peaks due to molecular ions are at M/e=166,167,168 with rel. intensities 100 : 11.19 : 2.275. Correction of the peak intensities for M/e=167,168 for satellites of M/e=166 due to D and ^{13}C is done by comparison with a mass spectrum of $C_{10}H_{14}$. Rel. peak intensities for M/e134,135,136 in $C_{10}H_{14}$ 100 : 11.03 : 0.55 [66]. ^{18}O-label=[(2.275-0.55)/(100+(11.19-11.03)+(2.275-0.55))]x100%=1.67% ^{18}O. Note, the absolute ^{18}O content is calculated; no correction for natural abundance is applied.

Camphor-hydrazone[67] was recrystallised from iso-octane. Stored at -20° over P_2O_5 it did not liquefy as observed in [67], and after a year the crystals had only turned slightly yellowish.

Camphor-enol-benzoate, prepared according to [68], appeared to be very impure (G.L.C.). The composition of the reaction product depends on the reaction time: when camphor is refluxed with benzoyl chloride during 4 hours, the enol-ester is the main product, but when refluxed overnight another component of the mixture (probably the benzoate of 1-hydroxy-camphene) becomes the main product. The enol-ester was purified by column chromatography over silica gel. Elution with carbon tetrachloride then gave pure camphor-enol-benzoate. The enol-ester is a liquid at room temperature. NMR data (CCl_4) (shifts with respect to TMS): three methyl groups at δ=0.791, 0.886, 1.042ppm; H attached to C_4 (bridge-head proton): triplet, δ=2.831ppm, J=2x3.50Hz; H attached to C_3 (vinylic proton): doublet, δ=5.742ppm, J=3.68Hz.

Labeling of camphor by hydrolysis of camphor-hydrazone. A mixture of camphor-hydrazone (8.3g), labeled water (3.6ml, 2.095 at.% ^{18}O [21]) and ethylene chloride (50ml) was placed in a heavy walled, long necked flask at a high vacuum line, degassed, and hydrogen bromide (1.671/20°/1atm.) was then frozen into it. The sealed mixture was left overnight, then heated whilst magnetically stirring for 8 hours at 80°. Normal isolation procedures then gave the labeled camphor which was purified twice by

sublimation to give 6.0g of camphor, label 2.26% ^{18}O.

Labeling of selenium dioxide by exchange. Highly labeled selenium dioxide was prepared by exchange between selenium dioxide (4.9g) and labeled water (1.0g, 91.8% ^{18}O; a gift of Prof. E. Heilbronner, Basel) (16 hours on a bath at 130°). The water was then removed with a rotatory evaporator until the residue crystallised. Drying was effected in an oven over P_2O_5 in vacuo. Label calculated on the basis of complete exchange 31.25% ^{18}O.

Oxidations of labeled camphor. Two selected experiments.

- A mixture of labeled camphor (3.0g, 2.19% ^{18}O), selenium dioxide (1.5g) and acetic anhydride (3ml) was heated for three hours at 145°. After removal of the solvent and sublimation the crude product (1.8g) was separated by prep. G.L.C. to give camphor (0.8g) and camphorquinone (0.5g, label 2.27% ^{18}O). Retention of label is 2.38% ^{18}O.
- A mixture of labeled camphor (2.5g, 2.19% ^{18}O), selenium dioxide (1.85g) and dry toluene (5ml) was refluxed for 15.5 hours, then the solvent was removed and the residue sublimed. Separation of the crude mixture (2.0g) gave camphor (1.4g) and camphorquinone (0.1g), label 2.32% ^{18}O. Retention of label is 2.38% ^{18}O.

Oxidation of camphor-enol-benzoate with labeled selenium dioxide. A stirred mixture of benzene (9ml), labeled selenium dioxide (3.0g, 31.25% ^{18}O) and camphor-enol-benzoate (4.4g) was heated at 150-160° in an autoclave for 3.3 hours. (The reaction can be carried out in xylene as well (4 hours, reflux), but we chose benzene because it can be removed more easily.) Methylene chloride was then added to the cooled reaction mixture which was filtered. Benzoic acid was removed by washing with $NaHCO_3$ solution. After sublimation the camphorquinone was purified by recrystallisation (2x) from cyclohexane; the mother liquors were worked-up by prep. G.L.C. (SE-30 column). Yield 2.0g; 30.95% of the molecules was labeled with one ^{18}O, 3.58% was doubly labeled; the fragment (M-CO) had a label of 19.00% ^{18}O (32.5eV spectrum), 19.07% ^{18}O (15eV spectrum). These data seem consistent with a diketone, label 19.14% ^{18}O, the ^{18}O randomly distributed over the carbonyl groups: viz., expected for this case 30.95% of the molecules labeled with one ^{18}O, 3.66% doubly labeled, a fragment (M-CO) with a label of 19.14% ^{18}O.

We should expect a random distribution of ^{18}O over the carbonyl groups only if both oxygen atoms of the diketone formed were provided by selenium dioxide. But the label of the diketone is about 2/3 of the value which this

mechanism would suggest (19.14% instead of 31.25% ^{18}O); this loss of label might be due to exchange prior to oxidation.

According to our measurements, when optically pure camphor is used for the preparation of the enol-benzoate, then oxidation of this enol-benzoate gives optically pure camphorquinone.

(+)-Fenchone-oxime (2) was prepared from (+)-fenchone (Fluka, purum) according to Wallach[69] in at least 80% yield. $[\alpha]_D$+41.19° (abs. EtOH), mp 162-4° after recrystallisation from heptane and dilute alcohol. Lit.[46]: $[\alpha]_D$+46.5° (EtOH), mp 167°.

Fenchylamine (3) was prepared from 2 by reduction[70] with sodium and alcohol. The hydrochloride after two recrystallisations from dioxane had a specific rotation of $[\alpha]_D$-4.53° (MeOH).

(-)-α-Fenchene (4). The amine 3 was regenerated from the hydrochloride and treated with nitrous acid[71]. The reaction products were separated by fractional distillation using a Nester-Faust spinning band column (∿20cm Hg). From 1.5kg of 1 86g of α-fenchene fractions was obtained (purity >87.4%) that were used for the preparation of α-fenchocamphorone (5). For the measurements more pure 4 was obtained by careful redistillation (∿20cm Hg, 2ml/hour) of a fore run. The purest sample (99.54%) had $[\alpha]_D$-42.62° (ethyl acetate).

(+)-α-Fenchocamphorone (5). Some early terpene chemists[72] have prepared 5 by ozonisation of 4, but Mattinen[35c] failed to reproduce their reasonable yields. We prepared 5 by oxidation of 4 with ruthenium tetroxide in methylene chloride in 65.5% yield. A sample of the crude ketone was sublimed: then mp 91-6°, $[\alpha]_D$+57.93° (MeOH) was found. Another sample was oxidized with selenium dioxide[24], and after distillation the oxidation product was purified by prep. G.L.C. (SE-30 column) in order to remove unreacted ketone. After sublimation the α-fenchocamphoronequinone had mp 139.0-9.5°. No effect in CD could be detected. Therefore 5 was not contaminated with β-fenchocamphorone (10), because it would have been possible to detect β-fenchocamphoronequinone (11) by CD[38].

(-)-α-Fenchocamphorone-hydrazone (6) was prepared from 5 in the manner of [67] in 74.4-82.2% yield. 6 was a liquid at room temperature, but crystallised on storing at -15°. Different angles of rotation were recorded for two preparations: $[\alpha]_D$-51.27 and -58.32° (MeOH).

Hydrolysis of 6, introduction of the label.

- Labeling procedure. In a degassed mixture of 6, labeled water and

ethylene chloride, attached to a high vacuum line, HBr was introduced. The method used is the same as was pursued for the labeling of camphor by hydrolysis of its hydrazone. But it was found more convenient to introduce HBr in the reaction mixture using a break-seal vessel. A break- seal vessel with two taps and a ground glass joint (see fig. 2-13) was flushed with HBr, the lower part of the vessel was then immersed in liquid nitrogen and the calculated quantity of HBr (2 moles of HBr : 1 mole of hydrazone) admitted and condensed. The taps were melted off. The the vessel was attached to the high vacuum line, the seal was broken, the liquid nitrogen removed, and HBr frozen into the reaction mixture. Because of the high price of water, highly enriched in ^{18}O, the excess of water for the hydrolysis of 6 must be as small as possible. As already described we used 4g of water for the hydrolysis of 8.3g of camphor-hydrazone, and we obtained 6.0g of camphor and 2.0g of residue (azine).

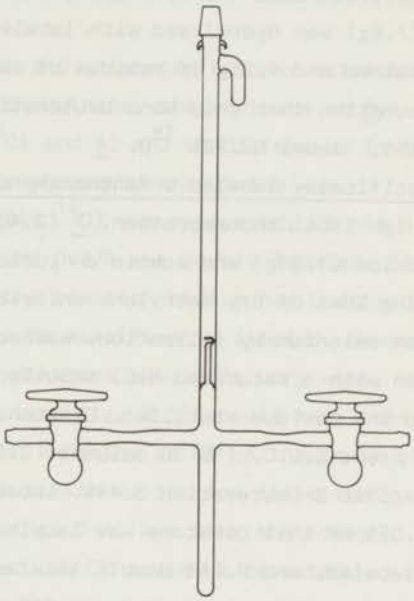


Figure 2-13

It might be expected that further reduction of the quantity of water with respect to the hydrazone would result in an increase of the yield of azine. In the case of 6 azine formation is sterically more easy than in the case of camphor-hydrazone. Thus when 8.3g of camphor-hydrazone was hydrolysed with 2.0g of water, 4.4g of camphor and 3.2g of residue was obtained, but 6 (7.6g), hydrolysed with water (2.0g) in ethylene chloride (50ml) gave 4.4g of residue and 2.65g of 5, mp 100-5°, $[\alpha]_D$+65.10° (MeOH).

- Labeling. Water containing 0.31 at.% ^{17}O, 62.88 at.% ^{18}O and 64.0 at.% D [21]) was used. We used deuterated water, enriched in ^{18}O, because it is less expensive than water, enriched in ^{18}O, where the deuterium content has been reduced to natural abundance. Thus 5 will be labeled with ^{18}O and deuterated, but only in the 3-position. Deuteration of norbornanones is well documented[73]. Introduction of D at the exo-3-position is easy, introduction of a second D is more difficult, and deuteration at the

6-position does not take place under our conditions.
6 (7.6g) was hydrolysed with labeled water (2.0g) and HBr; 7 (2.45g) was obtained and 4.75g of residue of sublimation. Labels were calculated in the assumption that only mono-deuteration had occurred. Specific 3-deuteration 3.25%, label 62.72% ^{18}O.

Specifically labeled α-fenchocamphoronequinone.

- High label incorporation. 7 (2.40g, 62.72% ^{18}O) was heated with selenium dioxide (1.53g) and acetic anhydride (2.2ml) (4 hours on a bath at 150°). Using 20ml of dry methylene chloride the reaction product was separated from selenium by filtration, washed with bicarbonate solution till neutral, then with a saturated NaCl solution. The solvent was removed with suction and the residue distilled. Diketone and unreacted monoketone were separated by prep. G.L.C. (SE-30 column). 0.88g of 7 was recovered, mp 108-10°, specific 3-deuteration 3.44%. label 60.19% ^{18}O; 0.55g of 8 was obtained, 48.05% of this diketone was labeled specifically with ^{18}O, 50.87% was unlabeled, and 0.08% doubly labeled with ^{18}O. A solution of 8 showed CD in both absorption bands between 250 and 520nm. That the observed CD in the visible region was due to isotopic substitution could not be called in question because the precursor 7 does not absorb there, but it happens to be that the second absorption band of 8 at about 300nm coincides with an absorption band of the precursor 7, thus it had to be made sure that the observed CD of 8 at about 300nm was indeed due to 8 and not due to the precursor. The CD band we observed in this region was shaped like the CD band of 7, but it had a very unusual fine structure. Because of this band shape and its place we had a shrewd suspicion that traces of 7 interfered with the CD measurement. Indeed we showed 8 by G.L.C. to be contaminated with 0.1-0.2% of 7. This impurity was removed by prep. G.L.C. to yield 8 (0.4g), mp 140.0-0.5°. Then CD was measured again; the then observed CD of 8 is displayed in fig. 2-1.

- The ultimate proof that the observed CD of 8 is due only to isotopic substitution is an exchange experiment. First CD and absorption was measured of a spectroscopic solution of 8 (24.2mg) in heptane (10ml). Then to this solution was added water (4g) and acetic acid (1g); this mixture was magnetically stirred at room temperature for 15.25 hours, neutralised, the layers were separated, the hydrocarbon layer dried and used for the measurement of CD and absorption. No CD could be detected, which serves as a proof for the purity of 8; the optical density in the visible region

decreased by ~50% during the experiment. This might be due to the formation of a hydrate[43].

- Experiment with labeled selenium dioxide and unlabeled ketone: attempted preparation of (1S)-2-^{18}O-α-fenchocamphoronequinone, the antipode of 8. Using labeled selenium dioxide (31.25% ^{18}O) and 5, and conditions as in the experiment with highly labeled 7, ^{18}O-α-fenchocamphoronequinone was obtained. Some unreacted ketone (label 0.86% ^{18}O) was recovered. Of the diketone was 10.62% labeled with one ^{18}O and 0.27% was doubly labeled. If no exchange between selenium dioxide and the reaction medium had occurred, we should expect 31.25% of the diketone to be specifically labeled. Because of the low label the effect in CD of this diketone should be very weak, but the two highest peaks in the visible band (see fig. 2-1) should have been above noise level. (The max. pen deflection expected in CD on the basis of the optical density of the solution of the diketone, its low isotopical purity (10.62%) and the observed CD of 8 (fig. 2-1) was 9mm; the noise level of the CD apparatus was 3mm.) However, no CD could be detected. Presumably partial racemisation had occurred.

Exchange experiment with 7 and 8 (both labeled by exchange) in Ac_2O.
A solution of 7 (0.4329g) and 8 (0.4013g) in acetic anhydride (2.1g) was heated under reflux. Water was added with a syringe in 5µl portions at intervals of three minutes. After addition of 30% of the calculated quantity of water (=30% of 0.37g) a sample of the mixture was taken for the determination of the labels; sampling was also done when 50, 70 and 90% of the water had been added. The results are shown in the table.

water added, %	diketone, labeled with one ^{18}O, %	ketone, % ^{18}O
0	19.24	30.2
30	13.70	29.4
50	11.25	28.9
70	7.31	27.4
90	5.84	26.3

α-Methylene-camphor cam be prepared after Dallacker[74] and after Snatzke[75]. α-Methylene-norcamphor is best prepared by means of a Mannich reaction[76]; Alder[77] has described a more complicated synthesis of this compound. Substituted α-methylene-camphors such as α-isopropylidene-camphor can be prepared by reaction of the Grignard reagent of α-bromo-camphor with aldehydes and ketones, followed by dehydratation[78].

α-Methylene-camphor, labeling by exchange. A mixture of α-methylene-camphor (5g), labeled water (15g, 2.095 at.% ^{18}O [21]), THF (20ml) and p.-toluene-sulphonic acid (0.5g) is refluxed for 23.5 hours. The layers are separated, the aqueous layer is extracted once with pentane (5ml). The combined organic layer and pentane extract then are washed with water, dried and distilled. Yield 3.8g, label 2.0 % ^{18}O.

Attempted synthesis of α-hydroxy-camphor-acetate. After refluxing overnight a mixture of α-bromo-camphor (10g) and silver acetate (7.9g; freshly prepared) in chloroform (100ml) no appreciable reaction had occurred. Therefore a solvent was used that permitted a higher reaction temperature. The same quantities of silver acetate and α-bromo-camphor in DMSO (100ml) were heated at 150° whilst magnetically stirring for 15 hours. From G.L.C.-measurements (SE-30 column) it was then deduced that reaction had occurred; only products were formed with a retention time shorter than the starting material. Mol. ratio of the only important reaction product and the starting material about 17:42. The reaction product was analysed as $C_{10}H_{14}O$. The same product was formed when α-bromo-camphor was refluxed with silver acetate in pyridine.

α-Amino-camphor-hydrochloride. Isonitrosocamphor[79] was reduced with zinc and base to give α-amino-camphor[80]. The hydrochloride was prepared by saturating an ethereal solution of the amine with hydrogen chloride. Then the ether was removed and the hydrochloride recrystallised from absolute alcohol : dioxane 1:1.

The Leuckart reaction. In a Carius tube was placed 0.5g of α-amino-camphor-hydrochloride. 0.69g of 1,3-dioxolane and 0.58g of labeled water (2.095 at.% ^{18}O [21]). The tube was evacuated, sealed, and heated in an oil bath at 145° for two hours. After cooling the crystals were removed by filtration. The filtrate was a brown liquid, pH= 2-3 (indicator paper). On recrystallisation of the dried crystals from hexane (3ml) camphorquinone was obtained (75mg, fine needles), label 4.44% ^{18}O. Retention of label is 2.28% ^{18}O. On standing the hexane of the mother liquor gradually evaporated and colourless crystals of a compound $C_{11}H_{16}O_2$ were formed. The above reaction was repeated on a larger scale, part of the camphorquinone was removed by crystallisation and the mixture of the unknown compound and camphorquinone separated by prep. G.L.C. (Apiezon, 220°) [81]. Starting with 6.5g of α-amino-camphor-hydrochloride there was obtained 0.75g of the unknown compound, mp 80-5° from hexane. This compound was not identified.

Acknowledgement.

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25) In the low label experiments the maximum absolute error in the

determination of ^{18}O-labels was ±0.10%. Therefore a statement such as "retention of label was observed" should read "relative loss of label was 5% or less".

[26] Thus the mechanism resposible for the loss of ^{18}O when a labeled aldehyde is treated with acetic anhydride (fig. 2-13) does not apply here:

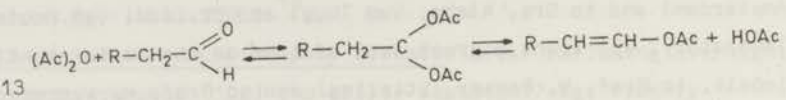


Figure 2-13

cf. Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart, Bd 7/1, 442 (1954).

[27] When camphor is treated with trichloroacetic acid anhydride (110-20°) a geminal di-ester is formed, 2,2-dihydroxy-camphene-di-trichloroacetate which decomposes to give after a Wagner-Meerwein rearrangement 1-hydroxy-camphene-trichloroacetate as the primary product (J. Libman, M. Sprecher and Y. Mazur, Tetrahedron, 25, 1679 (1969)).

[28] This quantity of water (0.3g) was chosen because it would have been formed when selenium dioxide has been added to the reaction mixture and had oxidized all of the ketone and nothing else.

[29] J.J. Postowsky and B.P. Lugowkin, Ber., 68, 854 (1935).
L. Rappen, J. Prakt. Chem., n.F. 157, 196 (1941).

[30] A sample of camphorquinone prepared from labeled camphor[24] had a label of 1.60% ^{18}O, and the fragment (M-CO) a label of 0.48% ^{18}O (15eV spectrum). If both carbonyl groups were equivalent, or if we had a randomly labeled diketone, we should expect the fragment (M-CO) to have a label of 0.80% ^{18}O.

[31] Assuming that the "chain branching rule" (cf. F.W. McLafferty, Interpretation of Mass Spectra, W.A. Benjamin Inc., 82 (1967)) can be used to predict that in camphorquinone the bond between C_1 and C_2 is broken preferential to the bond between C_3 and C_4, we conclude from the labels of [31] that 2-^{18}O-camphorquinone is the main or possibly the only reaction product. If preference for bond rupture should be opposite to the "chain branching rule", then 3-^{18}O-camphorquinone is the main or the only reaction product, and interchange of oxygen atoms within a molecule has taken place.

[32] J. Vène, Compt. Rend., 216, 272 (1943).

[33] Labeled selenium dioxide is commercially available (Miles Laboratories Inc.)

[34]) The absolute configurations follow from the absolute configuration of camphor (M.G. Northolt and J.H. Palm, Rec. Trav. Chim., 85, 143 (1966)) and the relative configurations of fenchone (1) and camphor (A. Fredga and J.K. Miettinen, Acta Chem. Scand., 1, 317 (1947)).

[35]) For syntheses of α-fenchene (4) the reader is referred to:

a/ J.L. Simonsen, The Terpenes, Cambridge University Press, 2nd ed., vol. 2, 538 (1949).

b/ E. Gildemeister and Fr. Hoffmann, Die Aetherischen Oele, Akademie-Verlag, Berlin, 4. Aufl., Bd IIIa, 197 (1960).

c/ V. Mattinen, Ann. Acad. Sc. Fennicae, AII 106, 20 (1961).

[36]) All syntheses of α-fenchene[35] involve a Wagner-Meerwein rearrangement of the fenchyl-cation (15). From 15 the cations of α- and β-fenchene, 16 resp. 17, may be formed (fig. 2-14). Formation of β-fenchene (9) is very undesirable because it can only be separated from α-fenchene by distillation with great difficulty. Whether β-fenchene will be formed depends on the reaction conditions. As is depicted in fig. 2-8 we have prepared α-fenchene from fenchylamine, and did not expect the formation of β-fenchene, because under the same conditions from the bornyl-cation (18) optically pure camphene (20a) [37]) is formed. Thus under those conditions the camphene cations (19a,b) do not equilibrate, because that would bring about racemisation.

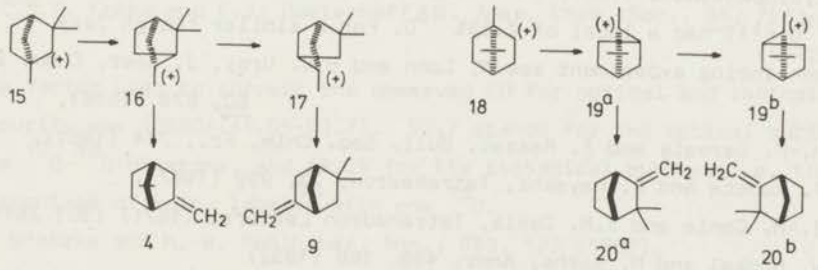


Figure 2-14 Wagner-Meerwein rearrangements (simplified).

[37]) W.Hückel and W. Tappe, Ber., 2769 (1936).
W. Hückel, Ann., 549, 186 (1941).
But a higher angle of rotation has been recorded for camphene, cf. J.P. Bain, A.H. Best, B.L. Hampton, G.A. Hawkins and L.J. Kitchen, J. Amer. Chem. Soc., 72, 3124 (1950).

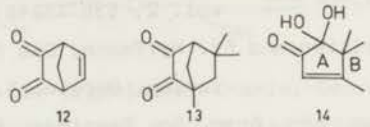
[38]) Unfortunately the CD of β-fenchocamphoronequinone (11) has not been published, but if we assume that its strongest CD band in the region

250-520nm has $\Delta\varepsilon$=0.1, which is a rather low value, then we would have detected 11 by CD if its concentration in α-fenchocamphoronequinone had been >0.35% .

39) The presence of doubly labeled diketone (0.08%) is due to the natural abundance of ^{18}O in the oxidizing agent.

40) In this contxt it may be of interest to mention some data found in the literature.

Figure 2-15



12 13 14

The yellow compound dehydronorcamphorquinone (12) gives a colourless solution in water. A hydrate is postulated[41]. Thus this diketone might undergo uncatalyzed oxygen exchange with water, whereas oxygen exchange between water and a ketone requires catalysis[42]./ Rassat[43] states that isofenchonequinone (13) is hydrated easily./ Some norsteroids with an α-diketone chromophore in the unsaturated A-ring (14) can be isolated as mono-hydrates[44]./ Cyclobutane-1,2-dione even reacts with water to give α-hydroxy-cyclopropanecarboxylic acid[45].

41) H.-D. Scharf, W. Droste and R. Liebig, Angew. Chem., 88, 195 (1968).

42) This statement does not hold at elevated temperatures, for example cyclopentanone recovered after heating in a sealed tube (2 hours, 150°) cyclopentanone (1ml), THF (1ml) and labeled water (0.5g, 12.062 at.% ^{18}O [21]) had a label of 7.33% ^{18}O. For a similar though less convincing experiment see M. Cohn and H.C. Urey, J. Amer. Chem. Soc., 60, 679 (1938).

43) H.-P. Gervais and A. Rassat, Bull. Soc. Chim. Fr., 744 (1961).

44) T. Kubota and F. Hayashi, Tetrahedron, 23, 999 (1967).

45) J.-M. Conia and J.M. Denis, Tetrahedron Letters, (1971) (30) 2845.

46) W. Hückel and M. Sachs, Ann., 498, 166 (1932)

47) C. Coulombeau and A. Rassat, Bull. Soc. Chim. Fr., 3752 (1966).

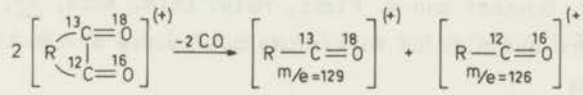
48) The angles of rotation of α-fenchocamphorone in MeOH and EtOH are identical within the experimental error.

49) E.J. Corey and J.P. Schaefer, J. Amer. Chem. Soc., 82, 918 (1960). J.P. Schaefer, J. Amer. Chem. Soc., 84, 713, 717 (1962).

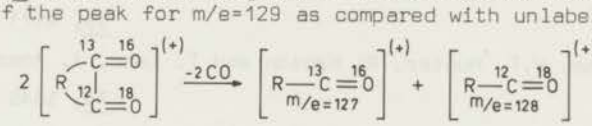
50) It is possible to prove rigorously, that oxidation of 7 is not accompanied by racemisation. In order to prove this 7 has to be prepared, enriched in ^{13}C in the 2- or 3-position. This ^{13}C-^{18}O-7 has

to be oxidized to give 8. Use has to be made of fragmentation reactions in the mass spectrograph: molecular ions of norcamphorquinones lose CO and OCCO very easy. We can exclude racemisation if:1/ the fragment (M- 56) is not enriched in ^{13}C, 2/ it follows from measurement of (M) that 8 is labeled specifically, 3/ it is proved by measurement of (M-CO) that oxidation of 2-^{13}C-2-^{18}O-7 e.g. gives rise exclusively to 2-^{13}C-2-^{18}O-8. This is possible because scrambling of ^{18}O (=inversion of the absolute configuration if the mol. was not enriched in ^{13}C) means formation of 2-^{13}C-3-^{18}O-8 which has a structure of the multiplet (M-CO) different from 2-^{13}C-2-^{18}O-8, cf. fig. 2-16.

Figure 2-16 A fragmentation reaction of 8 labeled with ^{13}C and ^{18}O in the chromophore (R=C_7H_{12}).



2-^{13}C-2-^{18}O-8 gives in the fragment (M-CO) a relative increase of intensity of the peak for m/e=129 as compared with unlabeled 8.



2-^{13}C-3-^{18}O-8 gives in the fragment (M-CO) a relative increase of intensity of the peaks for m/e=127,128 as compared with unlabeled 8.

51) W.C.M.C. Kokke and L.J. Oosterhoff, J. Amer. Chem. Soc., 94, 7583 (1972).

52) The factor used to correct the observed CD for optical and isotopical impurity was 10000/(48.05·90.7). 90.7 stands for the optical purity of the ^{16}O-^{18}O-diketone, and 48.05 for its isotopical purity, i.e. the percentage of mols. labeled with one ^{18}O.

53) G. Snatzke and H.-W. Fehlhaber, Ann., 663, 123 (1962).

54) F. Dallacker, L. Alroggen, H. Krings, B. Laur and M. Lipp, Ann., 647, 34 (1961).

55) Oxidation of α-methylene camphor with highly labeled RuO_4 is not possible because the latter compound is not commercially available (according to our correspondence with Miles Laboratories Inc.).

56) An unpublished ozonisation procedure was used, which was developed at Shell Research in Amsterdam.

57) Sodium acetate is known to react in the same manner with α-bromo-

camphor to give a product $C_{10}H_{14}O$, cf. [59].

[58] We found in the literature another example of the abstraction of hydrogen bromide by silver acetate: 1,2-dibromo-cyclohexane gives with siver acetate 1-bromo-cyclohex-2-ene. Cf. R. Cornubert, A. Rio and P. Sénéchal, Bull. Soc. Chim. Fr., 46 (1956).

[59] W.Z. Antkowiak, Bull. Acad. Pol. Sci., Ser. Sci. Chim., 14, 517 (1966).

[60] R. Ferrier, Compt. Rend., 220, 461 (1946).
G. Clément, M. Vilkas, G. Dupont and R. Dulou, Compt. Rend., 242, 1184 (1956).
This instability of 2-hydroxy-3-bromo-camphane is due to the easy autoxydation of this compound[59] to give camphor and camphorquinone.

[61] M.L. More , Organic Reactions, vol. 5, 301.

[62] H. Rupe, Fr. Buxtorf and W. Flatt, Helv. Chim. Acta, 13, 1026 (1930).

[63] For some more examples of this anomalous course of the Leuckart reaction see
H.T. Clarke, H.B. Gillespie and S.Z. Weisshaus, J. Amer. Chem. Soc., 55, 4571 (1933).
W.E. Parkham, W.T. Hunter, R. Hanson and T. Lahr, J. Amer. Chem. Soc., 74, 5646 (1952).

[64] For references see: Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart, Bd 6/3, 272 (1965).

[65] A. McKillop, J.D. Hunt, R.D. Naylor and E.C. Taylor, J. Amer. Chem. Soc., 93, 4918 (1971).

[66] J.H. Beynon and A.E. Williams, Mass and Abundance Tables for Use in Mass Spectroscopy, Elsevier Publishing Comp., (1963).

[67] W. Reusch, M.W. DiCarlo and L. Traynor, J. Org. Chem., 26, 1711 (1961).

[68] F.H. Lees, J. Chem. Soc., 83, 152 (1903).

[69] O. Wallach, Ann., 263, 136 (1891).

[70] O. Wallach, Ann., 272, 105 (1893).

[71] W. Hückel, Ber., 80, 39 (1947).

[72] G. Komppa and S.V. Hintikka, Ber., 47, 936 (1914).
R.H. Roschier, Ann. Acad. Sc. Fennicae, A10 (1), 56 (1917).

[73] A.F. Thomas and B. Willhalm, Tetrahedron Letters, (1965) (18) 1309.
J.M. Jerkunica, S. Borcic and D.E. Sunko, Tetrahedron Letters, (1965) (49) 4465.
A.F. Thomas, R.A. Schneider and J. Meinwald, J. Amer. Chem. Soc., 89, 68 (1967).

T.T. Thomas, J. Amer. Chem. Soc., 92, 1448 (1970).

74) See 54).

75) G. Snatzke and J. Himmelreich, Tetrahedron, 23, 4354 (1967).

76) H. Krieger, Suomen Kemistilehti, 35, 10 (1962).

77) K. Alder and A. Grell, Ber., 89, 2198 (1956).

78) S.M. Malmgren, Ber., 35, 3910 (1902); 36, 2608 (1903).

79) J. Bredt and W.H. Perkin, J. Chem. Soc., 103, 2210 (1913); for the purification compare: L. Claisen and O. Manasse, Ann., 274, 73 (1893).

80) P. Duden and W. Pritzkow, Ber., 32, 1539 (1899).

81) During the separation of this mixture the splitter of the prep. gaschromatograph got clogged, probably due to decomposition of the unknown compound.

% %

CHAPTER THREE

1-DEUTERO-α-FENCHOCAMPHORONEQUINONE

OPTICAL ACTIVITY DUE TO ISOTOPIC SUBSTITUTION. CIRCULAR DICHROISM OF (1R)-[1D]-α-FENCHOCAMPHORONEQUINONE.

Sir:

In recent years study of the molecular geometry of small cyclic molecules has yielded the information that such molecules are not necessarily rigid, but in some cases may be deformed easily, which results in low lying normal modes[1], or even may exist in conformations as has been shown in the case of four membered rings[2] and the bicyclo[2.2.2]octane skeleton[3]. In the bicyclo[2.2.1]heptane series occurrence of conformational equilibria has not yet been established although valence force calculations [4]) indicated that such equilibria may exist.

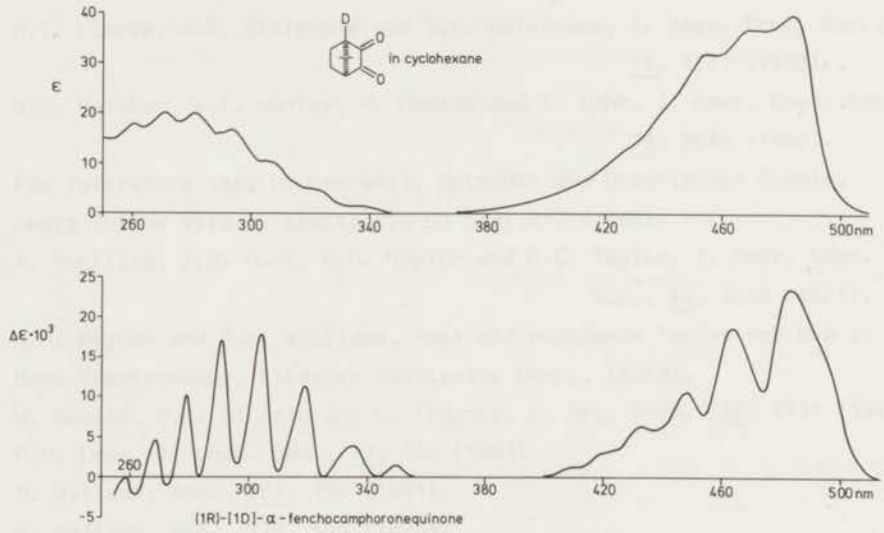


Figure 3-1

Because of our interest in the spectroscopy of α-diketones in the bicyclo[2.2.1]heptane series, which led us to study the optical activity due to ^{18}O-substitution in α-fenchocamphoronequinone[5] (I) (see chapter 2), we wondered if isotopical optical activity could be used as a tool for the detection of conformational equilibria: if I should exist in conformers, each with a twisted chromophore as in camphorquinone[6], then specific

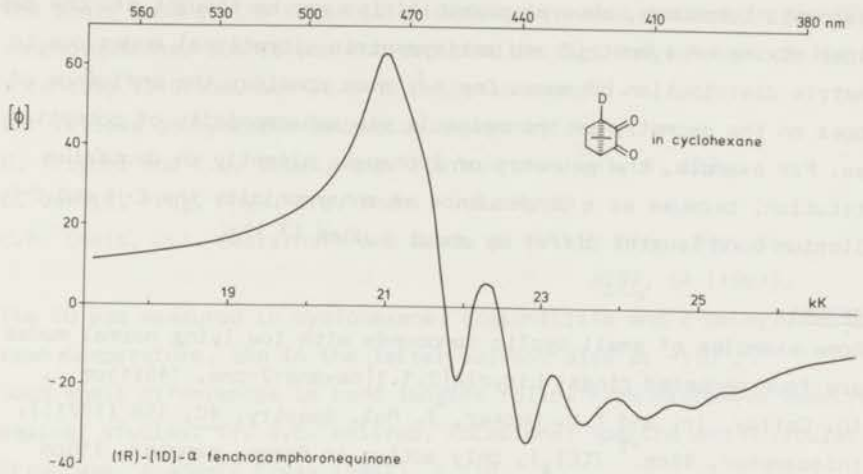


Figure 3-2 [7]

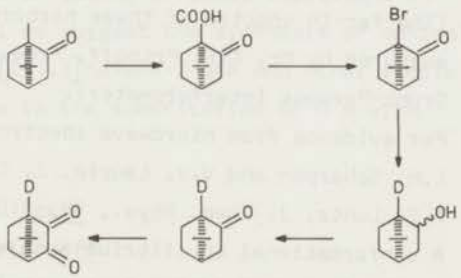


Figure 3-3 The synthesis of the title compound from (+)-(1R)-camphor.

replacement of a hydrogen atom by deuterium might shift the equilibrium between the conformers and detection of CD would be possible, provided the effect were large enough.

We synthesized (1R)-[1D]-α-fenchocamphoronequinone (II) and report that measurement of the CD of II was possible (fig. 3-1 [8 9]). It is the first example of a CD curve of a compound whose optical activity is due only to deuterium substitution[10]. Fig. 3-2 shows the calculated contribution[11] to the ORD of the CD band of II in the visible region. The route followed in the synthesis of II is shown in fig. 3-3.

However, as the observed CD of II is almost independent of solvent and temperature[12] we cannot ascribe the observed CD to a conformational equilibrium: either I does not exist in conformers or introduction of deuterium is insufficient to shift such an equilibrium.

For the explanation of the CD curve (fig. 3-1), which has a direct bearing on the theory of the electronic and geometrical structure of

α-dicarbonyl compounds, several possibilities may be thought of. One may consider mixing of symmetric and antisymmetric vibrational modes due to asymmetric distribution of mass. One may also consider the influence of isotopes on the geometry of the molecule via anharmonicity of potential curves. For example, the geometry of I changes slightly on deuterium substitution, because as a consequence of anharmonicity the C-H and C-D equilibrium bond lengths differ by about 0.004Å [13 14].

References.

[1] Some examples of small cyclic compounds with low lying normal modes are four membered rings; bicyclo|2.1.1|hexane-2-one, 140±15cm^{-1}, (D. Coffey, Jr. and T.E. Hooker, J. Mol. Spectry, 40, 158 (1971)); thiocamphor, 96cm^{-1} (CCl_4), only active in Raman; camphor, 116cm^{-1} (nujol); norcamphor, 128cm^{-1} (nujol); camphorquinone, 163cm^{-1} (nujol). (The far-IR spectra of these norbornane derivatives have been measured by Mr. G.F. Pothoff, Free University, Amsterdam, with a Grubb-Parsons interferometer).

[2] For evidence from microwave spectroscopy see:
L.H. Scharpen and V.W. Laurie, J. Chem. Phys., 49, 221, 3041 (1968).
A.C. Luntz, J. Chem. Phys., 50, 1109 (1969).
A conformational equilibrium should be the reason of a large solvent effect on the CD of 2,2,3-trimethylcyclobutanone, cf. J. Gore, C. Djerassi and J.-M. Conia, Bull. Soc. Chim. Fr., (1967) 950.

[3] O. Elmer and J.D. Dunitz, Helv. Chim. Acta, 52, 1861 (1969).
E. Hirota, J. Mol. Spectry, 38, 367 (1971)

[4] C. Altona and M. Sundralingan, J. Amer. Chem. Soc., 92, 1995 (1970).

[5] W.C.M.C. Kokke and L.J. Oosterhoff, J. Amer. Chem. Soc., 94, 7583 (1972).

[6] W. Hug and G. Wagnière, Helv. Chim. Acta, 54, 633 (1971).
E. Charney and L. Tsai, J. Amer. Chem. Soc., 93, 7123 (1971).
In both publications it is postulated that the skeleton of camphorquinone should be twisted, but there is disagreement as to the sense of twist. X-ray analysis proved the postulate of Charney & Tsai (loc. cit.) to be correct, at least in the solid state (L. Tsai, E. Charney, J.V. Silverton and W.M. Bright, to be published).

[7] The calculated amplitude of this curve is 97.5°.

[8] This CD has been corrected to optical and isotopical purity.

9) The small band in the CD of II at 345.0nm is also present in the CD of camphorquinone, but it was not depicted in fig. 2-2 because of its low intensity (346.5nm, $\Delta\varepsilon=+29.6\cdot10^{-3}$ (cyclohexane)).

10) For reviews on hydrogen-deuterium asymmetry see:
D. Arigoni and E.L. Eliel, Top. Stereochem., vol. 4, 122.
L. Verbit, Prog. Phys. Org. Chem., vol. 7, 51.

11) C.A. Emeis, L.J. Oosterhoff and Gonda de Vries, Proc. Roy. Soc., A297, 54 (1967).

12) The CD was measured in cyclohexane, acetonitrile and 2-methyl-THF at room temperature, and in the latter solvent also at -110^{o}.

13) Such small differences in bond lengths follow from microwave spectroscopical studies. Cf. J.E. Wollrab, Rotational Spectra and Molecular Structure, Academic Press (1967), p 110.

14) To obtain more information on the influence of small variations in bond lengths on optical activity, we suggest the synthesis of optically active [1D]-7,7-dimethyl-bicyclo[2.1.1]hexane-2-one and other simple ketones with optical activity due to the substitution of D α with respect to the carbonyl group.

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THE SYNTHESIS OF (1R)-[1D]-α-FENCHOCAMPHORONEQUINONE.

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Summary.

The title compound (6) was prepared from (1R)-[1D]-α-fenchocamphorone (5), which was obtained from (+)-camphor (1) via ketopinic acid (2). Introduction of deuterium was achieved by LAD reduction of 1-bromo-α--fenchocamphorone (3), a degradation product of ketopinic acid (2). (1R)-[1D]-α-Fenchocamphoronequinone, a diketone whose optical activity is due only to deuterium substitution, showed a small but measurable effect in CD of both low intensity absorption bands in the region 250-500nm.

Introduction.

In the recent literature several authors have published results[16] of calculations on the optical activity of the twisted α-dicarbonyl chromophore. Glyoxal was used as a model compound for these calculations. It was found that when in cis-glyoxal the formyl groups are slightly rotated with respect to each other around the C-C bond, the Cotton effects associated with the two low intensity absorption bands at longest wavelength should have an opposite sign. As it is known that the Cotton effects in camphorquinone at about 300 and 480nm have an opposite sign (see fig. 2-2), these authors[16] felt that the CD of camphorquinone corroborated their predictions and they assumed twist to be present in its α-dicarbonyl chromophore.

In view of the succesful synthesis of (1R)-2-^{18}O-α-fenchocamphoronequinone and of the measurement of its CD (see chapter 2) it seemed worth while to synthesize a similar compound with optical activity due to deuterium substitution in order to contribute to the knowledge of the electronic and geometrical structure of the α-dicarbonyl group in norcamphorquinones.

We were successful in synthesizing (1R)-[1D]-α-fenchocamphoronequinone (6) which showed a CD spectrum (fig. 3-1 [17])) differing in many respects from the CD spectrum of (1R)-2-^{18}O-α-fenchocamphoronequinone (fig. 2-1). This result suggests that in general optical activity due to isotopic substitution may provide new information about the structure of

chromophores.

Details of the synthesis.

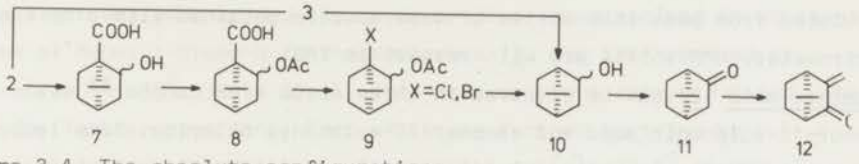

Figure 3-4 The absolute configurations of the compounds are depicted in the figures[21].

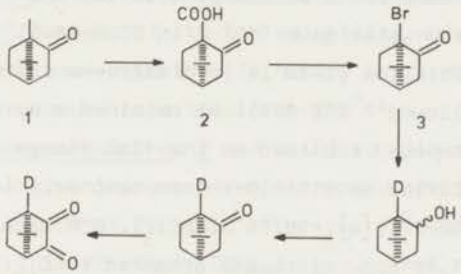

Figure 3-5

The route we followed to (1R)-[1D]-α-fenchocamphoronequinone (6) (fig. 3-5) is obvious once one knows that the bridge-head methyl group in camphor (1) can be converted into a methyl group in three steps.

To investigate the experimental conditions necessary for the replacement of the bridge-head halogen in 3 or 9 we chose α-bromo-camphor as a model compound. It was found that the halogen was resistent to LAH in boiling THF: the carbonyl group could be reduced selectively. However, when the reduction was carried out in N-methylmorpholine[22], a solvent permitting a higher reaction temperature, the halogen was reduced as well.

The bridge-head halogen compounds 3 and 9 were less reactive than α-bromo-camphor in LAH reduction in N-methylmorpholine, and a large excess of LAH and a reaction time of several days were necessary to achieve complete reduction.

After it was verified that α-fenchocamphorone (11) did not contain annoying impurities { it could be oxidized to give α-fenchocamphoronequinone (12) which was inactive in CD } the desired deuterium containing diketone (6) was synthesized following the same route.

Experimental.

Melting points are not corrected; angles of rotation were measured with a Perkin-Elmer polarimeter (model 131) at room temperature. Labels were calculated from peak intensities of mass spectra obtained with a MS-9 mass spectrometer. NMR shifts are with respect to TMS.

Ketopinic acid (2) can be prepared in three steps from camphor[23] via camphor-10-sulphonic acid and camphor-10-sulphonyl chloride. Some labor can be saved if one starts with (+)-(1S)-camphor-10-sulphonic acid which is commercially available.

Oxidation[24] of (1S)-camphor-10-sulphonyl chloride and recrystallisation of the crude product from water gave (1S)-2 in 20.9-24.5% yield, mp 226-8°, $[\alpha]_D$+25.8° (MeOH). This low yield is in disagreement with the yield claimed in the procedure followed[24] (38-43%). We obtained a by-product in this reaction: a white compound sublimed on the flat flange lid of the reaction vessel. It was identified as (1S)-10-chloro-camphor. Yield 2.7-2.9% after resublimation, mp 130-1°, $[\alpha]_D$+39.75° ($CHCl_3$). NMR data ($CDCl_3$): two methyl groups at δ=0.967, 1.111ppm; hydrogens attached to C_{10}: quartet at δ=3.69ppm, J_1=22.4Hz, J_2=12.2Hz. This chloro-camphor might have been formed during the preparation of the sulphonyl chloride because crude sulphonyl chloride was used for the preparation of 2.

Reduction of 2 [25] with Raney-nickel W-6 [26] gave (1S)-7,7-dimethyl-norbornane-2-ol-1-carboxylic acid (7) (mainly exo[25]) in 96% yield.

(1S)-7,7-Dimethyl-norbornane-2-ol-1-carboxylic acid-acetate (8) was prepared from 7 with acetyl chloride and pyridine, following a procedure[27] for the esterification of an isomer of 3.

Hunsdiecker degradation of 8. The silver salt of 4, which was soluble in ether and methanol, was treated with bromine in carbon tetrachloride according to "procedure C" of Wilder and Winston[28] who degradated bicyclo|2.2.2|octane-1-carboxylic acid. Yield 69.5%: a mixture of 1-chloro-9 (29%) and 1-bromo-9 (71%).

Degradation of 2 with bromine and mercuric oxide in dichloromethane has been reported[29]. We followed this procedure[29]. Because decarboxylation reactions as this one are radical reactions, usually the desired product is not the only product, e.g. it is known that when a Hunsdiecker reaction is carried out in carbon tetrachloride also chlorinated product is to be expected[30], as we observed after the degradation of 8. Analysis of the reaction mixture after the degradation of 2 showed that a by-product was

formed (20%) which was identified as α-fenchocamphorone (11). Formation of 11 was not reported in [29]. No chlorine containing product could be detected.

The solvent was removed and the crude product was dissolved in an equal volume of MeOH; 1-bromo-α-fenchocamphorone (3) was then removed by filtration at -15°. Yield 50-1%. This product, once recrystallised, was used for further reactions. Part of it was further purified by recrystallisation from heptane. Then it showed $[\alpha]_D$ +73.5° (MeOH), mp 190-1°. NMR data ($CDCl_3$): two methyl groups at δ=0.954, 1.087ppm.

The semicarbazone of 3, fine needles from alcohol, cannot be used for the characterisation of 3 because of its low solubility which does not permit measurement of the angle of rotation. It has no sharp mp: decomposition starts at 230°; the compound is a liquid at 245°.

1-Bromo-α-fenchocamphoronequinone. 3 was oxidized with selenium dioxide in acetic anhydride[31] to give 1-bromo-α-fenchocamphoronequinone, $[\alpha]_D$ -366° ($CHCl_3$), mp 201.5-2.0°, in 31.2% yield after recrystallisation (6x) from heptane. NMR data of this diketone ($CDCl_3$): two methyl peaks at δ=1.028, 1.187ppm.

LAH reductions of bromo-ketones and halo-esters. General: unless stated otherwise a solution of the compound to be reduced was added without stirring to a boiling mixture of LAH and solvent heated on an oil bath. The product was always isolated by steam distillation after water had been added to destroy the excess of unreacted LAH, and sufficient hydrochloric acid to acidify the mixture. When the condenser got clogged during the steam distillation it was cleaned with dichloromethane.

Reduction of α-bromo-camphor.

- A mixture of α-bromo-camphor (20g), LAH (5g =204% excess) and THF (100ml) was refluxed overnight. Analysis of the product showed that only the carbonyl group had been reduced: no borneol or isoborneol were formed. Thus a solvent was required permitting a higher reaction temperature.
- A mixture of α-bromo-camphor (20g), LAH (5g =204% excess) and N-methyl-morpholine (100ml) was refluxed overnight. Then reduction was complete.

Reduction of 9.

- When 9 (20g) was refluxed overnight with LAH (5g =118% excess) in N-methylmorpholine (100ml), it was found that only 15% of the product was α-fenchocamphorol (10), the remainder was 1-halo-α-fenchocamphorol. Clearly a longer reaction time and a larger excess of LAH were necessary.

- A mixture of 9 (20g), LAH (13.5g =488% excess) and N-methylmorpholine (120ml) was refluxed for one week. Then reduction was complete.
- A solution of 9 (33.5g) in diglym (50ml) was added to a mixture of diglym (120ml) and LAH (16g =318% excess), placed in a bath at 150°. The mixture was heated overnight at 150°. The product consisted of 10 (75%) and 1-halo-α-fenchocamphorol (25%).

Reduction of 3 and preparation of α-fenchocamphoronequinone (12).

- A mixture of 3 (35g), LAH (19g =529% excess) and N-methylmorpholine (200ml) was refluxed for 6 days. Then reduction was complete. It followed from G.L.C.-measurements (DEGA column) that we had obtained a mixture of exo-10 (87.1%) and endo-10 (12.9%).

a/ After the reduction part of the solution of the product in dichloromethane was evaporated and the residue sublimed. This exo-endo mixture (1.2g =5.3%) had $[\alpha]_D$-12.13° ($CHCl_3$).

b/ Another part of the product, meant for the preparation of 12, was purified by prep. G.L.C. (SE-30 column) under the same conditions as the deuterium containing alcohol 4 was purified (see below). The purified alcohol 10 was then oxidized with RuO_4 in CH_2Cl_2 to give α-fenchocamphorone (11) (2.8g =12.6% based on 3).

To show that 11 did not contain annoying impurities, crude 11 (2.0g) was oxidized[31] with selenium dioxide in acetic anhydride. To the product was added dichloromethane, it was filtered, washed free from acid and distilled. The distillate was purified by prep. G.L.C. (SE-30 column) in order to remove unreacted 11. Yield of 12 after sublimation 1.5g (=68%), mp 138.5-9.5°. Fortunately no CD of 12 could be detected, indicating the absence of annoying impurities. NMR data of 12 ($CDCl_3$): two methyl peaks at δ=1.094, 1.140ppm.

G.L.C.-measurement of crude 11 indicated the presence of two impurities. For measurements 11 was purified by prep. G.L.C. (Carbowax column). The most abundant impurity (2.0%) with a retention time shorter than 11 could completely be removed, whereas the other impurity (0.2%) with a retention time longer than 11 could partially be removed. Purified (1R)-11 had mp 100-5°, $[\alpha]_D$+66.5° (abs. EtOH); in NMR the two methyl peaks coincided at δ=1.043ppm. Lit.[19]: $[\alpha]_D$+73.94° (EtOH), mp 113.0-3.5°.

c/ The remainder of the solution of crude 10 in dichloromethane was cooled to -15°. The crystals (needles) were removed by filtration. Pure exo-11

(6.4g =28.3%) could be obtained by recrystallisation of these needles from pentane-dichloromethane 4:1 (4x); the crystals were removed by filtration at -15° after every recrystallisation.

Data of pure (1R)-exo-10: mp 140-1°, $[\alpha]_D$-15.45° ($CHCl_3$). NMR data ($CDCl_3$): two methyl peaks at δ=0.953, 1.224ppm; H attached to C_2: quartet, δ=3.842ppm, J_1=7.3Hz, J_2=4.0Hz. From the values of $[\alpha]_D$ of pure exo-10 and of the exo-endo mixture it follows that (1R)-endo-10 has $[\alpha]_D$+10.3° ($CHCl_3$)

evaporation of the mother-liquors of the recrystallisation of 10 gave impure 10 (6.95g =30.8%). Addition of this yield and of the yields of 10 and 11 claimed under a/, b/ and c/ indicates that the yield obtained in the reduction of 3 was 77.0%.

Characterisation of 11. Mattinen[19] purified 11 as the semicarbazone. We found that this semicarbazone could only be recrystallised with considerable loss of material from benzene or water-alcohol 1:1. We prepared[32] the 2,4-dinitrophenylhydrazone of 11, mp 141-2°, $[\alpha]_D$-79.9° ($CHCl_3$), in about 50% yield after recrystallisation (4x) from alcohol.

Experiments with deuterated compounds. Note: 3 necessary for the synthesis of both 6 and 12 was obtained in the same preparation.

- A mixture of 3 (20g), LAD (98% D; a fresh 10g package (Merck), 420% excess), and N-methylmorpholine (110ml) was refluxed for 6 days. Then reduction was incomplete[33]: 41.4% of the mixture was deuterated α-fenchocamphorol (4); 58.6% was 1-bromo-α-fenchocamphorol. The two alcohols were separated by prep. G.L.C. (SE-30 column). Yield of bromo-alcohol 8.7g (=73.6%; yield based on 3 and on the composition of the mixture of reduction products). NMR data of this bromo-alcohol ($CDCl_3$): two methyl peaks at δ=0.970, 1.129ppm; as a consequence of the high deuterium content of the LAD used, H attached to C_2 could not be detected by NMR.

- 4 was oxidized with RuO_4 in CH_2Cl_2 to give 5 (3.4g =64.6%; yield based on 3 and on the composition of the mixture of reduction products). Only 33.60% of 5 was labeled with one deuterium and 1.77% was doubly labeled with deuterium.

- 5 (2.0g) was oxidized as indicated above, and gave after purification by prep. G.L.C. 6 (1.4g =64%), mp 137.5-9.0°. 30.08% of 6 was labeled with one D and 0.53% was doubly labeled. This 6 was used for measurement of CD[34].

The observed CD was not caused by impurities because:

1/ Undeuterated diketone 12, prepared in the same manner as 6 from 3 was

inactive in CD.

2/ Recrystallisation of 6 (from heptane) did not affect the effect in CD.

3/ If the observed effect in CD were due only to an impurity having $\Delta\varepsilon=2$ (i.e. a much larger effect in CD than camphorquinone), this impurity should be present in the mixure for about 0.4%. Careful examination of 5 with capillary columns (SE-30, DEGA) indicated that in 5 only the same harmless impurities were present as in 11 and in about the same concentration.

Although it cannot be proved that in every molecule of 6 the deuterium is attached to C_1, contamination of 6 with deuterated isomers is very unlikely since there is no evidence for such isomerisations in the literature on LAD reductions.

Acknowledgement.

The authors are indebted to Prof. L.J. Oosterhoff for his interest in this work, and to Prof. H. Wynberg for reading the manuscript. The CD measurements were carried out with an instrument built by Mr. Dekkers in this department.

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In both publications it is assumed that the skeleton of camphorquinone is twisted, but there is disagreement as to the sense of twist. From X-ray analysis (L. Tsai, E. Charney, J.V. Silverton and W.M. Bright, to be published) it has been concluded that the sense of twist advocated by Charney and Tsai is correct, at least in the solid state.

17) The observed CD spectrum has been corrected to optical and isotopical purity[18].

18) For 11 we recorded $[\alpha]_D$ +66.5° (abs. EtOH); Mattinen[19] found $[\alpha]_D$ +73.94° (EtOH). Assuming his value[19] to be correct[20], our product has an optical purity of 89.9%. The correction factor applied to the observed spectrum was 10000/89.9·30.08, where 30.08 stands for the isotopical purity.

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derivatives sometimes occurs very easily. Cf. the oxidation of optically active norborneol (J.A. Berson, J.S. Walia, A. Remanic, S. Suzuki, P. Reynolds-Warnhoff and D. Willner, J. Amer. Chem. Soc., 83, 3986 (1961)), and the decomposition of epi-isoborneol-tosylate on column chromatography (W.Z. Antkowiak, Bull. Acad. Pol. Sci., Ser. Sci. Chim., 14, 431 (1966)).

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33) There seemed to be a large isotope effect in the reduction of 3: under conditions where LAH reduction of 3 was complete, LAD gave a mixture of the desired alcohol (4) (minor product) and 1-bromo-α-fenchocamphorol. But we have not investigated whether this result of LAD reduction is reproducible.

34) We have not investigated why the deuterium content of 5 and 6 was much lower than was expected.

% %

CHAPTER FOUR

A COMPARISON OF ELECTRONIC SPECTRA OF SOME NORCAMPHORQUINONES.

Hug & Wagnière and Charney & Tsai[1] have assumed that the norbornane skeleton in camphorquinone is twisted, i.e. according to them the bonds C_2-C_3 and C_5-C_6 in camphorquinone are not in the same plane.

We looked for experimental evidence corroborating this postulate by comparing the spectra of a number of substituted norcamphorquinones. The idea underlying our approach was, that if a small substituent such as the bridge head methyl group in camphorquinone was sufficient to cause twist in the norbornane skeleton or to shift a conformational equilibrium between twisted conformers, then a bulkier group attached to the skeleton in a well chosen position might increase the effect and accordingly enhance the rotatory strengths of the electronic transitions in the region 250-520nm. Although the introduction of t.-butyl groups was desirable, our experimental efforts were directed to more easily accessible compounds. All of the three prepared 7,7-dimethyl-norcamphorquinones showed an increase of rotatory strength of both bands as compared with camphorquinone (fig. 4-1,2 [2]). The absorption curves of these compounds in the visible region are displayed in fig. 4-3. For comparison the absorption curve of isofenchonequinone has been added (fig. 4-4).

Data of electronic spectra of some norcamphorquinones.

compound	solvent	UV-band	visible band		midpoint[3]
		$\Delta\varepsilon_{max}$	ε_{max}	$\Delta\varepsilon_{min}$	
6-endo-acetoxy-camphorquinone	$CHCl_3$	+1.93	46.1	-1.19	487.1nm
1-bromo-α-fenchocamphoronequinone	"	+1.14	53.9	-2.97	482.7nm
5-exo-acetoxy-camphorquinone	"	+0.55	52.2	-0.86	495.7nm
camphorquinone	"	+0.40	42.9	-0.47	489.6nm
"	i.oct.	+0.27	36.7	-0.43	491.8nm
isofenchonequinone	C_6H_{12}	+0.93	45.0	-0.40	502.3nm
α-fenchocamphoronequinone			39.8		491.7nm
"	CH_3CN		38.9		487.2nm

i.oct. = iso-octane C_6H_{12} = cyclohexane

If, following Hug & Wagnière and Charney & Tsai, we make the simplifying assumption that only the dihedral angle of the α-dicarbonyl chromophore determines the magnitude of the effect in CD and the position of the absorption bands, then we expect that increase of the dihedral angle of the chromophore should be accompanied by an increase of rotatory strength of both bands and by a decrease of the wavelength of the

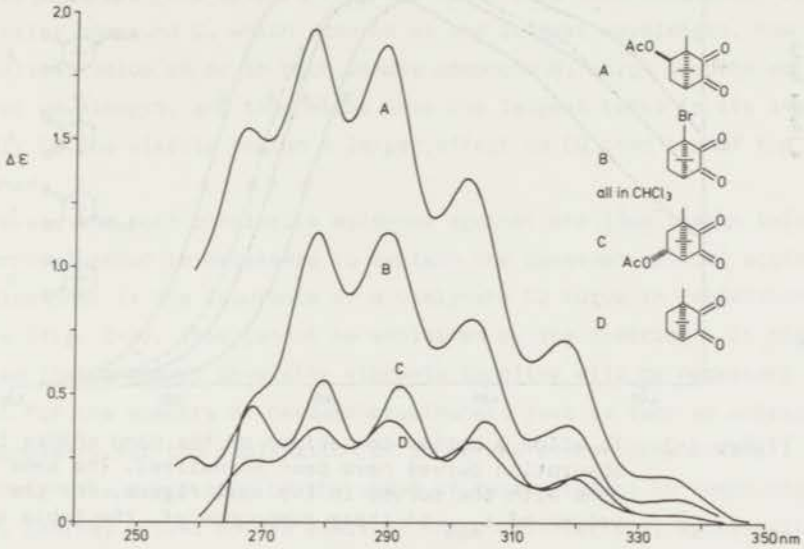


Figure 4-1

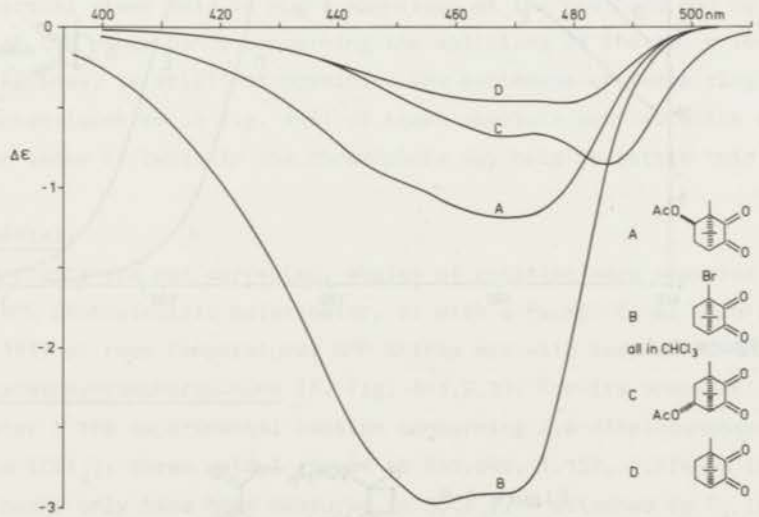


Figure 4-2

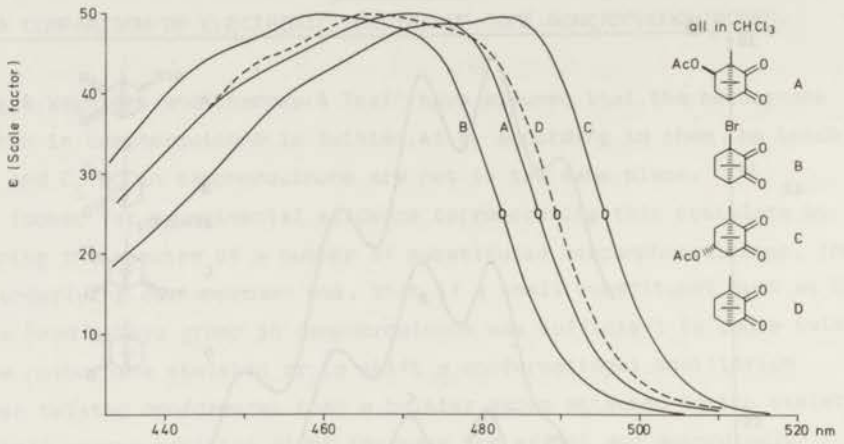


Figure 4-3 To allow a better comparison of the band shapes these absorption curves have been normalized. The same was done with the curves in the next figure. For the actual values of ε_{max} of these compounds cf. the table on p 50.

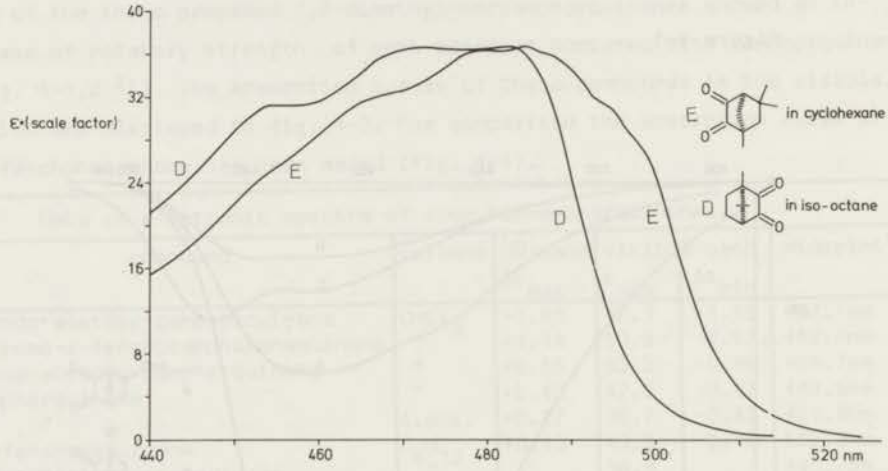
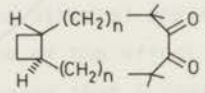


Figure 4-4

Figure 4-5



absorption maximum at least of the visible band[4].

It is seen from the spectra (fig. 4-1,2,3) that this assumption is too simplistic: compound C, which absorbs at the longest wavelength, has not the smallest value of $\Delta\varepsilon$ in both bands; compound B, which absorbs at the shortest wavelength, and thus might have the largest twist in its skeleton, has only in the visible region a larger effect in CD than any of the other diketones.

However, the most conclusive evidence against the idea that a twisted α-dicarbonyl group is necessary to explain the observed optical activity of α-diketones is the occurence of a bisignate CD curve in isofenchonequinone (fig. 2-3). This cannot be explained by the theories[1]. It might be expected that a theory involving vibronic coupling will be necessary to account for the spectra of norcamphorquinones, just as such an approach has been necessary for the explanation of CD curves of norbornanones[5 6].

Although the prediction of the sense of twist present in camphorquinone, made by Charney & Tsai on the basis of their calculations, agrees with results from X-ray analysis[1], we do not consider this agreement as a convincing proof for the justification of their model. In view of the discussion of our experimental results we are inclined to consider this agreement as rather fortuitous[7]. Therefore a choice between the controversial views held by Hug & Wagnière at the one hand and by Charney & Tsai at the other hand, concerning the splitting of the two n-levels in α-diketones, is still not possible. The synthesis of large ring α-diketones (such as in fig. 4-5) of known absolute configuration and thus of known sense of twist in the chromophore may help to settle this question.

Experimental.

Melting points are not corrected, angles of rotation were measured with a Bendix-NPL photoelectric polarimeter, or with a Perkin-Elmer polarimeter (model 141) at room temperature. NMR shifts are with respect to TMS.

6-Endo-acetoxy-camphorquinone (A, fig. 4-1,2,3). For its preparation see in chapter 5 the experimental section concerning 2,6-diketocamphane.

NMR data (CCl_4): three methyl groups at δ=0.946, 1.137, 1.174ppm (these methyl peaks only have been measured in $CDCl_3$); H attached to C_4 (bridge head): quartet, δ=1.516ppm, J_1=14.5Hz, J_2=3.0Hz; H attached to C_6: octuplet, δ=5.105ppm, J_1=9.6Hz, J_2=3.0Hz, J_3=1.1Hz.

1-Bromo-α-fenchocamphoronequinone (B, fig. 4-1,2,3) is described in

chapter 3.

The classical synthesis of isofenchonequinone (fig. 4-6)

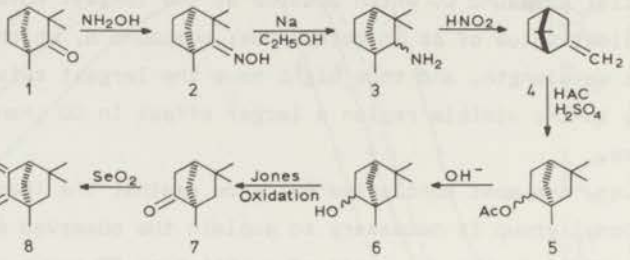


Figure 4-6

(-)-α-Fenchene (4) was prepared from (+)-fenchone (1). See chapter 2.

Isofenchylacetate (5) was prepared from 4 according to Wallach[8].

Isofenchol (6) was prepared from 5 by saponification[8]. Yield 79% based on 4

Isofenchone (7). Jones oxidation of 6, analogous to the preparation of norcamphor from norborneol[9], gave 7 in 60% yield. After purification as the semicarbazone, mp 222-3°, $[\alpha]_D$-12.6° (MeOH), (recrystallised from alcohol), (lit.[8]: mp 221-2°, $[\alpha]_D$-8.27° (MeOH)), the ketone had $[\alpha]_D$-28.5° (MeOH). No specific rotation of 7 in MeOH was to be found in the literature. Rassat[10] only gives ORD data in MeOH.

Isofenchonequinone (8). 7 (3.0g, purified as the semicarbazone) was oxidized with selenium dioxide in acetic anhydride[11]. To the reaction mixture was added dichloromethane, it was filtered and washed with $NaHCO_3$ solution till neutral. The red colour could not be removed by filtering through silica gel. Then the solvent was removed and the residue distilled. The distillate was purified by prep. G.L.C. (SE-30 column). Yield 0.8g, mp 68.5-71.0°, $[\alpha]_D$-4.0±0.5° (cyclohexane). Lit.[10]: mp 65°. There does not seem to be a reliable value for the specific rotation of 8 in the literature. Some Russian authors, referred to by [10]), give a specific rotation of 8 but they do not give the solvent used for this measurement. Rassat[10] gives ORD data (cyclohexane), but a value of $[\alpha]_D$ extrapolated from these ORD data is much higher than we have recorded; Rassat also gives an absorption curve (cyclohexane), but in the visible region his value of ε_{max} (=77) is much higher than we have found (ε_{max}=45.0). Only when we calculated the contribution of the CD band in the visible region to the ORD[12] (fig. 4-7) a reasonable agreement of the corresponding part of the ORD curve of Rassat was found

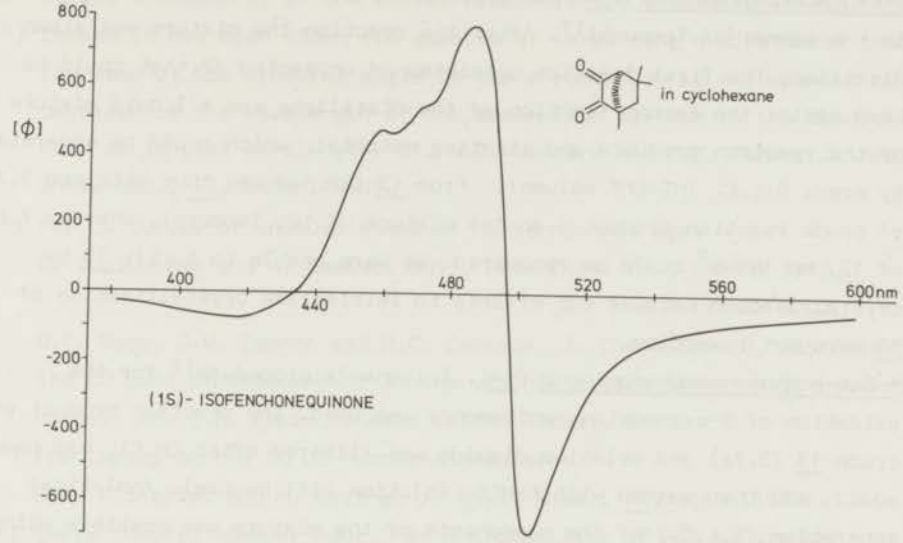


Figure 4-7 Calculated contribution of the CD band of isofenchonequinone to the ORD.

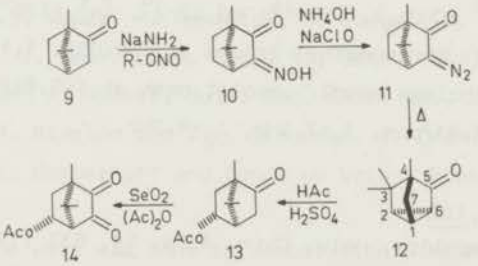


Figure 4-8

(shape, amplitude). Calculated amplitude 1351°; Rassat[10] gives 1385°.

The synthesis of 5-exo-acetoxy-camphorquinone (fig. 4-8)[13].

Isonitrosocamphor (10) was prepared from (+)-camphor (BDH) analogous to [14].

α-Diazocamphor (11) was prepared from 10 using the Forster reaction[15].

β-Pericyclocamphanone (12). Cf. [16]. A round-bottomed 100ml-flask, provided with a condenser and containing 11 (5g) and copper bronze (7.5g) is placed in an oil bath. The temperature of the bath is slowly raised to 120°. At a temperature of about 110° 11 decomposes. The product is isolated either by sublimation from the flask or by scratching from the condenser. Yield 78%. The product (12) contains about 1% of 11 as an impurity.

5-Exo-acetoxy-camphor (13) was prepared by addition of acetic acid to 12 in the manner of Takeuchi[17]. After the reaction the mixture was steam distilled. The first fraction consisted of unreacted 12 that could be used again; the second fraction of the distillate was a liquid mixture of the reaction products and starting material, which could be separated by prep. G.L.C. (HI-EFF column). From 12 (27.5g) was thus obtained 3.7g of crude reaction product (an 1:4 mixture of two isomers), whereas 7.0g of 12, mp 163-5° could be recovered. We were unable to purify 13 by crystallisation because our efforts to initiallize crystallisation of 13 were not rewarding.

5-Exo-acetoxy-camphorquinone (14). Toivonen's procedure[18] for the oxidation of 6-exo-acetoxy-epicamphor was used. The reaction product of crude 13 (3.7g) and selenium dioxide was filtered after CH_2Cl_2 had been added, and then washed with $NaHCO_3$ solution till neutral. Analytical separation (G.L.C.) of the components of the mixture was possible using a HI-EFF column. Two diketones were formed but the main product could be obtained pure by recrystallisation (4x) from heptane. Yield 1.5g, mp 91-2°, $[\alpha]_D$-142° ($CHCl_3$). Lit.[19]: mp 92-3°, $[\alpha]_D$-136° ($CHCl_3$). NMR data (CCl_4): three methyl groups at δ=0.906, 1.114, 1.259ppm; H attached to C_4 (bridge head): unsplit peak at δ=2.828ppm; H attached to C_5: quartet, δ=4.917ppm, J_1=7.1Hz, J_2=4.3Hz.

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E. Charney and L. Tsai, J. Amer. Chem. Soc., 93, 7123 (1971).
In both publications it is assumed that tha skeleton of camphorquinone is twisted, but there is disagreement as to the sense of twist. From X-ray analysis (L.Tsai, E. Charney, J.V. Silverton and W.M. Bright, to be published) it has been concluded that the sense of twist advocated by Charney & Tsai is correct, at least in the solid state.

2) The absolute configurations of the compounds are depicted in the figures.

3) The shape of the top of the absorption curves of α-diketones in the visible region is rather irregular. The intersection of the line $\varepsilon(\lambda)=\frac{1}{2}\varepsilon_{max}$ with the absorption curve in the visible region at longest wavelength is more characteristic than the absorption maximum for this absorption band. Therefore we give the wavelength of this point, to be

called a midpoint, in the table. Midpoints are indicated in fig. 4-3.

[4]) Indeed it has been shown (in spectra of large ring α-diketones) that increase of the dihedral angle in the chromophore is accompanied by a decrease of the wavelength of the absorption maximum in the absorption band at longest wavelength. Cf. N.J. Leonard and P.M. Mader, J. Amer. Chem. Soc., 72, 5388 (1950).

[5]) For CD curves of unusual shape of norbornanones see:
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CHAPTER FIVE

TWO SYNTHESES OF OPTICALLY PURE (1R:2R)-1,2-DIMETHYLCYCLOPENTANE.

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Summary.

Two syntheses of optically pure (1R:2R)-1,2-dimethylcyclopentane are described. In the first synthesis (+)-pulegone was converted into 2,3-dimethylcyclopentanone whose semicarbazone on Wolff-reduction afforded a mixture of the title compound and meso-1,2-dimethylcyclopentane. In the second synthesis the title compound was prepared from 3,4-dimethylcyclopentanone which was synthesized from resolved 4-cyclohexene-1,2-dicarboxylic acid. The specific rotations found for the hydrocarbon were respectively $[\alpha]_D$ -49.7° and -51.5° ($CHCl_3$), in disagreement with a literature value of -35°.

Introduction.

Recently optically active trans-1,2-dimethylcyclopentane has been discovered in a crude oil[1]. The specific rotation found was 5.8° but a theoretical estimate made many years ago in this department resulted in a much higher value[2]. Therefore it became of interest to synthesize this substance. When we had completed the synthesis from (+)-pulegone (fig.5-1)

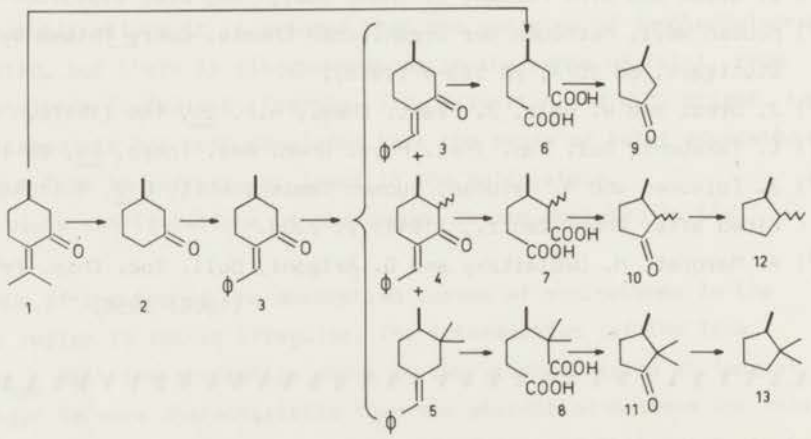


Fig. 5-1

(The absolute configurations of the compounds are depicted in the figures")

we became aware of a paper by Hill, et.al.[3] which we had overlooked before. In their work on the absolute configuration of the antibioticum sarcomycin they also prepared trans-1,2-dimethylcyclopentane from (+)-pulegone, but by a route different from our route (fig. 5-2). Taking absolute values,

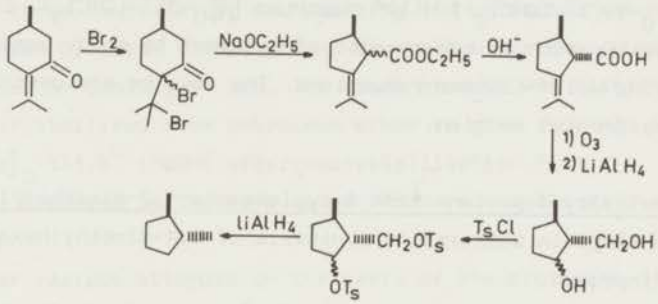


Fig. 5-2 Hill's synthesis of dimethylcyclopentane[3].

the angle of rotation we found was 42% higher than the highest value reported by Hill[3]. Therefore it became of importance to follow a second route to the same substance.

The route we chose was an obvious extension of a synthesis used by Walborski, et.al.[5] for the determination of the absolute configuration of resolved 4-cyclohexene-1,2-dicarboxylic acid (fig. 5-3). Both syntheses

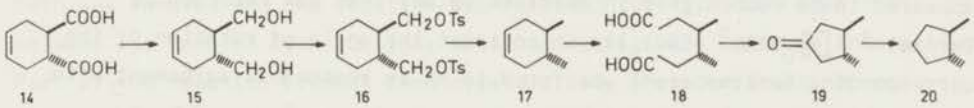


Fig. 5-3

led to compounds with nearly identical values of the angle of rotation. Therefore it can be stated that the specific rotation of optically pure (1R:2R)-1,2-dimethylcyclopentane is $[\alpha]_D$ -51.5° ($CHCl_3$).

Dimethylcyclopentane from pulegone (fig. 5-1).

Pulegone was hydrolysed to give 3-methylcyclohexanone. The 6-position in this ketone was blocked by condensation with benzaldehyde, yielding α-benzylidene-ketone[6]. Methylation of this compound gave a mixture of mono- and di-methylated product, together with unreacted α-benzylidene-ketone. Oxidation of this mixture and decarboxylation of the acids obtained yielded a mixture of 3-methylcyclopentanone, 2,3-dimethylcyclopentanone

2,2,3-trimethylcyclopentanone. The ketones were separated by distillation. The semicarbazone of 2,3-dimethylcyclopentanone gave on Wolff-reduction a mixture of optically active and meso dimethylcyclopentane (83.3 : 16.7%). Corrected to chemical purity trans-1,2-dimethylcyclopentane showed $[\alpha]_D$-49.7° ($CHCl_3$). Hill[3] reported $[\alpha]_D$-35° ($CHCl_3$). In the course of this investigation it became also of interest to study possible epimerisation during Wolff-Kishner-reductions. The results are described in the experimental section.

Dimethylcyclopentane from 4-cyclohexene-1,2-dicarboxylic acid (fig. 5-3). Two steps in Walborski's synthesis of 3,4-dimethylhexanedioic acid[5] could be improved.

We recommend N-methylmorpholine[7] as a solvent for the preparation of low-molecular-weight hydrocarbons by LAH-reduction of sulphonic esters the hydrocarbon is easily obtained pure and in high yield when the reaction mixture is worked-up by steam distillation[8].

The resolution of 4-cyclohexene-1,2-dicarboxylic acid was reinvestigated. It was found that the best results are obtained when quinidine is used.

The angle of rotation of 3,4-dimethylcyclopentanone ($[\alpha]_D$-241° ($CHCl_3$)) appeared to be much higher in absolute value, than was recorded by Carnmalm[9] ($[\alpha]_D$-160° ($CHCl_3$)); in contrast the angle of rotation of the corresponding semicarbazone was found to be in reasonable agreement with his results.

We also tried to resolve racemic 3,4-dimethylcyclopentanone with the Woodward reagent "menthydrazide"[10], but our efforts were not rewarding.

Experimental.

Melting and boiling points are not corrected. Angles of rotation were determined with a Bendix-NPL photo-electric polarimeter, or with a Perkin-Elmer polarimeter (model 141) at room temperature.

Pulegone (1) was isolated from pennyroyal oil (Dragoco, Holzminden, W. Germany) as the sodium bisulphite adduct[11], prepared at pH=7. After distillation over an efficient column it had $[\alpha]_D$+23.8° (MeOH).

(3R)-3-Methylcyclohexanone (2), $|\alpha|_D$+8.60° (MeOH), was prepared by hydrolysis of 1 in 65% yield[12].

(3R)-3-Methyl-6-benzylidene-cyclohexanone (3) was prepared by Wallach[13] by condensation of 2 with benzaldehyde in alcohol. To prevent the formation of dibenzylidene-ketone it is convenient to use water instead of alcohol[14]. A mixture of 2 (152g), benzaldehyde (152g) and 4% KOH-solution (1520g) was vigorously boiled for three hours. After neutralizing the unreacted ketone and aldehyde were removed by steam distillation. The yellow residue in the steam flask crystallised on cooling in ice. The crude product was distilled and the distillate recrystallised from petroleum ether to give 208g =72.5% of 3, mp 61.5-3.0°, $[\alpha]_D$-151.6° (MeOH) after recrystallisation from THF-hexane. Racemic 3, prepared in the same manner from rac. 2 (Fluka) had mp 38-41°.

Methylation of 3. After various attempts on the basis of the procedure of W.S. Johnson[15] for the methylation of 2-methyl-6-benzylidene-cyclohexanone it was found that the following procedure gave the highest yield of distillable reaction product.

In a 2l-flask, provided with an efficient stirrer[16], potassium (23.0g) was dissolved in tert.-butanol (1½l, dried on sieves) under nitrogen. This solution was placed in an ice-salt mixture, and when it was cooled to 22° a solution of 3 (100g) in methyl iodide (213g) was added at once. The temperature then rose to 31-4°. When the mixture was cooled to 25°, the bath was removed and the solution was refluxed for 1½ hours, then the solvent was removed with suction; water and ether were added to the residue. Part of the reaction product then crystallised. These crystals had mp 101.0-2.5°, $[\alpha]_D$-70.5° (MeOH), after recrystallisation from hexane and ether. It was found to be (mass spectroscopy) almost pure (3R)-2,2,3-trimethyl-6-benzylidene-cyclohexanone (5), the impurity being a few percent (3R)-2,3-dimethyl-6-benzylidene-cyclohexanone (4). The part of the reaction product which dissolved in ether was distilled. Yield (distillate + crystals) 68g. Mass spectroscopy showed 5 to be the main product; there was more starting material 3 in the mixture than mono-methylated product 4, which is not surprising because Conia[17] has shown an α-alkyl-ketone to be more reactive in alkylation than a ketone without an α-alkyl group.

Oxidation of the methylation products. The procedure of W.S. Johnson[18] for the oxidation of cis-2-benzylidene-9-methyldecalone was used. In our case the working-up was simple because the methyl-substituted adipic acids 6, 7,

and 8 are much better soluble in water than benzoic acid, and most of the latter could be removed by filtration. 3 (450g) gave after methylation and oxidation a mixture of 6, 7 and 8 (175.5g, a dark brown oil).

A mixture of cyclopentanones 9, 10 and 11 (74.65g) was prepared by heating the crude mixture of dicarboxylic acids 6, 7 and 8 (175.5g) with $Ba(OH)_2$[19]. The ketones were separated by distillation, using a Nester-Faust spinning band column, to yield 9, 7.8g, bp_{175} 106°; 10, 3.6g, bp_{175} 115-7°; 11, 20.4g, bp_{175} 124-5°.

(3R)-3-Methylcyclopentanone (9), bp 144-6°, $[\alpha]_D$+154.8° (MeOH), was prepared by ozonisation[20] of 1 to give (3R)-3-methylhexanedioic acid (6), decarboxylation with $Ba(OH)_2$[19], and purification as the semicarbazone, mp 171-3°, $[\alpha]_D$+40.5° ($CHCl_3$). Corroborating Tétry's result[6] we found for the methylcyclopentanone fraction of the distillation of the mixture of 9, 10 and 11 physical constants in agreement with the data of this reference, prepared by ozonisation of 1 etc..

(3R)-2,2,3-Trimethylcyclopentanone (11), bp 162-4°, $[\alpha]_D$+79.6° (MeOH), which has not been described before, was obtained by purification of the corresponding fraction of the distillation of the mixture of 9, 10 and 11 as the semicarbazone, $[\alpha]_D$+24.1° ($CHCl_3$). This semicarbazone (recrystallised from alcohol) turns yellow at 210°; on rapid heating mp 216-8° is found.

(2R)-1,1,2-Trimethylcyclopentane (13). Using the conditions of Kohlrausch[21] for the reduction of 3-methylcyclopentanone-semicarbazone, the semicarbazone of 11 gave 13 on Wolff-reduction. We always worked-up reaction products of Wolff-reductions by steam distillation, shaking the upper layer of the distillate with an equal volume of conc. H_2SO_4, washing with water, drying on and distillation from sodium. 13 was found to be contaminated with 2.32 mole% of (-)-12 and 0.48 mole% of meso-12. Corrected to chemical purity 13 had $[\alpha]_D$-8.07° ($CHCl_3$). Yield 66%.

(1R:2R)-1,2-Dimethylcyclopentane ((-)-12). The semicarbazone of 10, prepared from the corresponding fraction of the distillation of 9, 10 and 11, after recrystallisation from alcohol, had $[\alpha]_D$+94.1° ($CHCl_3$), mp 200-2°; the crystals turn yellow between 195 and 200°. Reduction[21] of this semicarbazone gave (-)-12, contaminated with 16.3 mole% of meso-12, 1.52 mole% of 13 and 0.40 mole% of methylcyclopentane in 59% yield. Corrected to chemical purity (-)-12 had $[\alpha]_D$-49.7° ($CHCl_3$).

Rac. trans-4-cyclohexene-1,2-dicarboxylic acid (rac. 14). The Diels-Alder

adduct from diethylfumarate (Merck) and butadiene was saponificated to give rac. 14, mp 166.0-8.5° after recrystallisation from water.

Resolution of trans-4-cyclohexene-1,2-dicarboxylic acid (14). Walborski's procedure[5] for the resolution of 14 is cumbersome, and that was for us an inducement to reinvestigate the resolution. Bases used were ephedrine, quinine[22], strychnine, brucine, cinchonidine, cinchonine and quinidine. The latter gave the best results.

- Preparation of the quinidine salt. In a 1l-flask is refluxed till homogeneous anhydrous quinidine (Brocades, The Hague, The Netherlands, or Dr. Lamers & Dr. Indemans N.V., Bois-le-Duc, The Netherlands) (81g), 14 (21.2g) (2 moles of alkaloid : 1 mole of 14) and alcohol (500ml). In the case the mixture is not homogeneous after 30 minutes, it is filtered. The alcohol is removed with a rotatory evaporator, and to the residue is added water (500ml) and alcohol (150ml); on heating a clear solution is obtained which is left to cool. Every time when it becomes turbid the turbidity is removed by the addition of some alcohol (about 60ml of alcohol is necessary). Seeding is recommended. After standing for two days at room temperature the crystals are filtered off and are recrystallised. We used water (6.5l) and alcohol (2.5l) for the recrystallisation of quinidine salt from 14 (292g) and quinidine (1120g), seeded, left to crystallise for two days, and obtained 486.25g of salt.

- Regeneration of the quinidine salt. Recrystallised quinidine salt (108g) was stirred with $CHCl_3$ (340ml) and a solution of NaOH (20g) in water (120ml) for 1.5 hour. Then the $CHCl_3$-layer containing the alkaloid was separated from the alkaline layer containing the sodium salt of (1R:2R)-14. The latter solution was acidified with conc. hydrochloric acid, and the dicarboxylic acid was isolated by ether extraction. From quinidine salt (486.25g from 292g of rac. 14) was thus obtained (1R:2R)-14 (98.0g =67.1% of one antipode), $[\alpha]_D$-161° (abs. EtOH). Lit.[5]: $[\alpha]_D$-161° (abs. EtOH).

- The mother-liquor of the resolution of 14 (292g) with anhydrous quinidine (1120g) was evaporated to dryness to give an oil, which was treated with NaOH solution and $CHCl_3$ etc. as indicated above to give optically impure (1S:2S)-14 (166.5g), $[\alpha]_D$+90° (abs. EtOH).

- Quinidine can be recovered in high yield by evaporating its $CHCl_3$-solutions to dryness and recrystallising the residue from MeOH (∿30g of alkaloid : 1l of MeOH).

(1R:2R)-4-Cyclohexene-1,2-dimethanol (15) was prepared by LAH reduction of

(1R:2R)-14 in THF in 94% yield.

(1R:2R)-4-Cyclohexene-1,2-dimethanol-ditosylate (16) was prepared from 15 with A.R. p.-toluenesulphonylchloride in A.R. pyridine. Yield 84% after recrystallisation from alcohol, mp 107-8°, $[\alpha]_D$-43.7° ($CHCl_3$).

(1R:2R)-1,2-Dimethyl-4-cyclohexene (17). A mixture of N-methylmorpholine (Merck or EGA) (1630ml) and LAH (77g) was heated to 60°. Caution: this starting temperature is necessary because 16 is not reduced at room temperature. Then 16 (395g) was added in a few gram portions at a time at such a rate that the temperature was kept <75°. Because the mixture became viscous an efficient stirrer[16] was necessary. After the addition the mixture was kept at 70° for 1.5 hour, then heated to 100°, left to cool, and worked-up by careful addition of water (500ml) and steam distillation. The upper layer of the distillate was washed with dilute HCl and dried on sodium. Yield 83.3g =84.5%, $[\alpha]_D$-143.8° ($CHCl_3$). Lit.[5]: $[\alpha]_D$-138° ($CHCl_3$).

(3R:4R)-3,4-Dimethylhexanedioic acid (18) was prepared from 17 using Cope's procedure[23] for the oxidation of bicyclo[6.1.0]nonene. The crude product, obtained in 57.3% yield, was an oil which soldified on standing.

(3R:4R)-3,4-Dimethylcyclopentanone (19). Crude 18 was decarboxylated[19] with $Ba(OH)_2$ to give crude 19 in 88.8% yield. After purification as the semicarbazone, mp 205-8° (yellow melt), $[\alpha]_D$-73.4° ($CHCl_3$) (lit.[9]: $[\alpha]_D$-76° ($CHCl_3$)) 19 had $[\alpha]_D$-241° ($CHCl_3$) (lit.[9]: $[\alpha]_D$-160° ($CHCl_3$)), g-factor 0.152 (cyclohexane). The CD of 19 is displayed in fig. 5-4 together with the absorption curve.

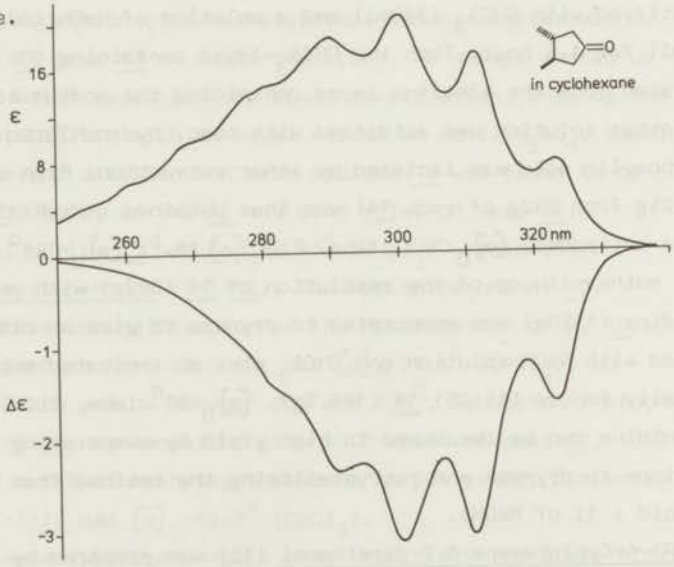


Fig. 5-4

(1R:2R)-1,2-Dimethylcyclopentane (20) was prepared by reduction[21] of the semicarbazone of 19 in 50% yield. $[\alpha]_D = [\alpha]_{589}$ -51.5°; $[\alpha]_{578}$ -53.6°; $[\alpha]_{546}$ -61.0°; $[\alpha]_{436}$ -102.7°; $[\alpha]_{365}$ -158.0° ($CHCl_3$).

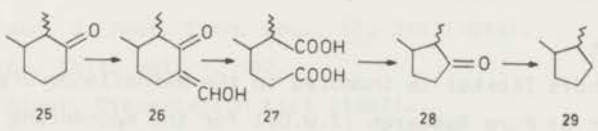
Attempted resolution of rac. 19. Rac. 19, prepared from rac. 14 in the same manner as (3R:4R)-19, was treated with "menthydrazide"[10] under conditions as used for the preparation of the α-ionone derivative[24]. The solution was evaporated to dryness and the residue recrystallised from heptane. Neither mp nor angle of rotation changed on further recrystallisation. Regeneration of the derivative, mp 124.5-6.0°, $[\alpha]_D$ -63.0° (MeOH), after the 3rd recrystallisation then gave the ketone, small neg. Cotton effect around 290nm, g-factor 0.0097 (cyclohexane), i.e. optical purity 6.4%. The semicarbazone of this ketone gave optically impure 20, $[\alpha]_D$ -3.77° ($CHCl_3$), on reduction[21].

Isomerisation during the Wolff-reduction. As already mentionned Wolff-reduction of the semicarbazone of 2,3-dimethylcyclopentanone yielded a mixture of (-)- and meso-dimethylcyclopentane. We found it worth while to investigate whether the observed cis-trans ratio was due to careless purification of the semicarbazone, or to epimerisation during the reduction, or both.

Epimerisation during Wolff-Kishner reductions has been frequently observed[25], but in those cases a hydrazone was decomposed without intermediate purification, so it was not been established whether epimerisation occured during the preparation of the hydrazone, or during its decomposition.

Epimerisation clearly is a limitation of the Wolff-reduction, for we found that menthone-semicarbazone (21), which is easily obtained free from its epimer isomenthone-semicarbazone (24)[26], gave a 1:1 mixture of cis- and trans-p.-menthane (fig. 5-5) on reduction[21]. After this experiment it was

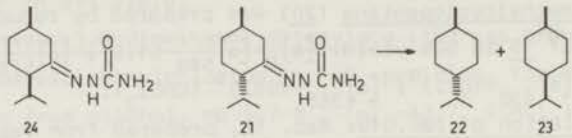
Fig. 5-5



not surprising that the semicarbazone of rac. 2,3-dimethylcyclopentanone gave on reduction[21] the same cis-trans ratio as was found when working with the corresponding optically active compound.

Rac. 2,3-dimethylcyclopentanone was prepared according to fig. 5-6 [27]).

Fig. 5-6



24 21 22 23

Menthone-semicarbazone (21). Menthone, prepared by oxidation[28] of (-)-menthol (Fluka) was converted into its semicarbazone, mp 186-9° after recrystallisation (2x) from alcohol. Reduction[21] then gave an 1:1 mixture of 22 and 23.

2,3-Dimethylcyclohexanone (25). Chromic acid oxidation[29] of 2,3-dimethylcyclohexanol (Aldrich) gave 25 in 94% yield.

2,3-Dimethyl-6-hydroxymethylene-cyclohexanone (26). A procedure for the preparation of hydroxymethylene-cyclohexanone[30] was used to give 26 in 70.7% yield.

2,3-Dimethylhexanedioic acid (27)[27]. Because 1 can be ozonised to give 6 in high yield[20], it was worth while trying to prepare 27 from 26 in the same manner. 26 (55.0g) dissolved in CCl_4 and cooled in ice was ozonised. To the solution of the ozonide water (300ml) was added, and while vigorously stirring the CCl_4 was distilled off. The aqueous solution, made alkaline, was extracted with ether, then made acid, and 27 was isolated by ether extraction. From 26 (159.9g) was obtained in this manner crude 27 (149g =82.4%): an orange-red oil.

2,3-Dimethylcyclopentanone (28). Crude 27 (149g) was decarboxylated[19] with $Ba(OH)_2$ to give pure 28 (62.0g =64.6%) after distillation.

1,2-Dimethylcyclopentane (29). 28 was converted into its semicarbazone. Part of the crude semicarbazone was kept, the remainder was recrystallised (3x) from n. butanol. The purified semicarbazone had mp 210.0-4.5° (d) on rapid heating. Reduction[21] of both crude and purified semicarbazone gave a mixture of cis-29 (16.5%) and trans-29 (83.5%).

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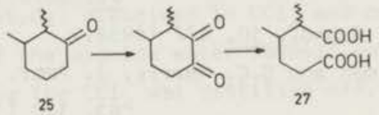
[27]) A plan for the preparation of 27 by selenium dioxide oxidation of 25 followed by H_2O_2-oxidation of the diketone obtained (fig. 5-7) was

Fig. 5-7



rejected because cyclohexanedione can be prepared from cyclohexanone only in low yield based on ketone: 10.4% (Org. Synth., 32, 35 (1952)), 19.6% (A.I. Vogel, Practical Organic Chemistry, 3rd ed., 975).

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CHAPTER SIX

TWO METHODS FOR THE DETERMINATION OF OPTICAL PURITY.

DETERMINATION OF OPTICAL PURITY USING CIRCULAR POLARIZATION OF LUMINESCENSE.

Sir:

The method of circular polarization of luminescense (CPL), which has been developed by Emeis and Oosterhoff[1,2], has many potential applications[1,3,4]. One of them, the determination of optical purity, has been proposed by Eaton[5]. The suggested procedure[5] requires the measurement of CPL of the mixture of enantiomers of which the optical purity has to be determined and of a racemic mixture. However, a racemic mixture may not always be at hand, e.g. if the mixture of enantiomers has resulted from the conversion of a natural product. Moreover, the effect in CPL of a racemate might be too small for measurement because it is a factor $\frac{1}{2}g$ smaller than the effect of an optically pure compound[3].

It will be shown that the use of a racemate can be avoided.

Let us consider a homogeneous mixture of enantiomers, L and R, containing n_L molecules of L and n_R molecules of R. A quantity p related to the optical purity ($=100|p|$ (%)) is then defined as

$$p=\frac{n_L-n_R}{n_L+n_R}\,; \qquad -1\leq p\leq +1\ . \tag{1}$$

Irradiation of this mixture with left circularly polarized (l) light gives rise to excited state populations of L and R, n_L^* and n_R^*,

$$n_L^*=a_1 n_L\ ;\ n_R^*=a_2 n_R\ , \tag{2}$$

whereas irradiation with right circularly polarized (r) light of the same wavelenght and intensity results in

$$n_L^*=a_2 n_L\ ;\ n_R^*=a_1 n_R\ . \tag{3}$$

The coefficient a_1 is proportional to the intensity of the exciting light, and to the molar extinction coefficient ε_1 pertaining to molecules of L aborbing l-light or to molecules of R absorbing r-light[6].

It is convenient to introduce a quantity X as

$$X=\frac{a_1-a_2}{a_1+a_2}=\frac{\varepsilon_1-\varepsilon_2}{\varepsilon_1+\varepsilon_2} \tag{4}$$

The intensities of l-light and r-light, I_l and I_r, in the luminescense excited by l-light depend on the excited state populations according to

$$I_l = s(en_L^* + (1-e)n_R^*) \; ; \qquad (5)$$
$$I_r = s((1-e)n_L^* + en_R^*).$$

We define e as the fraction of the intensity of the light emitted by L which is l-light at the wavelenght of observation; s is a proportionality constant.

It is useful to introduce

$$X_l = \frac{I_l - I_r}{I_l + I_r} = Y \frac{a_1 n_L - a_2 n_R}{a_1 n_L + a_2 n_R} = Y \frac{p+X}{1+pX}, \qquad (6)$$

where Y is defined as

$$Y = 2e-1 = \tfrac{1}{2} g_{lum} , \qquad (7)$$

and the index l of X indicates that the mixture has been irradiated with l-light. Similarly one finds

$$X_r = Y \frac{p-X}{1-pX} . \qquad (8)$$

Numerical values for X_l and X_r follow from CPL measurements.

The third equation to determine the optical purity (=100|p|) is obtained by measuring the CD and absorption of the mixture. We define Φ as the half of the ratio of the effects in CD and in absorption.

$$\Phi = \frac{\varepsilon_l - \varepsilon_r}{\varepsilon_l + \varepsilon_r} = pX , \qquad (9)$$

where ε_l is the extinction coefficient of the mixture of L and R for l-light. To derive that $\Phi = pX$ use has been made of formula (10) and the analogue expression for ε_r.

$$\varepsilon_l = \frac{n_L}{n_L + n_R} \varepsilon_1 + \frac{n_R}{n_L + n_R} \varepsilon_2 \qquad (10)$$

Then p can be calculated using the formula

$$p^2 = \Phi \frac{X_l + X_r + \Phi(X_l - X_r)}{X_l - X_r + \Phi(X_l + X_r)} \qquad (11)$$

which follows from (6), (8) and (9).

When p is determined then the numerical values of $g = 2\Phi/|p|$ and $g_{lum} = 2Y$ which characterize the optical activity of a molecule in its ground state and in its excited state can be found by straightforward calculations[7].

ACKNOWLEDGEMENT: The author is indebted to Prof. L.J. Oosterhoff for his help in improving the presentation of this paper. This work has been sponsored by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

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[4]) A. Gafni and I.Z. Steinberg, Photochem. Photobiol., 15, 93 (1972).

[5]) S.S. Eaton, Chem. Phys. Letters, 8, 251 (1971).

[6]) Note: (2) and (3) only hold if Lambert-Beer's law is valid.

[7]) For the evaluation of Y from (6) or (8) and (9) the sign of p, calculated from (11), is chosen in such a way that Y gets the same sign as $(\chi_l+\chi_r)$.

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PHOTOCHEMICAL DETERMINATION OF OPTICAL PURITY.

Sir:

When an aqueous solution of optically active potassium trisoxalato chromate-(III) is irradiated, interconversion of the two antipodes, which with unpolarized light leads to racemisation, takes place. Stevenson[8], using circularly polarized light, showed that partial photoresolution of this compound and of several other complexes could be realized. He derived that the ultimate attainable optical purity in such a reaction could be $|\frac{1}{2}g(\lambda)|\cdot 100\%$ if the assumption that there are no absorbing intermediates holds. Although this maximum attainable optical purity is rather low, in the case of potassium trisoxalato chromate-(III) it was enough to permit CD measurement from which the effect in CD of the optically pure complex could be calculated.

We suggest an extention of Stevenson's idea to the photochemical determination of optical purity of organic compounds. The method consists in calculating the optical purity of a suitable organic compound from the time dependence of its effect in CD on irradiation with right circularly polarized (r) light and with left circularly polarized (l) light. The method is applicable only to compounds which on irradiation give rise to photoproducts that do not absorb the exciting light[2].

Let us consider a homogeneous mixture of enantiomers, L and R, containing n_L molecules of L and n_R molecules of R. A quantity p related to the optical purity ($=100|p|$ (%)) is then defined as

$$p=\frac{n_L-n_R}{n_L+n_R}; \quad -1\leqslant p\leqslant +1 \quad . \tag{1}$$

Irradiation of this mixture with l-light gives rise to excited state populations of L and R, n_L^* and n_R^*,

$$n_L^*=a_1 n_L \quad ; \quad n_R^*=a_2 n_R \quad , \tag{2}$$

whereas irradiation with r-light of the same wavelength and intensity results in

$$n_L^*=a_2 n_L \quad ; \quad n_R^*=a_1 n_R \quad . \tag{3}$$

The coefficient a_1 is proportional to the intensity of the excitng light, and to the molar extinction coefficient ε_1 pertaining to molecules of L absorbing l-light or to molecules of R absorbing r-light[10].

In the following it is assumed that the compound decomposes unimolecularly on irradiation with unpolarized light.

We define R to be the antipode having a positive effect in CD at the wavelength of irradiation. Then because $a_2 > a_1$ L will decompose faster than R when the mixture is irradiated with r-light:

$$n_L(t)=n_L(0)\exp(-\alpha a_2 t) \quad ; \quad n_R(t)=n_R(0)\exp(-\alpha a_1 t) \tag{4}$$

where

$$\alpha a_1=\beta(\varepsilon-\tfrac{1}{2}|\Delta\varepsilon|) \quad \text{and} \quad a_2=\beta(\varepsilon+\tfrac{1}{2}|\Delta\varepsilon|) \tag{5}$$

are rate constants which depend on the intensity of the exciting light and on the quantum yield of the photo reaction.

It is useful to introduce a quantity X(t) as the ratio of the effects in CD during and at the beginning of the irradiation experiment.

$$X(t)=\frac{n_L(t)-n_R(t)}{n_L(0)-n_R(0)} \tag{6}$$

Substitution of (4) in (6), using (5) gives

$$X_r(t)=\exp(-\beta\varepsilon t)\,\frac{n_L(0)\exp(-\tfrac{1}{2}\beta t|\Delta\varepsilon|)-n_R(0)\exp(\tfrac{1}{2}\beta t|\Delta\varepsilon|)}{n_L(0)-n_R(0)}, \tag{7}$$

where the index r of X indicates that the expression refers to irradiation with r-light.

This expression can be simplified when $\exp(-\tfrac{1}{2}\beta t|\Delta\varepsilon|)$ and $\exp(\tfrac{1}{2}\beta t|\Delta\varepsilon|)$ are expanded in a Taylor series:

$$X_r(t)+\exp(-\beta\varepsilon t)\left[1+\tfrac{1}{2}\beta t\Phi/p^2+\tfrac{1}{2}(\tfrac{1}{2}\beta t\Phi/p)^2+\cdots\cdots\right] \tag{8}$$

where $\Phi=|p|\Delta\varepsilon$ is the effect in CD of the mixture of enantiomers at t=0 at the wavelength of irradiation.

Numerical evaluation of the terms in between brackets in (8) shows that $\frac{1}{2}(\frac{1}{2}\beta t\Phi/p)^2$ is small compared with the other two terms and in most cases can be neglected.

The expression, similar to (8), for irradiation with l-light is

$$X_l(t)=\exp(-\beta\varepsilon t)\left[1-\tfrac{1}{2}\beta t\Phi/p^2\right] . \tag{9}$$

Numerical values of β follow from the sum of (8) and (9):

$$\ln(\tfrac{1}{2}X_l(t)+\tfrac{1}{2}X_r(t))=-\beta\varepsilon t \quad {}^{11\ 12}). \tag{10}$$

Then p follows from

$$\frac{X_l(t)-X_r(t)}{X_l(t)+X_r(t)}=\frac{-\beta t\Phi}{2p^2} . \tag{11}$$

ACKNOWLEDGEMENT: The author is indebted to Prof. L.J. Oosterhoff for his interest in this work.

References.

[8]) K.L. Stevenson, Thesis University of Chicago (1968), Univ. Microfilms, Ann Arbor (Mich.), order number 69-1245.

K.L. Stevenson and L. Verdieck, J. Amer. Chem. Soc., 90, 2974 (1968).

[9]) The method might be applied to α-diketones, cf. B.M. Monroe, Adv. Photochem., vol. 8, 77 (1971).

[10]) The derivation holds only if the Labert-Beer law is valid.

[11]) In principle the decay, due to excitation with l- and r-light, of the optically impure compound can be followed in absorption as well, but these decay curves $\tilde{X}(t)=(n_L(t)+n_R(t))/(n_L(0)+n_R(0))$ are less sensitive to the value of p than the decay curves obtained from CD measurements. F.e. one derives:

$\tilde{X}_r(t)=\exp(-\beta\varepsilon t)\left[1+\beta t\Phi+\frac{1}{2}(\frac{1}{2}\beta t\Phi/p)^2+\cdots\cdots\right]$,

so that p only occurs in the third term which in most cases is neglegible.

[12]) In principle both β and Φ can be derived from only one decay curve but the proposed method is much more accurate.

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APPENDIX

INCOMPLETED WORK ON ^{16}O-^{18}O-DIKETONES AND SUGGESTIONS FOR FURTHER WORK

General.

The stages in the synthesis of an ^{16}O-^{18}O-diketone are:

1/ The preparation of a compound of known absolute configuration and optical purity, suited to introduce the ^{18}O-label.

2/ Introduction of the label. This ^{18}O-label must be high because the effect in optical activity due to ^{18}O-substitution will always be very small compared with the effect in optical activity of e.g. a C_2-ketone.

3/ The conversion of the labeled compound into the desired diketone.

Much work in stage 1 can be saved if a natural product can be chosen as a starting material, because then work for the resolution and determination of optical purity can be avoided.

It is economically attractive trying to combine stage 2 and 3, thus making the introduction of ^{18}O the last step in the synthesis.

The possibilities for the introduction of isotopes of oxygen are exchange, hydrolysis and oxidation[1].

- Labeling of a carbonyl compound is generally carried out by heating a mixture of the compound with water, enriched in ^{18}O, if necessary with some solvent, and a catalyst[2], although even without a catalyst exchange can be effected[3]. Another possibility for labeling by exchange is irradiation of a mixture of $^{18}O_2$ and ketone at about 300nm[4]. But then partial photolysis cannot be avoided.

OXYGEN-18 ENRICHED WATER*
unnormalized ($D_2{}^{18}O$)

isotopic enrichment (atom %)	standard packages size (max.)	price
1.5	200g	$ 70
3	50g	$ 135
10	15g	$ 300
20	5g	$ 225
40	3g	$ 320
60	2g	$ 400
80	1g	$ 320
90	1g	$ 360
97	1g	$ 400

*) Miles Laboratories Inc.

Labeling by exchange is the most expensive manner (based on costs of ^{18}O) for the introduction of an ^{18}O-label, because for the introduction of a label of e.g. 60% ^{18}O, an excess of expensive, more highly labeled water is necessary (cf. table). In principle it is possible to recover labeled water after such an exchange reaction, but its label will be too low to permit its usage for the synthesis of another ^{16}O-^{18}O-diketone. Thus for economical reasons the possibility of labeling by exchange can only be

considered if other attempts for the introduction of a label have failed.
- For the labeling of a ketone by hydrolysis of a functional derivative, every functional derivative which does not contain oxygen and can be hydrolysed easily is suitable, such as hydrazone, enamine, N-isopropyl-imine and thioketone. In addition functional derivatives such as acetale or enol-ether can be used, because under normal conditions of hydrolysis of these compounds, the alcohol formed cannot exchange oxygen with labeled water.
Sometimes it will be convenient to select a crystalline derivative of the ketone for labeling because then purification of the ketone and labeling can be done in one step.
- The only practical method for the preparation of an highly labeled ^{18}O-ketone by oxidation, is the photo-oxidation of a thioketone with $^{18}O_2$.

A discussion of the particular projects.

It is considered useful to describe in this appendix incompleted work and to add suggestions for futher syntheses, because together with the work in chapter 2 this might give a clear picture of experimental difficulties to be encountered in this kind of isotopic synthesis.

Fig. 7-1 gives the structural formulae of the diketones discussed in this appendix. These compounds belong (at least time-averaged) to the point groups C_s, C_{2h} or C_i before introduction of the isotope and are chosen

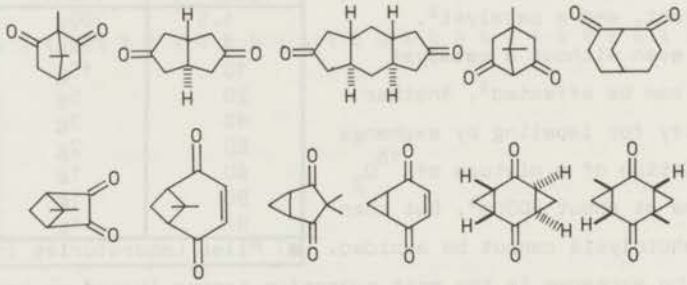


Figure 7-1

subject to the condition that they should be as small as possible and preferentially rigid, otherwise it will be far too difficult, if not impossible to analyse the CD spectra of their optically active ^{16}O-^{18}O-analogues. Open chain diketones are not interesting because of the many conformations in which they may exist.

We have devoted our experimental attention to the first three compounds (fig. 7-1) only. Referring to the other projects suggestions are given

which might be useful if a synthesis of such an ^{16}O-^{18}O-diketone for the study of its optical activity is started.

2,6-Diketo-camphane (7)

It is probably possible to prepare specifically labeled ^{18}O-2,6-diketo-camphane (7) following the classical synthesis of this compound[5] (fig.7-2).

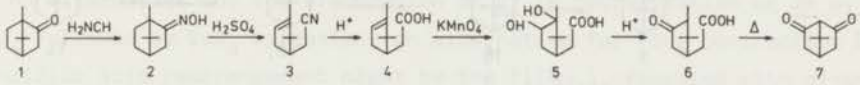
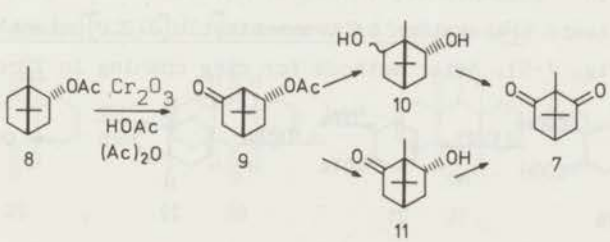


Figure 7-2

One might introduce the label in α-campholonic acid (6) by exchange with water, enriched in ^{18}O. Selective labeling of the carbonyl group in 6 is possible because a carbonyl group exchanges oxygen faster than the carboxyl group of a weak acid (cf. the labeling of butyric acid[6]).

As already explained labeling by exchange is expensive, and to save money a synthetical route to ^{18}O-7, not involving labeling by exchange, had to be developed (fig. 7-3). It was known that in the oxidation of

Figure 7-3



bornylacetate (8) with chromic anhydride in acetic acid/ acetic anhydride, except for 6-acetoxy-epicamphor, 6-acetoxy-camphor (9) was also formed[7], although 9 had never been isolated. We succeeded in separating 9 and 6-acetoxy-epicamphor by distillation, but preparation of 9 or 11 with the carbonyl group labeled with ^{18}O (by hydrolysis of a funtional derivative or photo-oxidation of a thioketone) was not possible, because suitable derivatives of 9 could not be obtained.
Thus the ways left were either to label 6, 9 or 11 by exchange[8], or to find another route to 7.

The new route proposed is a variation of the classical synthesis of 7 (fig. 7-4). None of the steps in this synthesis will present, in principle, any insurmountable difficulty, except for the preparation of 6-methylene-camphor (16) by thermal ring closure of the acetylenic ketone 15. Conia[9]

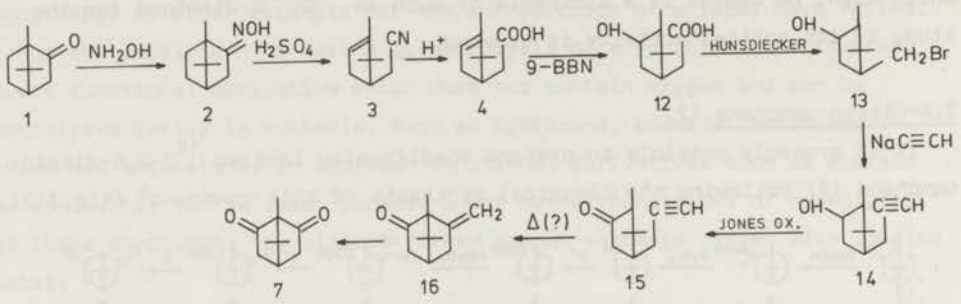


Figure 7-4

has described the preparation of 8-methylene-bicyclo[3.3.1]nonane-2-one by such a ring closure, but it is not known whether this ring closure reaction is applicable to the preparation of smaller ring systems such as 16.

Trans-bicyclo[3.3.0]octane-3,7-dione (23)

Because 5-hydrindene-2-one (22) ("hydrindenone") had been prepared in the Department of Theoretical Organic Chemistry in Leiden[10] before interest had risen in ^{18}O-compounds, it was an obvious extension of this earlier work to attempt preparation of trans-bicyclo[3.3.0]octane-3,7-dione (23) from 22 (fig. 7-5). After methods for ring opening in 22 or in

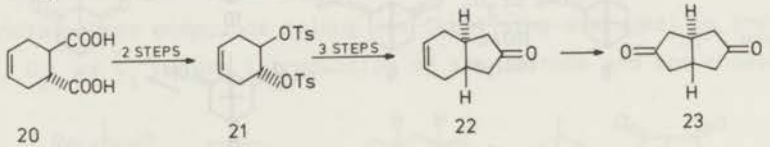


Figure 7-5

hydrindenylacetate (24, fig. 7-7) had failed or were found unsatisfactory, synthesis of 23 from 22 was attempted via ring contraction.

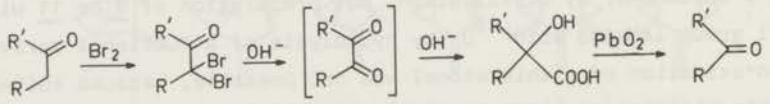


Figure 7-6

We based our approach (fig. 7-7) on an idea of Wallach[11] for ring contraction of cycloalkanones (fig. 7-6) after we had verified that lead dioxide oxidation of α-hydroxy-cyclopentane-carboxylic acid gives a high yield of cyclopentanone, and because a high yield is reported in the benzillic acid rearrangement of cyclohexanedione[12]. The dione 27 was

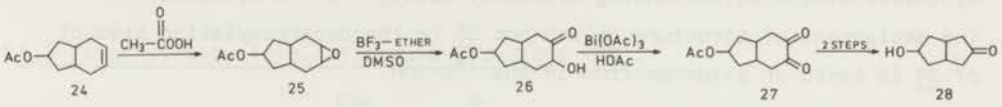


Figure 7-7

prepared as indicated in fig. 7-7, but the synthesis was not completed.

An alternative for the preparation of 27 is hydroxylation of 24 by OsO_4 followed by RuO_4-oxidation; an alternative for ring contraction by benzillic acid rearrangement might be the $Tl(NO_3)_3$-reaction with alkenes[13]: from hydrindenol then bicyclo[3.3.0]octane-3-ol-7-carboxaldehyde should be formed, which, after conversion into the corresponding carboxylic acid, might be converted into 23 using standard degradation procedures.

The resolution of 4-cyclohexene-1,2-dicarboxylic acid is described in chapter 5, thus the preparation of optically active 22 presents no difficulties. We have also attempted the resolution of 22 with the Woodward reagent[14] "menthydrazide", and with 4-(endo-2-fenchyl)-semicarbazide, but our efforts were not rewarding.

(1s:3r:7r:9s)-Tricyclo[7.3.0.$0^{3,7}$]dodecane-5,11-dione (35).

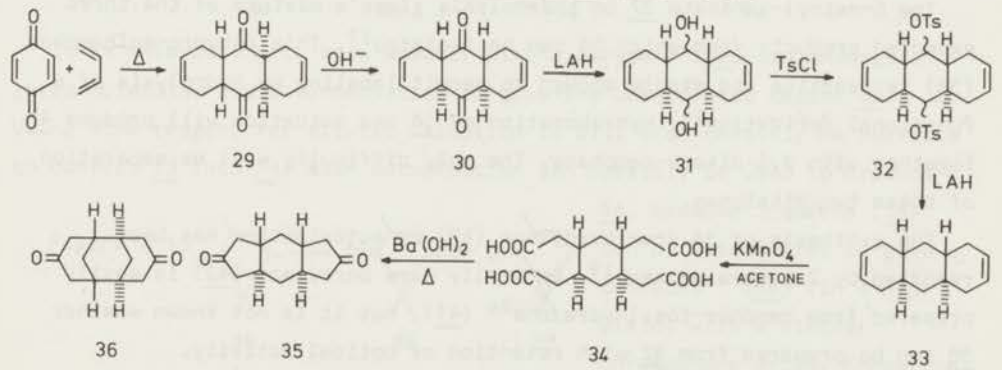


Figure 7-8

The synthesis of 35 (fig. 7-8) was started after we had found in the literature that sterically pure 33 had already been described[15]. The easy synthesis of 33 is based on the happy circumstance that the diketone 30 has a mp about 90° higher than any of its epimers[16], resulting in an easy purification of 30. The oxidation of 33 and the subsequent decarboxylation proceed in low yield, making it difficult to prepare larger quantities of 35, which are necessary if the synthesis of 35 is to be extended to the

synthesis of the corresponding optically active ^{16}O-^{18}O-diketone. The assignment of structure 35 and not 36 to the decarboxylation product of 34 is based on evidence from IR and ^{13}C-NMR.

3,5-Diketocamphane (40).

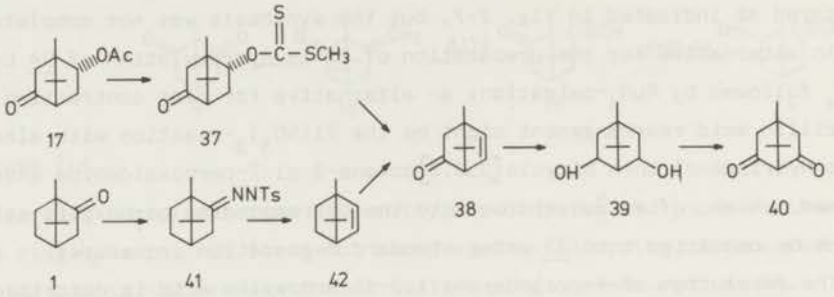


Figure 7-9

The synthesis of 3,5-diketo-camphane (40, fig. 7-9) is a side path of the synthesis of 2,6-diketo-camphane (7, fig. 7-3) because a by-product of the latter synthesis, 6-acetoxy-epicamphor (17), can be used for the preparation of 40.

The S-methyl-xanthate 37 on thermolysis gives a mixture of the three expected products from which 38 can be isolated[17]. This dehydro-epicamphor (38) is reactive and stable enough to permit labeling by hydrolysis of a functional derivative[18]. Hydroboration of 38 and oxidation will produce 40 together with 2,5-diketo-camphane. The only difficulty will be separation of these two diketones.

The synthesis of 38 from bornylene (42) by autoxidation has been reported by Japanese workers[19]. Optically pure bornylene (42) is easily prepared from camphor-tosylhydrazone[20] (41), but it is not known whether 38 can be prepared from 42 with retention of optical activity.

Bicyclo[3.3.1]nonane-2,8-dione (45).

As already mentionned in connection with a planned synthesis of 2,6-diketo-camphane (7, fig. 7-4) the acetylenic ketone 43 (fig. 7-10) ondergoes ring closure on heating[9] to give 8-methylene-bicyclo[3.3.1]-nonane-2-one (44). If 44 can be resolved and labeled, then preparation

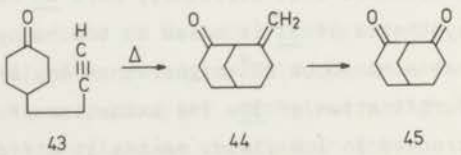
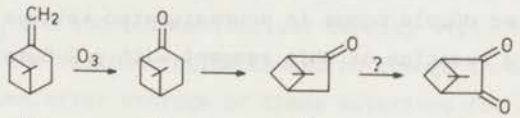


Figure 7-10

of optically active ^{16}O-^{18}O-45 will probably present no difficulties.

5,5-Dimethyl-bicyclo[2.1.1]hexane-2,3-dione (49).

Figure 7-11

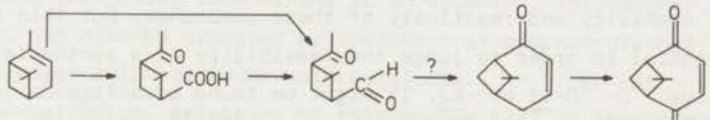


46 47 48 49

Meinwald[21] prepared 5,5-dimethyl-bicyclo[2.1.1]hexane-2-one (48, fig. 7-11) from nopinone (47) by ring contraction. The corresponding diketone 49 is still unknown. The best starting material for attempting the preparation of a bicyclo[2.1.1]hexane-2,3-dione is the unmethylated analogue of 48, because this mono-ketone is available by photo-cyclisation of vinyl-(2-propenyl)-ketone[22].

7,7-Dimethyl-bicyclo[4.1.1]-3-octene-2,5-dione (54).

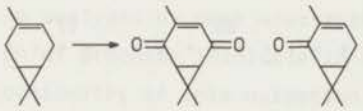
Figure 7-12



50 51 52 53 54

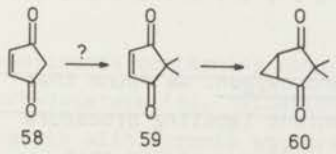
It is interesting to know whether pinonaldehyde[23] (52) can undergo an intra-molecular aldol condensation to give the unsaturated ketone 53. Using some reagent for allylic oxidation it will then cerainly be possible to convert 53 into 54; even autoxidation can possibly be used to produce 54, because 3-carene (55) can be autoxidized to give a compound[24] (56) (in a poor yield) with a similar chromophore as 54. Formation of 56 from carenone (57) has not been reported.

Figure 7-13



55 56 57

3,3-Dimethyl-bicyclo[3.1.0]hexane-2,4-dione (60).



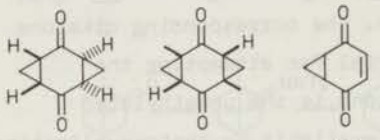
58 59 60

Figure 7-14

Cyclopentene-3,5-dione (58) is easily obtained (in two steps) from cyclopentene[25]; it will be possible to prepare the corresponding 4,4-dimethyl-compound (59) from dimethyl-cyclopentene, but preparation of 59

by methylation of 56 or a derivative will be difficult if possible at all [26]. A best chance for the closure of the three membered ring is to use the Corey reagent dimethyl-oxo-sulphonium-methylide[27], which is known to react with activated double bonds in α-unsaturated ketones. However, no example is known of a reaction of this reagent with a 2-butene-1,4-dione chromophore.

Compounds with a tricyclo[5.1.0.$0^{3,5}$]octane-2,6-dione structure.

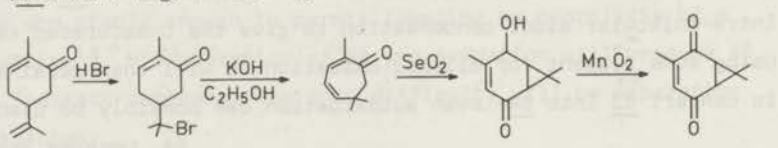


61 62 63

Figure 7-15

Little experimental attention has been paid to compounds with the tricyclo-[5.1.0.$0^{3,5}$]octane-2,6-dione structure (61, 62). Both 61 and its cis-analogue have been reported[28], and also the cis-analogue of 61 with all of its bridge-heads methylated[29]. Little is known about the stability and reactivity of these compounds. But this knowledge will be essential in order to judge the feasibility of a synthesis of optically active ^{16}O-^{18}O-61 or -62. It might be found advantageous to synthesize ^{16}O-^{18}O-61 not from trans-61, but from ^{16}O-^{18}O-bicyclo[4.1.0]-3-heptene-2,5-dione (63). In that case 3,7,7-trimethyl-61 (=68) which can be prepared from carvone[30] (64) (cf. fig. 7-16) might be used as a model compound.

Figure 7-16



64 65 66 67 68

Experimental.

Melting and boiling points are not corrected. Angles of rotation were measured with a Bendix-NPL photoelectric polarimeter, or with a Perkin-Elmer polarimeter (model 131) at room temperature; mass spectra were obtained with a MS-9 mass spectrometer.

Experiments concerning section "general".

Thiocamphor, stability in the absence of light and oxygen. We found that photo-oxidation of a thioketone could be a convenient labeling procedure because in a reference[31] in a review on thioketones[32] was stated that

thiocamphor is not stable, whereas we had kept a sample of thiocamphor in a refrigerator for over a year without any detectable chemical change. It was found that irradiation of carefully degassed solutions of thiocamphor in CCl_4, benzene, $CHCl_3$ and iso-octane (optical density ∿1.5 (1cm cell)) in the absorption band in the visible region caused no change in the absorption spectrum. Even after storage of these solutions for over three years the absorption spectra had not changed at all. But irradiation of solutions of thiocamphor in the presence of oxygen gave camphor as the most important reaction product. A similar photo-oxidation reaction of thiobenzophenone has already been described in the literature[33].

Thiocamphor, preparation[32]. If a small quantity of thiocamphor is desired, this is most conveniently prepared from camphor and P_2S_5 [34]), or by saturating an alcoholic solution of camphor with hydrogen sulphide and hydrogen chloride. Unreacted camphor then can be removed by column chromatography over silica gel, using some alkane as an eluent[34]. Thiocamphor, free from camphor, can also be prepared by treatment of camphor-diethylacetale[32] with hydrogen sulphide under acid catalysis.

Thiocamphor, photo-oxidation. Solutions of thiocamphor (2g) in iso-octane, benzene, CCl_4 and $CHCl_3$ (100ml) in a pressure bottle with oxygen were irradiated during 4-8 hours with a high pressure Hg-lamp (500W, Philips, $NaNO_2$-filter) till the orange red colour had disappeared. The pressure in the bottle was kept at 4atm. during the reaction. It was shown by G.L.C. that the solvent did not influence the composition of the mixture of reaction products: camphor was the main product (50%); three other products (together 7%) were analyzed by mass spectroscopy as $C_{10}H_{14}OS$, $C_{10}H_{16}O_2$ and $C_{20}H_{28}S$. Formation of products insoluble in the reaction medium was also observed. The stochiometry of this oxidation reaction has not been established. It might be that oxygen reacts with a thioketone to give ketone and sulphur monoxide (SO). The latter is known to be a vigorous oxidizing agent[35] which might attack the reactants thus decreasing the yield of desired product.

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Experiments concerning compound 7.

Bornylacetate (8), oxidation. Procedures for the oxidation of bornylacetate with chromic anhydride have been given by various authors[7 36 37 38 39]). We used Asahina's procedure[7] with two modifications: choice of a

higher reaction temperature, and a different isolation procedure.
A mixture of l-bornylacetate (50g, Aldrich), acetic acid (200ml) and acetic anhydride (100ml) in an 1l-flask provided with stirrer and thermometer is heated to 85°. Then CrO_3 (60g) and acetic anhydride are added, in 5g and 8½ml portions resp., at intervals of 5 minutes. By occasional cooling the temperature is kept between 90 and 100°. After the addition of all of the oxidizing agent, stirring is continued till the temperature has fallen to 50°. Most of the solvent is removed at aspirator pressure. To the residue is added CH_2Cl_2 (300ml); the mixture is refluxed on a water bath for one hour, then the inorganic material is left to settle, and the supernatant liquid is decanted. This procedure is repeated 4x with 100ml portions of CH_2Cl_2. The combined CH_2Cl_2-extracts are neutralized, filtered and dried. (Probably it is more convenient to use steam distillation than extraction for the isolation of the reaction product after the oxidation). The solvent and the bulk of unreacted 8 were removed at 15mm Hg, the ketonic esters from the oxidation of 8 (1kg) were carefully fractionated using a Nester-Faust spinning band column (2ml/hour; 120-30°/10mm Hg). 51.9g of fractions mainly consisting of 6-acetoxycamphor (9) was then obtained. To these fractions hexane (25ml) was added; storage of the resulting solution at -20° afforded crystalline 9 (35g), mp 49-57°. Continuation of the distillation using a Claisen distillation head, and recrystallisation of the crystalline distillate from hexane gave 6-acetoxy-epicamphor (17, fig. 7-17), 136g, mp 60-72°. Note: 9 and 17 can also be separated by prep. G.L.C. (LAC column).

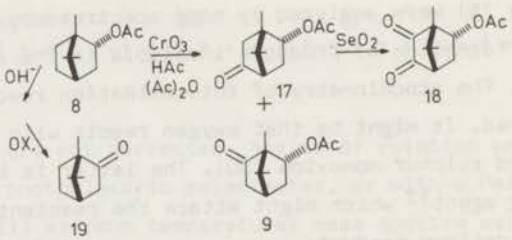

Figure 7-17: absolute configurations are depicted[40].

6-Endo-acetoxy-epicamphor (17) was purified by prep. G.L.C. (LAC column) and recrystallised from hexane. Mp 72.5-4.0°, $[\alpha]_D$-98.5° (abs. EtOH). Lit.: mp 78°, $[\alpha]_D$-87.9° (EtOH)[7]; mp 78°, $[\alpha]_D$+87.44° (EtOH)[39] (other antipode).
6-Endo-acetoxy-camphorquinone (18). Toivonen's method[36] was used. From 17 (10g) and SeO_2 (5.3g), heated without solvent on an oil bath (155°, 1 hour), after recrystallisation (4x) from petroleum ether 60-80°, was

obtained 18 (2.8g), mp 102-4°, $[\alpha]_D$-187.7° (abs. EtOH). Lit.: mp 109°, $[\alpha]_D$-191.4° (abs. EtOH)[7]; mp 103-5°, $[\alpha]_D$-190° (abs. EtOH)[38].

6-Endo-acetoxy-camphor (9) had never been isolated before, although Asahina[7] had proved that both 9 and 17 were formed on CrO_3-oxidation of 8. We proved that the ketonic ester which was separated from 17 by distillation had the assigned structure (9) because SeO_2-oxidation of this ester gave the same diketone (18) as was obtained from 17.

The purest sample of 9, mp 60.0-1.5°, $[\alpha]_D$+44.32° (abs. EtOH), was obtained after the attempted preparation of the corresponding N-isopropylimine. Under conditions as used for the preparation of camphor-N-isopropylimine[41] 17 reacted with isopropylamine and $TiCl_4$ in toluene to give (in 70% yield) the desired N-isopropylimine, which was shown by G.L.C. to be free from starting material (17). However, after the reaction of 9 (6.0g) in the same manner was obtained a liquid product (5.45g), mainly consisting of unreacted 9. Using prep. G.L.C. (SE-30 column) 9 was recovered, and after recrystallisation from hexane had physical constants as indicated above.

6-Endo-hydroxy-epicamphor. A mixture of 17 (10g) and 10% K_2CO_3-solution (268ml) was refluxed for 5 hours. Part of the 6-endo-hydroxy-epicamphor (5g) crystallised on cooling (fine needles). Another 2.5g could be removed by filtration after the mother-liquor had been concentrated to 100ml. The product was purified by recrystallisation from hexane-benzene and sublimation. Yield 6.2g, mp 243.5-5.0°, $[\alpha]_D$-79.0° (abs. EtOH). Lit.: mp 226-30°, $[\alpha]_D$+64.3° (abs. EtOH)[37] (other antipode); $[\alpha]_D$+71.4° (EtOH)[39] (other antipode).

6-Endo-hydroxy-epicamphor-hydrazone. A mixture of 17 (4.0g), anhydrous hydrazine[42] (2.43g) and absolute alcohol (4ml) was refluxed for three hours. The crystals obtained on cooling were recrystallised from THF to yield 6-endo-hydroxy-epicamphor-hydrazone, 2.1g, mp 136-43°. (The IR spectrum of the reaction product showed that hydrazinolysis of the ester group of 17 had taken place, as was expected).

6-Endo-hydroxy-camphor-hydrazone was prepared analogue to the preparation of 6-endo-hydroxy-epicamphor-hydrazone. Since no crystallisation took place on cooling of the reaction mixture, it was evaporated to dryness. Recrystallisation of the residue from benzene then gave 6-endo-hydroxy-camphor-hydrazone, mp 85-90°.

Attempted preparation of chemically pure 6-endo-hydroxy-camphor (11).

Although 6-hydroxy-fenchone has been prepared by saponification of the corresponding benzoate[43] we failed to prepare pure 11 from 9.

- A mixture of 9 (1.5g), alcohol (3.5ml) and KOH (0.7g) was refluxed for 2.5 hours. The mixture turned deep red. The alcohol was removed. When the residue was neutralized after ether had been added, the colour changed to yellow. The ethereal layer was separated; the organic material (1.1g) obtained on evaporating the ether, did not crystallise. Steam distillation of this product gave a water-insoluble, non volatile residue (0.6g) and no yield because no CD could be measured of a sample of the (homogeneous) distillate.
- A mixture of 9 (1.0g) and 10% K_2CO_3-solution (27ml) was refluxed for 5 hours. Again, evaporation of the ether extract gave no crystalline product.
- A mixture of 6-endo-hydroxy-camphor-hydrazone (0.9g), conc. HCl (1.35g) and ethylene chloride (6.5ml) was refluxed for 17 hours. From G.L.C.-measurement of the brownish-red solution it was then deduced, that the yield of 11 was low. (Under similar conditions camphor-hydrazone (0.82g) was hydrolysed to give camphor (0.7g)).
- A mixture of 9 (1.0g), ½N HCl (1ml) and dioxane (2ml) was refluxed for 22 hours. Then G.L.C.-measurements (SE-30 column) showed that 9 had almost disappeared from the mixture. Three products with a retention time shorter than 11 were formed; the most abundant product (∿84%) was analyzed by mass spectroscopy as $C_{10}H_{16}O_2$ (11). But again, an oil was obtained from the ether-extract of the reaction mixture. Isolation of 11 from the mixture, using prep. G.L.C., has not been attempted.

Attempted preparation of the diethyl-acetale of 6-endo-acetoxy-camphor (9).

Camphor-diethyl-acetale has been prepared in two different manners in the literature: from camphor and orthoformic acid-triethyl ester[44 45], and by treatment with sodium ethanolate of O-ethyl-camphor-oxonium-fluoborate[46], which can be prepared from camphor and triethyl-oxonium-fluoborate. The latter method is superior by far. Both methods have been tried for the preparation of the diethyl-acetale of 9.

- A mixture of 9 (4.0g), orthoformic acid-triethyl ester (5ml), super dry alcohol (6ml) and concentrated H_2SO_4 (0.1ml) was left to stand at room temperature. The reaction was followed by G.L.C. (1% OV-17 column). Only products were formed with a retention time shorter than the retention time of 9. After a few days two of the reaction products were isolated

by G.L.C. and analyzed by mass spectroscopy, but none was the desired acetale of 9 or the corresponding enol-ether.

Because the available quantity of 17 was larger than the quantity of 9, first the preparation of an acetale via an O-ethyl-oxonium-fluoborate was attempted from 17. The procedure for the preparation of the corresponding camphor derivative[47] was used when the preparation of the O-ethyl-fluoborate of 17 was attempted.

Initially the mixture of 17 (6.83g) and triethyl-oxonium-fluoborate (6.2g)[48] in methylene chloride (9ml) consisted of two layers, but after standing for 1.25 hours it was homogeneous. However, the reaction product did not crystallise, as does O-ethyl-camphor-oxonium-fluoborate, not even when the mixture was stored at -15^{o}. The residue, obtained on evaporation of the solvent, was a viscous liquid, which on treatment with an alcoholic solution of sodium ethanolate did not give an acetale. This was deduced from G.L.C., and from the faillure of the reaction product to give the pink colour of a thioketone on treatment with H_2S under acid catalysis.

After this negative result the preparation of the acetale of 17 was not attempted in the same manner.

Attempted preparation of the thioketone corresponding to 6-endo-acetoxy-camphor (9). Preparation of the thioketone corresponding to 6-endo-acetoxy-epicamphor (17) presented no difficulty: as was shown by G.L.C. and mass spectroscopy this was the only reaction product when 17 (4.0g) was refluxed with P_2S_5 (3.5g) in toluene (40ml) for three hours.

The same thioketone together with its hydrolysis product 6-endo-hydroxy-thioepicamphor was formed when in an autoclave a mixture of 17 (3.95g) with a solution of HCl (2.1g) in absolute alcohol (15.3g) and H_2S was left to stand at room temperature for four days. (H_2S has been introduced into the autoclave by connecting a lecture bottle to the closed autoclave, and then opening both taps). These thioketones were not purified.

Preparation of the thioketone corresponding to 6-endo-acetoxy-camphor (9) presented difficulties. The reaction product from 9 (4.0g) and a solution of HCl (2.4g) in absolute alcohol (15.25g) in an autoclave (3 days) as above, partially consisted of pink polymeric material which was visible in the glass G.L.C.-column (1% SE-30) after the analysis of the mixture. The main (volatile) product was not the desired thioketone as followed from mass spectroscopic measurements.

The experiments with P_2S_5 were not succesful either:

- A mixture of 9 (4.0g), P_2S_5 (3.5g) and toluene (40ml) is refluxed for 2.7 hours. Then the mixture is brown whereas it should be red. G.L.C. (glass 1% SE-30 column) shows that at least 3 products are formed, but in low yield.
- A mixture of 9 (0.9g), P_2S_5 (0.85g) and toluene (9ml) is refluxed for 5 hours. The mixture then is dark brown. But now the relative yield of one of the reaction products is higher than in the previous experiment, which suggests that the other products are thermally less stable. The main product was isolated by G.L.C. and analyzed by mass spectroscopy as $C_{12}H_{18}O_2S$ (i.e. the composition of the desired product).
  A solution of the reaction products in CCl_4 was irradiated in the visible region till the red colour had disappeared, while oxygen was bubbled through the mixture. Then a gaschromatogram of the colourless solution showed, that the peaks of the reaction products, except for the peak of the main product, had disappeared. Thus the main product, being colourless, could not be a thioketone.

Conclusion from the experiments on 2,6-diketo-camphane (7).

Because of the unavailability of derivatives (N-isopropylamine, acetale, thioketone) of 6-endo-acetoxy-camphor (9), suited for the introduction of the ^{18}O-label by hydrolysis, the only way left for the praration of specifically labeled 2,6-diketo-camphane (7) from (9) (fig. 7-17) seems to be to label 9 by exchange, then to remove the ester group by reduction, and to oxidize the diol 10 obtained. But we have not yet verified whether the oxidation of an ^{18}O-alcohol can be carried out with retention of label.

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Experiments concerning compound 23 [49]).

4-Cyclohexene-1,2-dimethanol-ditosylate (21). The preparation of 21 from 4-cyclohexene-1,2-dicarboxylic acid is described in chapter 5.

4-Cyclohexene-1,2-diacetonitrile. Cope's procedure[50] for the preparation of a nitrile from a tosylate with KCN in DMSO was used to obtain 4-cyclohexene-1,2-diacetonitrile from 21. After the volume of the reaction mixture was doubled by the addition of water, the dinitrile was isolated[51] by extraction with an equal volume of benzene, divided over 5 portions. The extract was dried with water, dried and evaporated to give the crude dinitrile, mp 76-9°, (lit.[52]: mp 79.5-80.5°), in 98% yield.

4-Cyclohexene-1,2-diacetic acid. The above dinitrile (176.5g) was refluxed with KOH (176.5g), alcohol (243ml) and water (567ml) for 24 hours. The crystals which precipitated on addition of conc. HCl were recrystallised from water to give the diacetic acid (167.6g, i.e 77%), mp 183-9°. Lit.[52]: mp 199-200°.

Hydrindenone (22). A standard procedure[53] was used for the decarboxylation of 4-cyclohexene-1,2-diacetic acid. The crystalline product was dissolved in ether and washed with a bicarbonate solution till free from acid. On evaporation of the ether 22, mp 57-63°, was obtained in only 59% yield. Recrystallisation from heptane raised the mp to 67.5-8.8°. 22 gave a semi-carbazone, mp 218-22° (d) (recrystallised from alcohol).

Hydrindenol. To a stirred solution of 22 (32g), A.R. MeOH (50ml) and water (35ml) was added dropwise a solution of $NaBH_4$ (6g) and NaOH (5g) in water (35ml). The temperature was kept between 40 and 50° during the addition. After the addition the reaction mixture was kept (with stirring) at 50° (24 hours) till only a trace of 22 was left (G.L.C.). Then the reaction mixture was poured into water. The crystalline alcohol was dissolved in ether and shaken with a saturated $NaHSO_3$-solution. Evaporation of the ether gave hydrindenol in 84% yield.

Hydrindenylacetate (24). Hydrindenol, treated with acetic anhydride in pyridine, gave 24 in 93% yield.

Attempted ring opening of the bicyclo[4.3.0]nonene skeleton of 22 and 24.

- Cope's procedure[54] for the ring opening of bicyclo[7.1.0]nonene with $KMnO_4$ in acetone was used for the oxidation of 22 (25g), but no yield was obtained. When after the reaction the solvent was evaporated, using a rotatory evaporator, rather unexpectedly some unreacted ketone (7.8g) was recovered. Presumably selective oxidation of the double bond in 22 is not possible by this method.
- Cope 's procedure[54] was then used for the oxidation of 24; only a poor yield was obtained.
- An ozonisation procedure[55] was used for the oxidation of 24. The product was not (NMR, mass spectroscopy) the desired di-aldehyde.

3,4-Epoxy-trans-bicyclo[4.3.0]nonane-8-ol-acetate (25) was prepared analogue to the preparation of 1,2-epoxy-cyclohexane from cyclohexene[56]. Yield 85%, mp 40-50°, bp_2 113-7°. The peracetic acid used for this epoxidation was prepared[57] from boric-acetic-acid anhydride[58] and conc. hydrogen peroxide[59].

Oxidation of 25 with DMSO. Cohen and Tsuji[60] have reported that epoxides can be oxidized with DMSO in the presence of a catalytical amount of BF_3-ether complex to give acyloins in good yield.
First we attempted oxidation of 1,2-epoxycyclohexane[56] and found (G.L.C.) that under the conditions of [60]) not all of the epoxide was oxidized. More BF_3-complex was then added and the reaction was continued till all of the epoxide had disappeared. A high yield of acyloin was obtained. 25 was oxidized in the same manner[60]; again more BF_3-complex had to be added to achieve complete oxidation. The reaction product (26), obtained in quantitative yield by $CHCl_3$-extraction after the reaction mixture had been poured on ice, was a viscous liquid.
Oxidation of the crude acyloin (26). Rigby's method[61] was used for the oxidation of 26. A mixture of Bi_2O_3 (16.4g) and acetic acid (30g) was refluxed for 2.5 hours. Then the acyloin (26, 18.3g) was added and heating was continued on a bath at 100° for 1 hour. The mixture was filtered and the precipitate washed with CH_2Cl_2. The solvent of the filtrate was evaporated; a green coloured impurity of the residue could be removed by column chromatography (silicagel, ether). Yield 18g. This product was shown by NMR to contain polymeric material. Distillation of the product and recrystallisation of the distillate from heptane-toluene gave 27, 4.2g, mp 119.8-21.4°. Presumably milder reaction conditions are necessary if one wants to prepare 27 from 26 in an reasonable yield. Mild oxidation of acyloins seems to be possible[62] using $Pb(OAc)_4$.
Attempted resolution of 22 with "menthydrazide". For preparation of the derivative of 22 with "menthydrazide" [14]) the procedure for the preparation of the corresponding derivative of α-ionone[63] was used. After refluxing for 12 hours the solvent was removed and the residue dissolved in n.-heptane and filtered while hot. Yield 7.6g (from 5g of 22), mp 135-6°. Regeneration of this derivative gave 22, small negative Cotton effect, optical purity 4.5% [64]).
Attempted resolution of 22 with 4-(endo-2-fenchyl)-semicarbazide. A mixture of 22 (5g), 4-(endo-2-fenchyl)-semicarbazide·p.-toluenesulphonic acid (15.2g), $NaOAc \cdot 3H_2O$ (6.8g) and alcohol (150ml) was refluxed for 12 hours. The crystals obtained on cooling were recrystallised from alcohol. Yield 7.45g, beautiful needles, mp 219-25°. Regeneration of the derivative gave 22, small negative Cotton effect, optical purity 2.3% [64]).
4-(Endo-2-fenchyl)-semicarbazide·p.-toluenesulphonic acid.

The procedure of Goodson[65] for the preparation of 4-alkyl-substituted semicarbazides was used to prepare 4-(endo-2-fenchyl)-semicarbazide· p.-toluenesulphonic acid from fenchylamine.

- Endo-2-fenchylamine. Crude fenchylamine (see chapter 2) was shown by G.L.C. to be a mixture of two compounds, as was expected (partial separation with a Carbowax column). The minor component of this mixture could be removed by recrystallisation of the amine-hydrochloride from dioxane (2x). The assignment of the endo-configuration to the sterically pure amine is based on the stereochemistry of reductions with sodium and alcohol in the norbornane series.
- 4-(Endo-2-fenchyl)-acetone-semicarbazone was prepared[65] by addition of acetone-semicarbazone to heated endo-2-fenchylamine. Yield 63% (after recrystallisation from alcohol), mp 208-10^{o}.
- Hydrolysis of 4-(endo-2-fenchyl)-acetone-semicarbazone with hydrochloric acid[65] was unsatisfactory because the hydrochloride of 4-(endo-2-fenchyl) -semicarbazide was found to be good soluble in water. The hydrolysis experiment was repeated with p.-toluenesulphonic acid of about the same concentration as the hydrochloric acid used in the previous experiment. A toluenesulphonic salt crystallised on cooling of the reaction mixture after the hydrolysis, but it was found to be reasonably soluble in water, thus concentration of the mother-liquor was necessary to improve the yield.

Oxidation of α-hydroxy-cyclopentane-carboxylic acid. α-Hydroxy-cyclopentane-carboxylic acid was prepared[66] by hydrolysis of cyclopentanone-cyanohydrine[67].

In a round-bottommed flask, provided with a distillation head, was heated a mixture of PbO_2 (32g), α-hydroxy-cyclopentanone-carboxylic acid (10g) and water (100ml). After the evolution of carbon dioxide had stopped, more water was to the reaction mixture, and then a mixture of cyclopentanone and water (∿100ml) was removed by distillation. The cyclopentanone in the receiver was precipitated as the semicarbazone. For comparison the theoretical amount of cyclopentanone, that could have been formed in this oxidation, was dissolved in water (100ml) and then precipitated as the semicarbazone. Comparison of the weights of the two portions of semicarbazones indicated that the yield in the oxidation reaction was 87%.

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Experiments concerning compound 35 [49].

(1s:3s:8r:10r)-Tricyclo[8.4.0.$0^{3,8}$]tetradeca-5,12-diene-2,9-dione (29) was prepared from p.-benzoquinone and butadiene in toluene[15], and was recrystallised from toluene. Mp 137°; lit.[15]: 154-5°.

(1s:3r:8r:10s)-Tricyclo[8.4.0.$0^{3,8}$]tetradeca-5,12-diene-2,9-dione (30). The purified diketone 29 was dissolved in alcohol, and to this solution while hot was added an alcoholic solution of potassium hydroxide[15]. The product (30) was purified by recrystallisation from THF or ethyl acetate. Mp 241-2; lit.[15]: 244-5°.

(1s:3r:8r:10s)-Tricyclo[8.4.0.$0^{3,8}$]tetradeca-5,12-diene-2,9-diol (31). The diketone 31 (257g) was added, using a Soxleth, to a mixture of LAH (60g) and THF (31). After the reduction most of the THF was removed by distillation and replaced by ether. 31 was found to be only slightly soluble in ether. After careful addition of water to the reaction mixture to destroy the unreacted LAH, enough ice and conc. HCl was added to permit isolation of 31 by filtration. Yield 94%. This diol was not purified.

Ditosylate of 31 (32). This ditosylate was prepared from 31 using Hill's procedure[68]. The crude product, prepared in 86% yield, was brown. The coloured impurity could be removed by boiling the crystals with n.-butanol; the crystals were then removed by filtration when the mixture was cooled.

(1s:3r:8r:10s)-Tricyclo[8.4.0.$0^{3,8}$]tetradeca-5,12-diene (33). Crossley's procedure[15] for the preparation of 33 by LAH reduction of 32 was used with some modifications. It was not necessary to use a Soxleth for the introduction of 32 in the reaction mixture: all of 32 could be added at once; the reduction is slow because of the very low solubility of 32 in boiling THF. We refluxed for 7 days, then most of the THF was removed by distillation, and water was carefully added. 33 could be removed by filtration after the reaction mixture had been made strongly acid with conc. HCl. 33 was purified by sublimation (95°, 2mm Hg). Yield 70-75%, mp 108.0-10.5°; lit.[15]: mp 112-3°. We noticed that a brown impurity was formed on storing of 33; this impurity is probably an autoxidation product.

(1s:2s:4r:5r)-Cyclohexane-1,2,4,5-tetra-acetic acid (34). After attempts to preparepreparе 34 from 33 by ozonisation (0°, CCl_4 and CCl_4-ethyl acetate) had been given up because insoluble ozonides were formed, Cope's procedure [54]) for the oxidation of bicyclo[6.1.0]nonene was used to give 34 in 22% yield. Mp 290-5° (d) after recrystallisation from water.

(1s:3r:7r:9s)-Tricyclo[7.3.0.0^{3,7}]dodecane-5,11-dione (35). The usual procedure[53] for the preparation of a ketone from a dicarboxylic acid was used, but now the decarboxylation was done at 15mm. The diketone 35, mp 215-6°, was obtained in 41% yield (after recrystallisation from alcohol). 35 has its C=O-stretch vibration at 1730cm^{-1} (KBr pellet), and at 1739cm^{-1} ($CHCl_3$). From empirical rules[69] it follows that the carbonyl group is attached to a 5-membered ring. There is also an empirical rule in ^{13}C-NMR spectroscopy[70] which relates the ^{13}C-shift of the carbon atom from the carbonyl group to the ring size. The ^{13}C-shifts (with respect to CS_2) of carbon atom from the carbonyl group of cyclohexanone, cyclopentanone and 35 are resp. -16ppm, -26ppm and -23.8ppm (in $CHCl_3$). Thus in view of this evidence from IR and ^{13}C-NMR we can state that our diketone has indeed structure 35, and not 36 (fig. 7-8).

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3) See chapter 2, ref. 42).

4) R. Srinivasan and W.A. Noyes, Jr., J. Amer Chem. Soc., 82, 5591 (1960).

5) See: J.L. Simonsen, The Terpenes, Cambridge University Press, 2nd ed., vol. 2, 438 (1949).

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SAMENVATTING

Het uitgangspunt voor het in dit proefschrift beschreven onderzoek was de verwachting, dat meting van circulair dichroïsme van verbindingen, die alleen optisch actief zijn door isotopensubstitutie, nieuwe en nuttige informatie zou kunnen geven over de electronenstructuur van deze verbindingen.

Omdat effecten in optische activiteit ten gevolge van isotopensubstitutie byzonder klein zijn vergeleken met effecten in optische activiteit van (bv.) natuurstoffen, was het niet verwonderlijk dat nooit eerder CD van een dergelijk type optisch actieve verbinding gemeten was. De mogelijkheid deze kleine effecten te meten hangt af van een gelukkige keuze van de te meten verbinding èn het beschikbaar zijn van een gevoelig CD apparaat. Op de Afdeling Theoretische Organische Chemie is aan het tweede vereiste voldaan doordat Drs. H.P.J.M. Dekkers voor zijn promotie-onderzoek een dergelijk apparaat gebouwd heeft.

In hoofdstuk 1 van dit proefschrift wordt duidelijk gemaakt waarom het wenselijk is aan isotopengesubstitueerde carbonylverbindingen te werken als men een redelijke kans wil hebben ook CD van zo'n verbinding te meten.

In de twee daarop volgende hoofdstukken zyn de syntheses beschreven van (^{16}O, ^{18}O)-α-fenchocamphoronchinon en 1-deutero-α-fenchocamphoronchinon, verbindingen, welke een meetbaar effect in CD bleken te vertonen.

Het overige beschreven werk, behalve het laatste hoofdstuk waar twee methoden voor de bepaling van optische zuiverheid gegeven zijn, houdt hiermee verband. In hoofdstuk 4 is op grond van absorbtie- en CD-metingen aan een aantal norkamferchinonen geconcludeerd, dat de interpretaties in de literatuur van het CD-spectrum van kamferchinon aan ernstige bedenkingen onderhevig zijn. In de appendix wordt een verantwoording gegeven over onvoltooid werk aan ^{16}O-^{18}O-diketonen en wordt de synthese van een aantal interessante diketonen voorgesteld. Het werk aan trans-1,2-dimethylcyclopentaan, beschreven in hoofdstuk 5, houdt verband met één van de onvoltooide projecten in de appendix, en bovendien met een recente publicatie over het voorkomen van optisch actief 1,2-dimethylcyclopentaan in een ruwe olie. Van de in het laatste hoofdstuk beschreven methoden voor de bepaling van optische zuiverheid berust de ene op het gebruik van circulaire polarisatie van de luminescentie (CPL); de andere op de fotochemische ontleding van optisch actieve verbindingen.

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CURRICULUM VITAE

Na het behalen van het diploma H.B.S.-b aan het St. Stanislascollege in Delft begon ik in 1962 met de scheikundestudie aan de Rijksuniversiteit in Leiden. Het candidaatsexamen (letter F) werd in december 1964 afgelegd. Daarna werd de studie voortgezet met Theoretische Organische Chemie als hoofdvak (bij Prof. L.J. Oosterhoff); als bijvak werd Numerieke Wiskunde gekozen (bij Prof. G. Zoutendijk) en als derde richting Theoretische Natuurkunde (bij Prof. P.W. Kasteleyn). Na het doctoraalexamen, dat in september 1967 werd afgelegd, stelde Prof. L.J. Oosterhoff me in staat bij hem promotie-onderzoek te verrichten op het gebied van de optische activiteit, een onderwerp waarvan ik de synthetische aspecten al had leren kennen toen ik tijdens mijn hoofdvakstudie meehielp aan een deel van het promotie-onderzoek van Dr. C.A. Emeis.
Van 1 october 1967 tot 1 maart 1972 was ik als wetenschappelijk medewerker in dienst bij Z.W.O.; vanaf 1 maart 1972 ben ik als wetenschappelijk medewerker 1e klasse in dienst bij de Rijksuniversiteit in Leiden.

Proefschriften komen niet tot stand zonder de medewerking van een groot aantal anderen zoals het niet-wetenschappelijk personeel van het Gorlaeus Laboratorium. Van deze mensen wil ik met name danken de Heren amanuenses van de 8e verdieping, de Heren glasinstrumentmakers, en de Heer B. v. Vliet van de afdeling gaschromatografie, voor de wijze waarop ze hulp boden, als op hen een beroep gedaan werd.
De prettige samenwerking met de heren Drs. J.C.A. Windhorst en F.A. Varkevisser heb ik zeer op prijs gesteld. De laatste heeft ook daadwerkelijk hulp verleend bij mijn promotie-onderzoek.
Als Drs. H.P.J.M. Dekkers niet een gevoelig CD-apparaat gebouwd had, was het onmogelijk geweest CD te meten van de isotopengesubstitueerde α-fenchocamphoronchinonen.
De tekeningen in dit proefschrift werden verzorgd door de heren M. Pison en J.J. Pot.

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STELLINGEN

1/ Alvorens grotere hoeveelheden van een organische verbinding met ruthenium tetroxide te oxyderen is het wenselijk de reactie eerst op kleine schaal uit te voeren in aanwezigheid van een inerte ijkstof.

2/ De bewering, dat bij autoxydatie van optisch actief 3-careen racemisch 3,7,7-trimethyl-bicyclo[4.1.0]3-hepteen-2,5-dion zou ontstaan is onvoldoende gemotiveerd.
(A. Zabza & H. Kuczynski, Roczniki Chem., 40, 433 (1966)).

3/ Oxydatie van cis-β-decalon-hydrazon met HgO is wellicht de eenvoudigste manier om twistaan te synthetiseren.

4/ Schaefer en Horvath hebben over het hoofd gezien, dat het mogelijk is het voorkomen van een 1,3-diaryl-propenyl-carbonium ion, dat door hen werd voorgesteld als intermediair bij de oxydatie met selenium dioxide van 1,3-diaryl-propenen, te bewijzen door een combinatie van experiment en P.P.P.-berekeningen.
(J.P. Schaefer & B. Horvath, Tetrahedron Letters, (1964) (30) 2023).

5/ De experimentele resultaten van Volpi en Pietra betreffende de Tiffeneau-Demjanov-ringverwijding van norcamfer zijn zó onvolledig, dat publicatie beter achterwege had kunnen blijven.
(E. Volpi & F. Pietra, Tetrahedron Letters, (1972) (48) 4867).

6/ Het is aanbevelenswaardig in het leerplan kunstgeschiedenis ook achtergronden en toepassingen op te nemen van fysische en chemische methoden om de autenticiteit van kunstvoorwerpen vast te stellen.

7/ Hsia, Shang en Chou bronzen zijn geen goede geldbelegging.

8/ Het kan aanleiding geven tot maatschappelijke onrechtvaardigheid, dat strafrechtelijk beter kan worden opgetreden tegen iemand, die een dier mishandelt, dan tegen iemand, die een mens mishandelt.

9/ De bemoeienis van het R.I.B. met de aankoop van chemicaliën, die niet tot de standaard magazijnvoorraad van een rijksoverheidslaboratorium behoren, werkt remmend op het wetenschappelijk onderzoek en belangrijk kostenverhogend.

W.C.M.C. Kokke 29 maart 1973.