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THE OPTICAL AND PHOTOCHEMICAL PROPERTIES OF METHYLISOPULEGONE

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Abstract—UV irradiation of (—)methylisopulegone (II), the configuration of which is established by comparison of its CD with that of 2-isopropenyl-2-methylcyclohexanone made from (+)camphor, gives in high yield 3,6-dimethyl-7-methylenebicyclo[4,2,0]octan-1-ol (XVIII), which is further isomerized by acid to (—)3,4,7-trimethylcyclo-oct-3-enone (XIX).

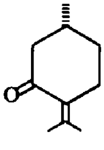
Methylation of pulegone (I) gives mainly (—)methylisopulegone, accompanied by some (about 17%) of the dextrorotatory epimer.[1] Djerassi *et al.*[2,3] assigned the rather unexpected configuration III to (–)methylisopulegone, and II to the epimer, by application of the quasi-racemate method to the glutaric acid produced on oxidation of the dihydro derivative. Soon afterwards, however, Norin[4] concluded that this acid had the opposite configuration (IV) on the basis of its formation by oxidation of dihydrosabinene, the confuguration of which was known as a member of the thujane group of monoterpenes. One way to settle the disagreement is to compare the optical properties of the ketone with those of a close relative of known configuration. The ideal reference compound (though apparently in racemic form) was described by Edwards and Lesage,[5] who made the unsaturated ketone VI by treatment of α-aminocamphor (V) with nitrous acid. The methylisopropenylcyclohexanone (VII) produced by reduction of the conjugated double bond with zinc and acetic acid differs from (–)methylisopulegone only in the absence of the 5-Me group.

Table 1. Circular dichroism in cyclohexane

II		VII	
λ_{max} (nm)	Δε	λ_{max} (nm)	Δε
318 sh	−1·75	317 sh	+2·17
307	−2·94	306	+3·59
298	−3·00	297	+3·67
290 sh	−2·40	290 sh	+3·05
220†	+ve	220†	−ve

† not maximum; zero Δε from ca. 230 to 240 nm.

We therefore made the ketone VII in optically active form from (+)camphor, the configuration of which is sure.[6] As summarized in Table 1, the CD spectra of the ketone VII and of (–)methylisopulegone are very similar, but of opposite sign. They have, therefore, the opposite configuration at the α-C atom, and (−)methylisopulegone is correctly represented by II[4], not III[2]. The correspondence in Δε can be made closer by making an approximate allowance for the contribution of the extra 5-Me group. Addition of Δε for 3-methylcyclohexanone (VIII) (+0·57 in EPA[7]) to the value for the enantiomorph of VII (−3·67) gives a figure of −3·1, in good agreement with the measured value of −3·0.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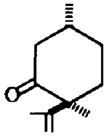
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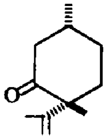
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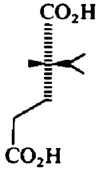
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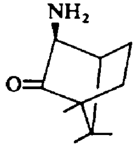
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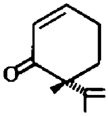
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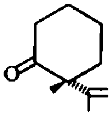
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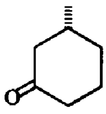
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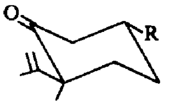
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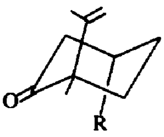
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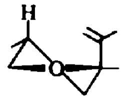
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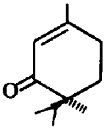
XII

Independent vindication of Norin's configuration (II) has recently been provided[8] by "an X-ray arbitration" on the rubidium salt of the half methyl ester of the glutaric acid IV.

While the configuration of (−)methylisopulegone follows from its CD, consideration of its conformation suggests that the close numerical agreement with Δε calculated from that for VII and VIII may be fortuitous. The enantiomorph of VII will probably exist mainly as the conformation IX (R = H) with smaller amounts of X and perhaps some XI. The axial isopropenyl group of X (R = H) will probably confer a relatively large ε† and negative Δε on that conformation[9] (i.e. positive for the enantiomorph VII), whereas the equatorial isopropenyl group of IX (R = H) is expected to have a smaller effect on the n → π* band, which will also depend on the rotational conformation about the isopropenyl-ring bond. The extra Me group would be expected to decrease the population of the conformation X (R = Me) (negative contribution to Δε from the isopropenyl group) in II compared with the parent system (enantiomorph of VII). So the almost equal and opposite Δε for II and VII and the relatively low ε suggest that the contribution of the axial isopropenyl

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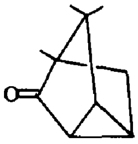
† In fact II and VII had almost identical UV spectra, with λ_{max} 298 (ε 42).

group may not be the dominant factor. Consideration of the ORD amplitudes of the epimeric 2,5-dimethyl-2-isopropylcyclohexanones produced by hydrogenation of the two methylisopulegones[3] indicates, in fact, that (−)methylisopulegone has the configuration II, rather than III as originally suggested. The hydrogenation of XII, derived from (−)methylisopulegone, mainly to the dimethylisopropylcyclohexanone that is the enantiomorph of the dihydro-derivative of (+)methylisopulegone,[3] also supports the configuration II for (−)methylisopulegone and III for the (+)isomer, if the catalyst delivers hydrogen to the double bond in XII faster from the side *cis* to the methyl group than *cis* to the isopropyl group.

In our experiments, which were done on a larger scale, the reported[5] products (VI, XIII, XIV, XV) of deamination of aminocamphor (V) were produced, but in rather different proportions from those of Edwards and Lesage: in particular there was more hydroxy-ketone (XV) and less VI. The first could be dehydrated to the second with thionyl chloride in pyridine. Treatment with nitrous acid of the dihydropyrazine (XVI), which is formed on reduction of oximinocamphor if the aminocamphor is not immediately stabilised as the hydrochloride, gave the pyrazine (XVII). The deamination products (VI, XIII, XIV, XV) that were also formed presumably arose from aminocamphor (V) produced by prior hydrolysis. The aromatic pyrazine ring in XVII caused a much larger difference in chemical shift between the three pairs of methyl groups than is usual in camphor derivatives. The 9-Me group appeared at τ 9·01, the 8-Me group, which is almost in the plane of the pyrazine ring, moved down to τ 8·73 and the 10-Me group, which is over the ring, moved up to τ 9·42.



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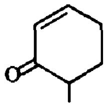

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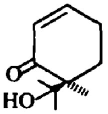

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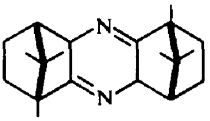

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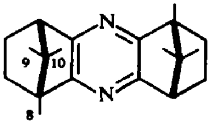

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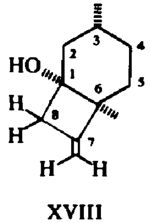

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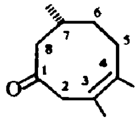

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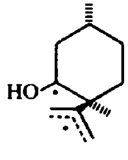

XX

UV irradiation of (−)methylisopulegone (II) in cyclohexane through Pyrex caused a change that was easily followed by IR spectroscopy or gas chromatography. An isomeric alcohol was isolated in about 70% yield, the structure of which (XVIII) followed from its spectral properties: ν_{max} 3420 (OH), 3075, 1670 and 880 cm^{-1} ($C{=}CH_2$) in the IR; and in the PMR spectrum (CCl_4) a doublet (J = 5·8 c/s at τ 9·05 (3-Me group), a singlet at τ 8·96 (6-Me group), two doublets (J_{gem} = −15·3 c/s) at τ 7·53 and 7·16 (8-methylene group) each split into a triplet (2·2 c/s) by allylic coupling with the exocyclic 7-methylene group, which gave an apparent quartet (splitting 2·2 c/s) centred on τ 5·21. Treatment of the alcohol (XVIII) with acid produced an isomeric ketone assigned the structure XIX (double bond assumed to have the less strained *cis* configuration) on the basis of the reaction likely to be initiated by protonation of the double bond, and of its spectral properties: the ultraviolet absorption (λ_{max} 301·5 nm, ε 129) suggested a βγ-unsaturated ketone;[10] the low CO stretching frequency (ν_{max} 1696 cm^{-1}), even though the UV spectrum showed no strong conjugation, indicating a medium-sized ring;[11] the PMR spectrum ($CDCl_3$) showed a doublet (J = 7 c/s) at τ 9·03 (7-Me group) a singlet at τ 8·33 (two allylic Me groups at C-3 and C-4) and a pair of doublets ($J_{gem} = -15{\cdot}5$ c/s) at τ 7·18 and 6·90 (2-methylene group). The CD of XIX has already been discussed.[12]

Presumably the cyclization of II proceeds by abstraction of an allylic H atom by the nπ* triplet of the CO group to form the diradical (XX) which then cyclizes, as in the familiar conversion of saturated ketones having a γ-H atom into cyclobutanols.[13] The triplet ketone with an equatorial isopropenyl group IX (R = Me), which is required for hydrogen transfer, may be reached by direct excitation in that conformation, or by conformational inversion of X or XI (R = Me) which will absorb more of the light. Since our work was completed (1964) there have been reports of the photochemical conversion of acyclic βγ-unsaturated ketones into methylenecyclobutanols.[14] Some of the products then arise from cleavage of the α-C—CO bond and reaction of the resulting free acyl and allyl radicals. Such a cleavage in our system would, of course, give a diradical that could recyclize (though perhaps with loss of stereochemistry).

EXPERIMENTAL

Irradiation of (−)*methylisopulegone* (II). The ketone II (1·09 g) in cyclohexane (100 ml) under N_2 was irradiated with a 125 W medium-press Hg vapour lamp through a water-cooled pyrex sleeve for 3·5 hr. (Gas chromatography or IR spectroscopy showed 90–95% conversion after 3 hr). Distillation gave a fraction (XVIII), b.p. 65–67° at 0·7 mm, that crystallized as needles, m.p. ca. 25°, 70% yield. (Found: C, 78·5; H, 10·7. $C_{11}H_{18}O$ requires: C, 79·5; H, 10·9%).

The alcohol XVIII (1·10 g) in ether was shaken with conc HCl for 2·5 hr, when gas chromatography showed that reaction was complete. The mixture was diluted with water, the ether layer was washed, dried and evaporated. After preliminary distillation below 90° at 1·2 mm, XIX was purified by gas chromatography. (Found: C, 79·5; H, 10·9, $C_{11}H_{18}O$ requires: C, 79·5; H, 10·9%).

Reaction of 3-endo-*aminocamphor hydrochloride* (V) with *nitrous acid*. Compound V, made by reduction of oximinocamphor from (+)camphor with Zn dust and aqueous AcOH,[15] had m.p. 256–258° and ν_{max} (Nujol or $CHCl_3$) 1760 cm^{-1}. $NaNO_2$ (33·8 g, 0·49 mole) in water (50 ml) was added over 30 min to a soln of V hydrochloride (20·4 g, 0·1 mole) in 0·2N H_2SO_4 (135 ml) kept at 25°. 10 min later the mixture was neutralized with sat Na_2CO_3aq and extracted with CH_2Cl_2. The yellow oil (13·6 g) from evaporation of the CH_2Cl_2 was chromatographed on silica gel (750 g). 2% of ether in benzene eluted an oil, separated by preparative gas chromatography on PPG at 100° into XIII and VI; ν_{max} (neat) 1755 (w), 1680 (s), 1645 cm^{-1}. 25% of ether in benzene eluted an oil as major product consisting of XV; ν_{max} (neat) 3500, 1765 (w), 1720 (w) and 1655 (s) cm^{-1}; PMR spectrum (CCl_4) singlets at τ 8·99 (6-Me) and 8·81 (Me_2COH), doublet (J = 10·2 c/s) of triplets (J = 1·6 c/s) at τ 4·17 (2-H) and a multiplet at 3·07 (3-H). Smaller quantities of 6-methylcyclohex-2-enone and of other ketones were also isolated.

2-*Isopropenyl-2-methylcyclohexanone* (VII). Compound VI (0·43 g), > 99% pure by GLC, in AcOH (15 ml) at 60° was treated with Zn dust (2 g) over 1·5 hr. After a further 1 hr's stirring at 60° the mixture was diluted with water and extracted with CH_2Cl_2. The oily VII that remained on evaporation of the solvent was > 95% pure by GLC; $[\alpha]_D$ 222°.

The pyrazine (XVII). Treatment of the product XVI of self-condensation of V with HNO_2 under similar conditions gave the same mixture of products as V itself (GLC), but the main product, eluted from silica gel with $CHCl_3$, was XVII, colourless needles from aqueous EtOH, m.p. 159·5–160°: ν_{max} ($CHCl_3$) *inter al.* 3000, 1490, 1465, 1400, 1395, 1380, 1370, 1285, 1180, 1145, 1110, 1070 cm^{-1}; λ_{max} (EtOH) 225 (2700), 293 (10,900) and 312 nm (ε 10,700); PMR (CCl_4) singlets at τ 9·42 (10-Me), 9·01 (9-Me), 8·73 (8-Me) and a doublet ($J = 4$ c/s) at τ 7·17 (4-H).

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[13] For examples of conversion of $\delta\varepsilon$-unsaturated ketones into 2-vinylcyclobutanols see N. C. Yang, A. Morduchowitz and D.-D. H. Yang, *J. Am. Chem. Soc.* **85**, 1017 (1963); K. H. Schulte-Elte and G. Ohloff, *Tetrahedron Letters* 1143 (1964); R. C. Cookson, *Pure Appl. Chem.* **9**, 575 (1964).

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