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BASE INDUCED ISOMERIZATIONS OF γ,δ-EPOXYKETONES—II*

SYNTHESES IN THE THUJANE SERIES. *D,L*-SABINA KETONE AND *D,L-CIS*-SABINENE HYDRATE

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Abstract—Base treatment of 4-(epoxyisopropylidene)cyclohexanone provides an entry into the bicyclo-[3.1.0]alkane series. In this way *d,l*-sabina ketone, *d,l-cis*-sabinene hydrate and a few related bicyclic compounds were synthesized.

The synthesis of substituted cyclopropyl ketones by base induced isomerizations of γ,δ-epoxyketones has been described recently,[1,2] It has now been found that the same reaction may be applied to the formation of carbobicyclic systems. The idea of constructing [3.1.0] bicyclic or transient bicyclic ring systems by intramolecular anionic displacement of suitably substituted cyclic carbonyl compounds goes back to the end of last century, with the transformation of dihydrocarvone to carvone and of carvone to eucarvone.[3] It has since been quite extensively used in synthesis,[4] but mainly with γ-halo- or γ-tosyloxyketones[3d,4,5,6] and only rarely with epoxyketones.[7]†‡ The use of the latter functionality may however be advantageous since it can be readily prepared and isolated, easily attached to and displaced from tertiary positions and it may sometimes succeed where a halogen has failed (*e.g.*, the attempted synthesis of sabina ketone from a haloketone derivative[7]).

This and the following paper[11] report the results of two such isomerizations, relating to six- and seven-membered ring ketones with a differently placed epoxide function, whereby *dl*-sabina ketone (**10**) and *dl-cis*-sabinene hydrate (**13**) were synthesized from **2** and bicyclo[4.1.0]heptane (norcarane) derivatives synthesised from epoxykarahanaenone.[11]

The first total syntheses of *dl*-sabinene and *dl*-sabinene hydrate, both proceeding through sabina ketone, have been reported only recently.[12,13,14] The synthesis of sabina ketone described here and the slight modification thereof, which proceeds through dehydrosabina ketone, constitute therefore further total syntheses of these compounds.

The key compound in the present synthesis is 4-isopropylidenecylcohexanone (**1**). It was obtained by known procedure[15] or by a direct Wittig reaction between 4,4-

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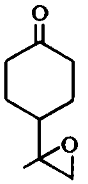
[*] Part 1, ref. 1.

[†] Vinylogous carbonyl compounds have been used recently in the synthesis of substituted carene derivatives.[8]

[‡] Epoxyketone isomerizations have been also applied to the construction of other, differently sized bi- and tricyclic ring systems.[9,10]

ethylenedioxycyclohexanone and triphenylisopropenylphosphorane, followed by deketalization. Although this last reaction could not be brought into completion, (yield *ca.* 35%), it may still replace the indirect method of Vig *et al.*[18] in which a carbethoxy function is reduced in two further steps to a methyl group to give about the same final yield of **1**, as its ethylene ketal.

A complex mixture was obtained by us on the last step of the Frank and McPherson synthesis[15, 16] of which **1** constituted ~30% (by VPC analysis). The total mixture was epoxidized and separated by column chromatography. The products isolated indicated that all four possible double bond positional isomers had been formed. Two of these four isomers were isolated as the epoxides, namely, the desired epoxide **2** and epoxide **3**; one of the isomers, cryptone (**4**),[17] had not suffered epoxidation, being an α,β-unsaturated ketone, and was therefore isolated as such; the last isomer, having yielded a β,γ-epoxy ketone (**5**), underwent a facile β-elimination, probably during work-up, to yield the keto-alcohol (**6**), which could be dehydrated to *p*-isopropylphenol (cumenol, **7**).



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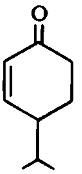

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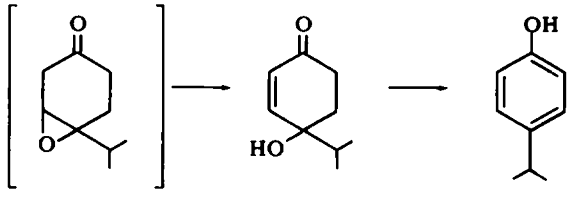
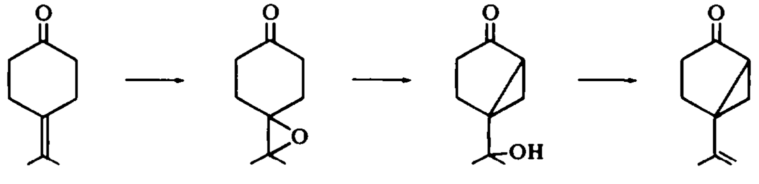


5 **6** **7**

Treatment of the epoxidation product of **1**, (epoxide **2**) with boiling ethanolic NaOH aq, or with NaOEt in EtOH for 15 min. yielded the bicyclic keto-alcohol **8** in over 90% yield. Compound **8** may now be converted into any number of thujane derivatives; illustrated by the following transformations.



1 **2** **8** **9**

Dehydration of **8** with *p*-TsOH in benzene gave the dehydrosabina ketone **9** as sole product (*cf.* ref. 1). Hydrogenation of the unsaturated ketone **9** was effected very smoothly, without any side reaction, by 5% Pt on $BaSO_4$ catalyst, yielding *d,l*-sabina ketone (**10**). Since the conversion of **10** into sabinene hydrate has already been described,[12, 13] we have used a slightly modified route to the latter compound.

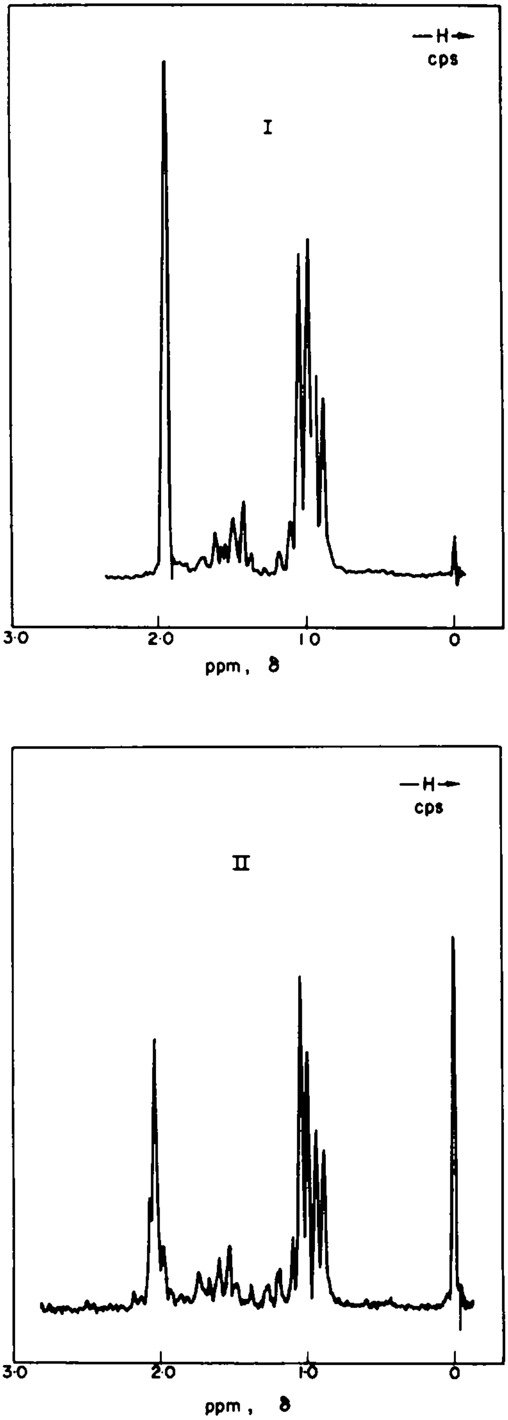
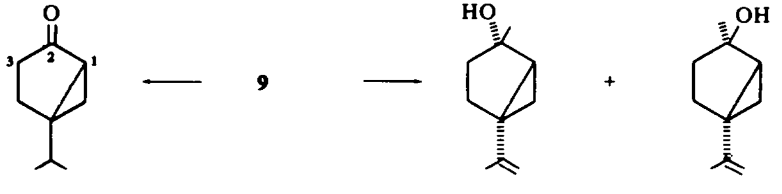
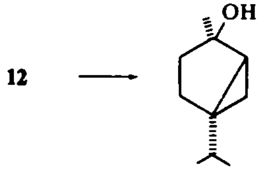


Fig 1. NMR spectrum (60 MHz) of *dl*-sabina ketone (10). (i) In CCl_4. (ii) With $CDCl_3$ added to the same solution, to make a 1:1 solvent mixture.



10 **11** **12**



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Reaction of **9** with MeLi in ether yielded two dehydrosabinene hydrates, **11** and **12**, in a ratio of 1:11. The major component, **12**, was shown to be the *cis*-isomer by its smooth catalytic hydrogenation (5% Pt on $BaSO_4$) to *dl*-*cis*-sabinene hydrate (**13**).[13] The minor component, **11**, m.p. 56–57°, was deduced to be the *trans*-isomer by comparison of its spectral and analytical data to those of **12** (see experimental).

The NMR spectra of ketones **9** and **10** in CCl_4 are interesting in that the four methylene protons of C-3 and C-4 fall into one sharp singlet at δ 2·12 for **9** and 1·95 for **10** (this apparent singlet is also mentioned by Wheeler *et al.*[19]), with a half-height width (hhw) of 2 Hz. By the addition of $CDCl_3$ to the CCl_4 solution, the same singlet of **10** spreads into a narrow multiplet, the spectrum corresponding to that published.[13, 14] (Fig 1.)

The presently described syntheses of sabina ketone and *cis*-sabinene hydrate compare favourably with the recently described methods involving inter-[13] or intramolecular[12, 14] carbene additions. The overall yield in the conversion of **1** to **9** is over 30% while the final steps occur with a high yield (**9** → **12**) or are practically quantitative (**9** → **10** or **12** → **13**).

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer spectrophotometer, Infracord Model 137. NMR spectra were observed on a Varian A-60 spectrometer. Mass Spectra were determined on an Atlas CH-4 spectrometer. VPC analysis or preparative separations were carried out on an Aerograph A-700 instrument, with columsn of 6% FFAP or 10% DC-710 on chromosorb-W and 5 or 10 feet length.

4-Isopropylidenecyclohexanone (**1**). 1,4-Cyclohexanedione was ketalized with ethylene glycol[20] and the mixture of monoketal, diketal and starting material separated by chromatography on Florisil in batches of 17–20 g. Altenratively, the monoketal was prepared from 2-carbethoxy-4,4-ethylenedioxycyclohexanone.[18, 21]

To a suspension of triphenylisopropylphosphonium iodide[22] (22 g, 0·051 mole) in ether (100 ml; N_2 atmosphere, stirring) was introduced the equivalent amount of a titrated solution of PhLi. After 20 min. the deep red colour of the ylide was fully developed. A solution of 5 g (0·032 mole) of 4,4-ethylenedioxycyclohexanone in 50 ml ether was then introduced to the ice-cooled ylide solution. The mixture was stirred (15 min) at room temp and for 2 h under reflux. A few ml of water were added to the cooled mixture and the precipitate filtered and ether washed. The combined ether washings were washed with sat. NaCl aq, dried (Na_2SO_4) and evaporated. Chromatography on Florisil (150 g) yielded upon elution with 5% ether in hexane 2·14 g (36%) of 1,1-ethylenedioxy-4-isopropylidenecyclohexane as a distillable oil.[21] δ (CCl_4) 1·4–1·6 (4H, m, ring protons), 1·67 (6H, s, vinylic Me's), 2·1–2·4 (4H, m, allylic ring protons), 3·90 (4H, s, ethylenedioxy protons). Further elution, with 40% ether in hexane, yielded 1·8 g of starting ketone.

Deketalization[18] of the 1,1-ethylenedioxy-4-isopropylidencyclohexane yielded **1** (80%) as a distillable oil. δ (CCl_4) 1·70 (s, vinylic Me's), 2·1–2·7 (m, ring protons).

4-(*Epoxyisopropylidene*)*cyclohexanone* (**2**). (a) Ketone **1** (4 g) was exposidized in CH_2Cl_2 (80 ml) at 0°, with 5·5 g of *m*-chloroperbenzoic acid. The crude epoxide (4·0 g) was crystallized from pentane, yielding 1·6 g of pure **2**, m.p. 50–51°, $\nu_{max}^{CCl_4}$ 2970, 1718, 1429, 1375, 1230, 1140, 1121, 925, 870 cm^{-1}, δ (CCl_4) 1·35 (6H, s, *gem*-dimethyl), 1·73–2·15 and 2·18–2·67 (two 4H multiplets, ring protons), (Found: C, 70·25; H, 8·98. $C_9H_{14}O_2$ requires: C, 70·10; H, 9·15%). The combined mother liquours from several preparations were purified by chromatography on Florisil, raising the average yield of **2** to *ca.* 70%.

(b) The mixture of unsaturated ketones from the distillation of γ-isopropenylpimelic acid over $BaCO_3$[15] was redistilled (b.p. 100–130°/20 mm) but could not be fractionated, all fractions showing mixtures on VPC. The recombined fractions of redistilled material (9·1 g) were epoxidized in CH_2Cl_2 with *m*-chloroperbenzoic acid (9·0 g) at 0° for 90 min. Work-up and repeated ether extraction yielded 9·4 g of a six compound mixture. Two of these, the first-eluted minor ones, totalling 7·5% of the mixture by VPC, were neglected. The following four major peaks were marked **a** (28·5%), **2** (29%), **b** and **d** (incompletely resolved; 35% together). The mixture was separated by chromatography on Kieselgel (250 g). Compound **a** was eluted with ether–hexane 1:4 and identified as cryptone[17] (4-isopropyl-2-cyclohexenone, **4**), $\nu_{max}^{CCl_4}$ 1686 cm^{-1}. δ (CCl_4) 1·00 (6H, d, J = 6·5 Hz, isopropyl Me's), 1·6–2·5 (6H, m), 5·90 d and 6·80 d (2H, AB pattern, both doublets showing a secondary splitting, J = 10 Hz, vinylic protons). *Semi-carbazone*, m.p. 197–198° (MeOH; lit.[17a] 187–188° or 184–185°[17b] for the semi-carbazone of (–)-**4**) (Found: C, 61·04; H, 8·74; N, 21·24. $C_{10}H_{17}N_3O$ requires: C, 61·51; H, 8·78; N, 21·52%).

Compound **2** was eluted with ether–hexane 3:7 and obtained as a solid (2·5 g) which was used as such in the isomerization reaction (see below).

Compounds **b** and **d** were only partly separated. Pure fractions of **b** were eluted with ether–hexane 3:2. It was obtained as an oil (0·3 g) and identified as 4-(epoxyisopropenyl)cyclohexanone, **3**, $\nu_{max}^{CCl_4}$ 1724, 1165 cm^{-1}. δ (CCl_4) 1·23 s, 1·3–2·7 m. *Semi-carbazone*, m.p. 182–183° (benzene–hexane): (Found: C, 56·61: H, 8·12; N, 19·64. $C_{10}H_{17}N_3O_2$ requires: C, 56·85; H, 8·11; N, 19·89%).

Compound **d** was also isolated as an oil (eluted with ether hexane 4:1; 1·78 g, pure by VPC) and identified as *4-hydroxy-4-isopropyl-2-cyclohexenone*, **6**, $\nu_{max}^{CCl_4}$ 3450, 1686, 943 cm^{-1}. δ (CCl_4) 0·95 d and 0·99 d (6H, $J_1 = J_2$ = 6·5 Hz, isopropyl Me's), 1·6–2·7 (5H, m), 3·95 (s, be, 1H, $O\underline{H}$), 5·85 d and 6·80 d (2H, AB pattern J = 10 Hz, vinylic protons). *Semi-carbazone*, m.p. 184–195° (MeOH) (Found: C, 56·74; H, 8·02; N, 20·07. $C_{10}H_{17}N_3O_2$ requires: C, 56·85: H, 8·11; N, 19·89%).

Mixed intermediate fractions were also collected; total material recovered from column: 7·6 g.

Dehydration of **6** over $KHSO_4$ at 170–180° yielded one compound, identified as cumenol (**7**), m.p. 63–64° (pentane). δ (CCl_4) 1·18 (6H, d, J = 7 Hz), 2·80 (1H, quintet, J = 7 Hz), 6·85 (AB-like pattern of 4 aromatic protons), 1·85 (s, $O\underline{H}$).

1-(1'-*Hydroxy*-1'-*methyl*)*ethylbicyclo*[3.1.0]*hexan*-4-*one* (7-*hydroxysabina ketone*, **8**). (a) To epoxide **2** (1·1 g) in EtOH (5 ml) were added 5 ml of 2N NaOH and the solution refluxed for 20 min. EtOH was removed at reduced pressure and sat. NaCl aq added to the residue, which was CH_2Cl_2 extracted. The dried solution yielded on evaporation 1·1 g of an oil showing one peak on VPC, which distilled to yield pure **8**, b.p. 130–140° (bath temperature)/1 mm, $\nu_{max}^{CCl_4}$ 3350, 2900, 1718, 1379, 1242, 1190, 1124, 1030, 950, 935 cm^{-1}. δ (CCl_4) 0·83–1·05 (1H, m), 1·15 (4H, s, Me), 1·25 (3H, s, Me), 1·25–2·20 (6H, m), 3·40 (1H, s, $O\underline{H}$).

(b) The epoxide **2** (2·1 g) was refluxed in a solution of EtONa in EtOH (25 ml; 0·45 g Na) for 15 min. Work-up as above yielded 2·0 g of practically pure **8** (VPC and NMR), which was distilled for further purification (Found: C, 70·30; H, 9·05; $C_9H_{14}N_2$ requires: C, 70·10; H, 9·15%).

1-*Isopropenylbicyclo*[3.1.0]*hexan*-4-*one* (**9**). The keto-alcohol **8** (1·7 g) was boiled in benzene (20 ml) with 85 mg of TsOH for 20 min., with azeotropic elimination of water. VPC (DC–710) then showed the absence of starting material and the formation of one product only. A few drops of pyridine and pentane (20 ml) were added to the cooled solution and the precipitate formed was filtered. The residual oil obtained upon evaporation of the solvent was distilled to yield 0·75 g (50%) of pure **9**, b.p. 85–90° (bath temperature)/1 mm, $\nu_{max}^{CCl_4}$ 1730, 1182, 1029, 965, 930, 910, 893 cm^{-1}. δ (CCl_4) 1·0–1·55 (2H, m), 1·74 (s, br, vinylic methyl, hhw 3 Hz), *ca.* 1·8–2·0 (1H, m), 2·12 (4H, s, C-3 and C-4 methylenes, hhw 2 Hz), 4·92 (s, br, 2H, $—C{=}C\underline{H}_2$) (Found: C, 79·60; H, 8·71. $C_9H_{12}O$ requires: C, 79·37; H, 8·88%).

d,l-*Sabina ketone* (**10**). The unsaturated ketone **9** (270 mg) was shaken in EtOAc (20 ml) with 100 mg of 5% Pt on $BaSO_4$ catalyst (The American Platinum Works, Newark, N.J.) under H_2, until it had ceased (59·4 ml, 32 min). VPC analysis (DC-710) during and after hydrogenation showed the disappearance of starting material and formation of one product. Filtration of catalyst, elimination of solvent and distillation of the residue yielded pure **10**, with physical properties and spectra in good accord with those published.[13,14,19] Mass spectrum *m/e* 138 (M^+). *Semi-carbazone*, m.p. 156–157° ($MeOH\text{-}H_2O$), mass spectrum *m/e* 195 (M^+) (Found: C, 61·51; H, 8·55; N, 21·40. $C_{10}H_{17}N_3O$ requires C, 61·51; H, 8·78; N, 21·52%).

Cis *and* trans-*dehydrosabinene hydrates* (**11** and **12**). Dehydrosabina ketone (**9**, 520 mg) in ether (10 ml) was added dropwise to a solution of 7 ml ~ 1N MeLi diluted with 20 ml of ether (stirring and N_2 atmosphere) at 0°. The solution was then refluxed for 15 min, cooled and decomposed with sat. NH_4Claq. The ether extracts were washed with saturated NaClaq and dried. Evaporation of the ether yielded 0·69 g of an oily residue, showing two close peaks on VPC (DC-710, 90°) in a ratio of 1:10 (retention times 6·8 and 8·8 min), accompanied by impurity (retention time −20 min; < 10% of total). Chromatography on Kieselgel (20 g) and elution with ether–hexane 1:9 separated the two substances, but the first one was accompanied by the above impurity. This was distilled to yield ~ 10 mg of an easily sublimable solid. Crystallization from pentane gave fine needles, m.p. 56–57° believed to be the *trans*-Δ^7-sabinenehydrate (**11**). Mass spectrum *m/e* 152 (M^+) and higher mass fragments, of lower intensity though, at *m/e* 168 and 180. (It is believed that the substance, being very volatile, was rapidly eliminated, leaving higher concentration of impurities). δ (CCl_4) 0·25–0·9 (3H, m), 1·17 (s, $O\underline{H}$), 1·23 (3H, s, Me) 1·3–2·1 (4H, m), 1·62 (s, br, 3H, vinylic methyl), 4·70 (s, br, 2H, $—C{=}C\underline{H}_2$). Sublimation at 40°/1 mm did not change the m.p. ν_{max}^{KBr} 3350, 1640, 1200, 1140, 1105, 925, 875 cm^{-1}.

The second eluted product (410 mg of an oil) was distilled to give 310 mg of pure cis-Δ^7-*sabinene hydrate* (**12**), b.p. 80° (bath temperature)/1 mm. $\nu_{max}^{CCl_4}$ 3340, 1633, 1176, 1123, 940, 880 cm^{-1}. δ (CCl_4) 0·53–1·0 (m, 3H), 1·15–2·05 m, 1·33 (s, Me), 1·63 (s, br, vinylic methyl), 3·30 (s, $O\underline{H}$), 4·75 (s, br, 2H) (Found: C, 78·72; H, 10·46. $C_{10}H_{16}O$ requires: C, 78·90; H, 10·59%).

dl-cis-*Sabinene hydrate* (**13**). Hydrogenation of **12** was carried out, as for **10** above, on 200 mg, with 80 mg of the Pt catalyst. Distillation yielded pure **13**, b.p. 80–90° (bath temperature)/1 mm, m.p. 18–20° (lit.[23] *l-cis*-sabinene hydrate; 36–37°). IR and NMR data in complete agreement with those published.[13]

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