

Reduction of Conjugated Cyclopropyl Ketones with Lithium in Liquid Ammonia

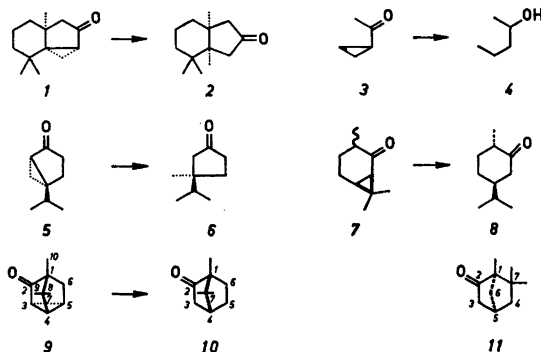
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The reduction of conjugated cyclopropyl ketones with lithium in liquid ammonia is shown to proceed *via* a highly stereospecific opening of the three-membered ring. The steric course of the reductions so far investigated appears to be determined by the configuration of the starting material. The cyclopropane bond which is cleaved is the one possessing maximum overlap with the π -orbital of the carbonyl group.

In connection with studies on the configuration of thujopsene the reduction of the cyclopropyl ketone (1) with lithium in liquid ammonia was investigated.¹ The reaction product, obtained in almost quantitative yield, was shown to possess structure (2). This reaction is analogous to the reduction of methylocyclopropyl ketone (3) with sodium and ammonium sulphate in liquid ammonia, where a mixture of starting material and pentan-2-ol (4) was obtained.²

The reaction with lithium in liquid ammonia appeared to be of general value for the stereospecific opening of the three-membered ring of a conjugated cyclopropyl ketone. To investigate this reaction in more detail, some further compounds have been studied.



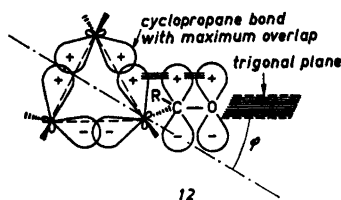
The reduction of (–)-sabinaketone (5) * with lithium in liquid ammonia gave (*R*)-(+)-3-methyl-3-isopropylcyclopentanone (6) the structure of which is firmly established by means of infrared and proton magnetic resonance studies.

Compound (6) exhibits an infrared band at 1738 cm^{-1} , characteristic of a five-membered ring ketone, and a band at 1420 cm^{-1} due to CH_2 -groups adjacent to the carbonyl function. The latter band has an integrated intensity almost double that of sabinaketone. Furthermore, the compound exhibits bands characteristic of a single methyl group (1375 cm^{-1}) and of an isopropyl group (1365 and 1386 cm^{-1}). The proton magnetic resonance spectrum of the reduction product is also in full accordance with structure (6). A signal at $\delta\ 0.92$ ppm (3 H) is assigned to the tertiary methyl group and a doublet at $\delta\ 0.93$ ppm (6 H, $J\ 6.5$ cps) to the methyls of the isopropyl group. The ring protons and the tertiary proton of the isopropyl group exhibit a complex signal group centered at about $\delta\ 1.9$ ppm (7 H).

On reduction with lithium in liquid ammonia (+)-carone (7) gave a product which was identified as (–)-carvomenthone (8) containing small amounts of the C(3)-isomer, (–)-isocarvomenthone.

The reduction of (+)-pericyclocamphanone (9) gave (+)-camphor (10) in an almost quantitative yield. The product was identified by a direct comparison with an authentic sample. No other monomeric products, such as the other possible ring cleavage product (11), could be detected in the reaction mixture.**

The steric course of the reductions so far investigated appears to be determined by the configuration of the starting material. The cyclopropane bond which is cleaved is the one possessing maximum overlap with the π -orbital of the carbonyl group (*cf.* formula 12; a schematic representation of a conjugated cyclopropylketone).



The highly stereospecific reduction of (+)-pericyclocamphanone (9) is remarkable. The steric repulsion between the C(8)-methyl group and the C(6)-proton, and between the C(9)-methyl group and the carbonyl group may slightly distort the ring system and thus cause the π -orbital of the carbonyl group to overlap sufficiently with the C(3)-C(9)-bond of the cyclopropane ring.

Further studies are needed in order to obtain more information about the mechanism of this type of reduction. The possible application of the reaction

* For the absolute configuration see Refs. 3, 4.

** A small amount of a dimeric product was detected by vapour phase chromatography.

to other types of conjugated three-membered ring ketones (e.g. epoxy-ketones) is also of interest.

EXPERIMENTAL

Vapour phase chromatographic (VPC) examinations were made on a "Pye Argon Chromatograph"; column length 1.2 m; internal column diameter, 5 mm. Unless otherwise stated a polyester column was used (3 % diethyleneglycol succinate on 120–140 mesh "Chromosorb W"; column temperature 95°). Preparative VPC separations were made on an "Aerograph Autoprep A 700" instrument equipped with a polyester column (10 % diethyleneglycol succinate on 60–80 mesh "Chromosorb W"; column length, 10'; internal column diameter, 1/4"; column temperature, 112°). Rotations were measured in chloroform.

Reductions with lithium in liquid ammonia. Lithium (0.25 g) was added with stirring to a mixture of cyclopropyl ketone (1 g) in liquid ammonia (50 ml). The stirring was continued for 2 h. Ammonium chloride was added until the blue colour of the reaction mixture disappeared. Ether (30 ml) was added and the ammonia was allowed to evaporate. The product, worked up in the usual way, was treated with an aqueous chromic acid solution according to the procedure of Brown *et al.*⁵ in order to transform small amounts of alcohols present in the reaction mixture to the corresponding ketones.

Reduction of (-)-sabinaketone (5). (-)-Sabinaketone with m.p. 14° and $[\alpha]_D -22^\circ$ (c 1.93) was obtained from an ozonisation of sabinene.¹ On reduction with lithium in liquid ammonia this ketone gave a mixture of (*R*)-(+)-3-methyl-3-isopropylcyclopentanone (6) (96 % of the reaction product) and unchanged starting material (4 %) as shown by VPC analysis. The relative retention time (sabinaketone taken as 1) for ketone (6) was 0.50. The main product, (*R*)-(+)-3-methyl-3-isopropylcyclopentanone (6), was separated by preparative VPC and had the following properties: $[\alpha]_D^{25} +162^\circ$ (c 1.63); n_D^{25} 1.4497. (Found: C 77.0; H 11.5. C₉H₁₆O requires C 77.1; H 11.5). The infrared data, see p. 1290, are those obtained from a spectrum of the pure oil. The proton magnetic resonance spectrum (p. 1290), was recorded from a carbon tetrachloride solution on a Varian A-60 instrument (60 Mc/s). The chemical shifts are given in ppm from tetramethylsilane as internal standard.

The ketone (6) formed a *semicarbazone*, m.p. 190–192° (decomp.) and a *monobenzylidene derivative*, m.p. 95–97°, $[\alpha]_D +157^\circ$ (c 2.81), $\lambda_{\max}^{\text{EtOH}}$ 296 μ (ϵ 23 900). The mass spectrum of the monobenzylidene derivative exhibits a molecular peak at 228 *m/e* and characteristic fragmentation peaks at *M*–15 (CH₃), *M*–28 (CO), *M*–43 (C₃H₇), and *M*–90 (C₆H₅·CH, benzylidene group). Even under vigorous conditions the yield of a dibenzylidene derivative was low as shown by VPC analysis (1 % silicon rubber gum, "E 301", on 100–120 mesh "Gas-Chrom P"; column temperature 154°; the relative retention time for the dibenzylidene derivative was 1.34 with the "monoderivative" taken as 1). Owing to shortage of material the dibenzylidene derivative was not separated.

Reduction of (+)-carone (7). A crude sample of (+)-carone was obtained from (+)-carvone $[\alpha]_D +82^\circ$ (c 2.10); n_D^{20} 1.4712, *via* the dihydrocarvone hydrochloride according to the method of Richter, Wolff and Presting⁶ (*cf.* also Ref. 7). This sample was dissolved in methylene chloride and treated with ozone at –70° until excess ozone was present. Water was added and the methylene chloride was evaporated under reduced pressure. The organic residue, dissolved in light petroleum (b.p. 40–60°) was absorbed on alumina (standard, activity I). Small amounts of ether (about 5 %) in light petroleum eluted (+)-carone which was homogeneous to VPC analysis and had the following properties: $[\alpha]_D +186^\circ$ (c 1.81); n_D^{25} 1.4760. Lit.: $[\alpha]_D +134^\circ$,⁶ $+173.8^\circ$,⁷ n_D^{16} 1.478,⁶ $n_D^{18.5}$ 1.4787.⁷

(+)-Carone (7), on reduction with lithium in liquid ammonia, gave a mixture of (–)-carvomethone (8) (85 % of the reaction product) and unchanged starting material (15 %) as shown by VPC analysis. The relative retention time for (–)-carvomethone was 0.77 with (+)-carone taken as 1. The main product was separated by preparative VPC and had the following properties: $[\alpha]_D -18^\circ$ (c 2.31); n_D^{25} 1.4538. Semicarbazone: m.p. 187–190°; $[\alpha]_D -14^\circ$ (c 2.08). The literature values for (–)-carvomethone are:⁸ $[\alpha]_D -16^\circ$; n_D^{17} 1.4548; semicarbazone, m.p. 192° and $[\alpha]_D -13.3$ (c 2.0). The minor discrepancies between the properties of the reduction product and those of a pure sample

seem to be due to the fact that the former contains small amounts of (–)-isocarvomenthone ($[\alpha]_D -56.5^\circ$; semicarbazone: m.p. $171-172^\circ$ and $[\alpha]_D -117^\circ$).⁸ In order to settle the identity of the reduction product, a sample of (–)-carvomenthone was prepared by catalytic hydrogenation of (–)-dihydrocarvone (containing small amounts of its C(3)-isomer, isodihydrocarvone). This sample contained small amounts of (–)-isocarvomenthone as shown by its properties: $[\alpha]_D -15^\circ$ (c 2.29); $n_D^{24} 1.4533$; semicarbazone, m.p. $180-186^\circ$ and $[\alpha]_D -18^\circ$ (c 2.45). The infrared spectrum of the sample was identical with that of the product obtained from the reduction of (+)-carvone. The infrared spectra of the two semicarbazones were also identical and the mixed m.p. of the two derivatives was undepressed ($180-186^\circ$).

Reduction of (+)-pericyclocamphanone (9). The reduction with lithium in liquid ammonia of (+)-pericyclocamphanone,⁹ m.p. $165-169^\circ$ (sealed tube), $[\alpha]_D +66.3^\circ$ (c 2.52), gave a solid product. On VPC analysis (+)-camphor and (+)-pericyclocamphanone were found not to separate on the column used. On a VPC analysis at 154° a very small peak, with an intensity corresponding to less than 1 % of the reaction product, was observed. The retention time of this minor peak corresponded to a C_{20} -compound. An analysis by thin layer chromatography (Merck's Silica gel "G"; liquid phase, 25 % ether in light petroleum; (+)-camphor, R_F 0.45; (+)-pericyclocamphanone, R_F 0.39) showed that the reduction product consisted of almost pure (+)-camphor.

A sublimation of the product at slightly reduced pressure (ca. 30 mm Hg) yielded (+)-camphor (10), m.p. and mixed m.p. $177-179^\circ$, $[\alpha]_D +47.9$ (c 2.2) and infrared spectrum identical with those of an authentic sample. The yield of (+)-camphor was about 90 %. A ca. 10 % loss was incurred during the working-up procedure owing to the high vapour pressure of the compound.

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