378. *Aspects of Stereochemistry. Part III.* Metal Reduction of Some Allylic Systems.*

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Lithium–ethylamine reduction of an optically active carvotanacetyl methyl ether yields racemic *p*-menth-1-ene showing that the reaction proceeds *via* a symmetrical intermediate. Conversion of an allylic alcohol into an olefin is often conveniently performed by metal–amine reduction of an ester, although if the hydroxyl group is hindered prior formation of an ester or ether may not be necessary.

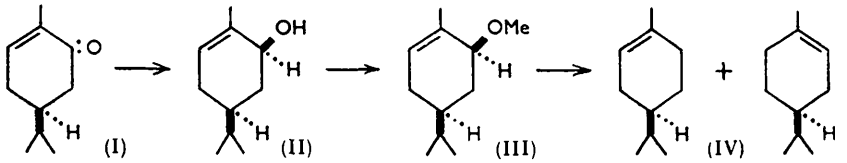
Seeking improved routes to certain olefins in the steroid series, we focused our interest on reduction of allylic systems by dissolving metals. Previous work,[1,2] mainly with sodium–ammonia, has demonstrated that allylic alcohols afford olefins or olefin mixtures, often accompanied by the dihydro-alcohol. Allylic ethers also yield olefins but no observations have been reported on the more easily prepared allylic esters.[3]

After migration of the olefinic bond during reduction had been observed in the steroid series, the nature of the intermediate stage was examined by reduction of a simpler system, (+)-*cis*-carvotanacetol (II) [readily prepared from (+)-carvone], where the extent of rearrangement on reduction could be ascertained from the optical rotation of the *p*-menth-1-ene produced, as the original and the rearranged olefin are enantiomorphic (IV). Reduction of the methyl ether (III) of (+)-*cis*-carvotanacetol gave racemic *p*-menthene (IV), the reaction proceeding therefore *via* a symmetrical intermediate. This intermediate is probably best regarded as a mesomeric carbanion resulting from successive addition of two electrons to the ether (III) (cf. Birch [1]).

* Part II, preceding paper.

[1] Birch, *Quart. Rev.*, 1950, **4**, 69.
[2] Watt, *Chem. Rev.*, 1950, **46**, 330.
[3] Part of this work was described in a preliminary note, *Chem. and Ind.*, 1956, 522.

The (+)-*cis*-carvotanacetol (II) was prepared by reduction with lithium aluminium hydride of (+)-carvotanacetone (I), the *cis*-alcohol (predominant in the mixture) being separated as its *p*-nitrobenzoate. Previous workers [4] had reduced (+)-carvotanacetone by the Ponndorf method obtaining the high-melting *p*-nitrobenzoate as the main product



and the *cis*-isomer only as by-product. From optical-rotation data Mills [5] has suggested that the higher-melting ester is a *cis–trans*-mixture, and the lower melting the pure *cis*-ester. For the lithium reduction it was desirable to use a single geometrical isomer, and the obtaining by reduction with hydride of an apparently much higher proportion of the *cis*-alcohol (II) was therefore advantageous. As allylic esters, *e.g.* benzoates, are usually reduced by lithium to olefins (below), reduction of the intermediate *cis*-*p*-nitrobenzoate was also attempted. No hydrocarbon was isolated and a red colour developed in place of the usual blue, indicating preferential attack on the nitro-group. Reduction with lithium of the *cis*-alcohol itself was not attempted as previous work [1] and our own results with steroids (below) had established that the reduction is more difficult and that prolongation of the reaction time was not desirable as isolated olefinic bonds can be reduced by dissolving metals.[6-8]

In the steroid series the reaction was studied in search for an improved route to cholest-4-ene (VI). Reduction by lithium aluminium hydride of cholest-4-en-3-one gave an alcohol mixture from which the major component, the 3β-alcohol, could be readily obtained as the benzoate (V; R = Bz). A good yield of cholest-4-ene was then obtained by reduction of the benzoate with lithium, and high yields were also obtained by similar reduction of the acetate and methyl ether (V; R = Ac and Me, respectively). Cholest-4-ene so obtained does not require purification *via* the dibromide, and this together with the reproducibility of the method represent improvements over the previous mercaptal route. In these reductions alternative reactions of the Bouveault–Blanc type (regenerating the 3β-alcohol) do not occur significantly. The assistance given by the double bond was shown by reduction of cholestanyl benzoate, cholestanol but no cholestane being produced.

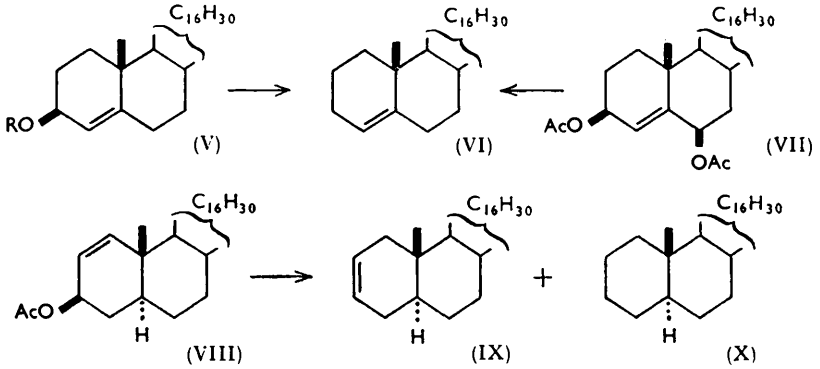
Reduction of the diacetoxy-olefin (VII) yielded slightly less pure cholest-4-ene. With this diester some cholest-5-ene might be formed by initial reductive scission of the 3-ester group followed by further reaction *via* the $C_{(4)}$–$C_{(5)}$–$C_{(6)}$ allylic carbanion.

The general procedure for these experiments was to add an excess of lithium to a solution of the compound in ethylamine.[8] Most steroids are moderately soluble in this amine but only sparingly soluble in boiling liquid ammonia.[9] Thus addition of an ethereal solution of the 3β-benzoate (V; R = PhCO) to lithium dissolved in ammonia gave only a low yield of cholest-4-ene, most of the ester being unchanged owing to precipitation. Reduction by lithium–ethylamine of the 3β-alcohol (V; R = H) afforded mostly starting material together with about 10% of cholest-4-ene : in this case the alcohol is probably converted rapidly into the difficultly reducible anion.

Cholest-2-ene (IX) is more stable than cholest-1-ene; [10,11] in the preparation of the latter from 3β-chlorocholest-1-ene, rearrangement could be avoided only by reduction with

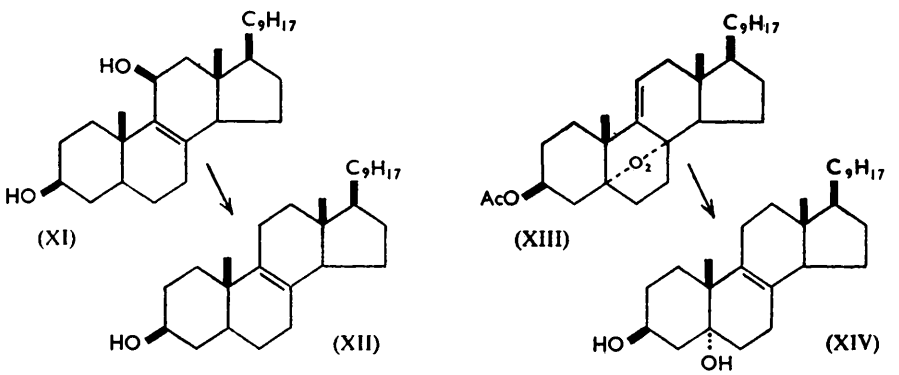
[4] Read and Swann, *J.*, 1937, 239.
[5] Mills, *J.*, 1952, 4976.
[6] King, *J.*, 1951, 898.
[7] Greenfield, Friedel, and Orchin, *J. Amer. Chem. Soc.*, 1954, **76**, 1258.
[8] Benkeser, Sauve, and Schroll, *ibid.*, 1955, **77**, 3378.
[9] Birch, *J. Proc. Roy. Soc. N.S.W.*, 1949, **83**, 249.
[10] Henbest, Meakins, and Wood, *J.*, 1954, 800.
[11] Turner, XIVth Internat. Congr. Pure and Applied Chem., 1955, Abs. paper 594.

lithium aluminium hydride in a poorly ionising solvent.[12] As reduction with metal–amine proceeds *via* mesomeric carbanions it was not surprising to obtain cholest-2-ene from reduction by lithium of 3β-acetoxycholest-1-ene (VIII). The course of this part of the reaction is thus controlled thermodynamically and not by ease of access of the proton donor to the intermediate carbanion [$C_{(1)}$ more hindered than $C_{(3)}$]. Cholestane (X) was the other product identified: its origin is uncertain as both cholest-1- and -2-enes are reduced to the saturated hydrocarbon by treatment with a large excess of lithium in ethylamine.



The only previous method of obtaining Δ^8-steroids (apart from some rather inaccessible natural steroids, *e.g.* zymosterol) involved hydrogenation of an 8 : 14-diene to a mixture of Δ^8- and $\Delta^{(8)14}$-olefins followed by a fractional crystallisation.[13]

For the new method, a Δ^8-11-ketone (of the ergostane series) was first reduced by lithium aluminium hydride to the 3β : 11β-diol (XI). This with lithium–ethylamine then afforded the Δ^8-compound (XII). Careful hydrogenation of its acetate then reduced the side-chain double bond to give the known 3β-acetoxyergost-8-ene. The more complete reduction of this 11-hydroxy-group, compared with that of the 3β-alcohol (V; R = H) described previously, may be a consequence of its more hindered position ensuring by steric inhibition of anion solvation [14] that not all of the 11-alcohol is in the (more heavily solvated) unreactive anionic form. Reduction of the 3β : 11β-diol was attempted as difficulty was expected in the preparation of esters or ethers from the hindered alcohol because of the ease of dehydration to the 7 : 9-diene.



Reduction by lithium of an 8-oxygenated-$\Delta^{9(11)}$-system should proceed *via* a similar $C_{(8)}$–$C_{(9)}$–$C_{(11)}$ anion and in agreement with this, the epidioxide (XIII) also afforded a

[12] Henbest and Wilson, *J.*, 1956, 3289.
[13] Barton and Cox, *J.*, 1949, 214.
[14] Cf. H. C. Brown, *J.*, 1956, 1248.

Δ^8-compound (XIV) (fission of the O–O bond probably first occurring). In this case the Δ^8-structure is assigned on the basis of ultraviolet absorption [15] and molecular-rotation data.[13] In contrast to the corresponding 5-hydrogen compound, the double bond was not isomerised into the $\Delta^{8(14)}$-position on prolonged shaking with hydrogen–platinum–acetic acid; the double bond in a Δ^7-5α-alcohol migrates to the $\Delta^{8(14)}$-position under these conditions,[16] but noticeably more slowly than in the 5-hydrogen compound.

An advantage of these methods over the previous route to Δ^8-compounds is that side-chain double bonds are not reduced; the procedure should thus be adaptable to the synthesis of natural Δ^8-compounds of the steroid and trimethylsteroid series.

[*Added later on Manuscript.*—Reduction with lithium–ethylamine of 4β-acetoxycholest-5-ene or 6β-acetoxycholest-4-ene has been found to give a similar mixture of cholest-4-ene (45—50%) and cholest-5-ene (50—55%).]

Experimental

(+)-cis-*Carvotanacetol* (II).—(+)-Carvone (from caraway oil) was hydrogenated in the presence of Adams's catalyst until 1 mol. of hydrogen had been absorbed. Purification of the product *via* its bisulphite compound yielded (+)-carvotanacetone, b. p. 105—106°/17 mm., $[\alpha]_D$ +56° (homog.), n_D^{20} 1·4794 {lit. values [4] $[\alpha]_D$ +55·2° (homog.), n_D^{21} 1·4791}. A solution of (+)-carvotanacetone (10 g.) in dry ether (20 c.c.) was added to a stirred solution of lithium aluminium hydride (0·85 g.) in dry ether (30 c.c.) during 0·5 hr. The mixture was heated under reflux for 1 hr., and then treated with an excess of 5% sodium hydroxide solution. The ether solution yielded the carvotanacetol mixture (9·8 g.), which (9 g.) in light petroleum (150 c.c.) containing pyridine (5·1 g.) was treated (with stirring) with a solution of *p*-nitrobenzoyl chloride (11 g.) in dry benzene (75 c.c.), the temperature being kept below 35°. After being stirred for 3 hr. the solution was shaken with water (100 c.c.) and filtered. After being washed with 5% sodium hydroxide solution and dried, the solution was evaporated to give the ester mixture (14·5 g.). This was separated by fractional crystallisation from light petroleum into the *cis*-ester (5·5 g.) (more soluble), m. p. 60—61°, $[\alpha]_D$ −51° (in $CHCl_3$), $[\alpha]_D$ −32° (in benzene), and the higher-melting ester (probably *cis–trans* mixture), m. p. 93—94°. For the lower-melting ester Read and Swann [4] record m. p. 60—62°, $[\alpha]_D$ −51° (in $CHCl_3$).

A solution of the *cis*-ester (5 g.) in methanolic potassium hydroxide solution (42 c.c.; 5%) was heated under reflux for 10 min. Most of the methanol was removed under reduced pressure and the carvotanacetol isolated with light petroleum. Distillation gave pure (+)-cis-*carvotanacetol* (2·3 g.), b. p. 64°/0·5 mm., m. p. 22°, $[\alpha]_D$ +56·5° (in benzene) (Found: C, 77·8; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%).

Preparation and Reduction of (+)-cis-*Carvotanacetyl Methyl Ether* (III).—The alcohol (2 g.) was added to a solution of potassium *tert.*-butoxide [from potassium (5·1 g.) and *tert.*-butyl alcohol (130 c.c.)] and methyl iodide (18·5 g.; 10 mol.) was then added with stirring during 15 min. The mixture was stirred for 2 hr. and the product then isolated with light petroleum. It was remethylated by the same procedure and the product finally fractionated to give pure *methyl ether* (0·9 g.), b. p. 63—64° (bath)/1 mm., $[\alpha]_D$ +70° (in benzene), n_D^{20} 1·4653 (Found: C, 78·3; H, 11·8. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). Infrared spectrum confirmed the presence of methoxyl (1100 $cm.^{-1}$ band) and the absence of hydroxyl group.

Freshly cut lithium slices (0·4 g.) were added rapidly to a solution of the methyl ether (0·8 g.) in ethylamine (25 g.), and the mixture was shaken mechanically for 5 min. longer than required for the initial appearance of a blue colour. Isolation with ether and distillation afforded optically inactive *p*-menth-1-ene (0·36 g.), b. p. 175° (bath), n_D^{21} 1·4570 (lit. values [17] for the racemic compound b. p. 174—175°, n_D^{21} 1·4551). The infrared spectrum of the olefin was identical with that of a sample of (+)-*p*-menth-1-ene, $[\alpha]_D$ +105° (homog.). prepared by partial hydrogenation of (+)-limonene.

Concentrated hydrochloric acid (0·35 c.c.) was added to a mixture of the hydrocarbon (0·3 g.; from the reduction), pentyl nitrite (0·3 g.), and acetic acid (0·1 c.c.) so that the temperature did not rise above −10°. After the mixture had been kept at −15° for 10 min., the

[15] Bladon, Henbest, and Wood, *J.*, 1952, 2737.
[16] Clayton, Henbest, and Jones, *J.*, 1953, 2015.
[17] Wallach, *Annalen*, 1911, **381**, 58.

solid product (0·225 g.) was collected. Crystallisation from acetone gave the pure optically inactive nitrosochloride, m. p. 94—95° (lit. value [17] m. p. 95—96°, for the racemic compound).

General Technique for Reduction of Steroids by Lithium–Ethylamine.—The steroid was dissolved in dry ethylamine in a glass-stoppered bottle. Small pieces of freshly cut lithium were added and, when the initial effervescence had ceased, the stopper was fitted firmly and the mixture shaken vigorously until a blue colour persisted. The bottle was cooled to 0° before opening, the steroid then being isolated with ether in the usual way. As considerable pressure develops, a tube with stopcock was often used in place of the stopper for periodical release of pressure.

Cholest-4-ene (VI).—(*a*) 3β-Acetoxycholest-4-ene (0·4 g.) was reduced with lithium (0·1 g.) in ethylamine (20 c.c.). The product was isolated and a light-petroleum solution filtered through alumina (25 g.) to give material which on crystallisation from methanol–acetone gave cholest-4-ene (0·325 g.), m. p. 83—84°, $[\alpha]_D$ +73°.

(*b*) Similar reduction of 3β-methoxycholest-4-ene (0·195 g.) with lithium (0·1 g.) in ethylamine (15 c.c.) afforded cholest-4-ene (0·147 g.), m. p. 82—83°, $[\alpha]_D$ +73°.

(*c*) Reduction of 3β-benzoyloxycholest-4-ene (0·4 g.; see below) with lithium (0·1 g.) in ethylamine yielded cholest-4-ene (0·224 g.), m. p. 83—84°, $[\alpha]_D$ +75°. Material prepared by the thiol method followed by purification *via* the dibromide [18] had m. p. 82—83·5°, $[\alpha]_D$ +76°.

(*d*) Reduction of 3β : 6β-diacetoxycholest-4-ene (0·4 g.) with lithium (0·2 g.) in ethylamine (20 c.c.) gave cholest-4-ene (0·286 g.), m. p. 77—79°, $[\alpha]_D$ +68°.

(*e*) Cholest-4-en-3β-ol (0·26 g.) was reduced with lithium (0·1 g.) in ethylamine (15 c.c.), and the product (0·236 g.) was chromatographed on deactivated alumina (20 g.). Elution with light petroleum gave cholest-4-ene (35 mg.), m. p. 81—82°. Elution with benzene–ether (4 : 1) afforded starting alcohol (0·147 g.), m. p. and mixed m. p. 132—134°.

Reduction of Cholestanyl Benzoate.—The steroid (0·2 g.) was reduced with lithium (50 mg.) in ethylamine (10 c.c.) by the general technique. Chromatography of the product on alumina (10 g.) did not give a hydrocarbon fraction, but elution with benzene–ether (9 : 1) afforded cholestanol (0·11 g.), m. p. and mixed m. p. 140—141°.

3β-*Benzoyloxycholest-4-ene* (V; R = Bz).—A solution of cholest-4-en-3-one (30 g.) and lithium aluminium hydride (5 g.) in dry ether (500 c.c.) was heated under reflux for 30 min. The steroid was isolated with ether and then treated with an excess of benzoyl chloride in pyridine at 20° for 15 min. Two crystallisations from methanol–acetone gave the pure *benzoate* (22 g.), m. p. 125—128°, $[\alpha]_D$ 0° (Found : C, 83·5; H, 10·3. $C_{34}H_{50}O_2$ requires C, 83·2; H, 10·3%).

Reduction of 3β-*Acetoxycholest*-1-*ene* (VIII).—The steroid (0·232 g.) was reduced with lithium (0·15 g.) in ethylamine (15 c.c.) (solution blue for 5 min.). The infrared spectrum of the product showed the presence of cholest-2-ene (peaks at 664 and 773 cm.$^{-1}$) and the virtual absence of cholest-1-ene (no peaks at 700 and 718 cm.$^{-1}$). A solution of the product (0·147 g.) and osmium tetroxide (0·15 g.) in ether (20 c.c.) and pyridine (5 c.c.) was kept at 20° for 3 days, then evaporated to dryness under reduced pressure, and the residue treated with an excess of lithium aluminium hydride in boiling ether solution. This material (0·107 g.) was chromatographed on deactivated alumina (10 g.). Light petroleum eluted cholestane (37 mg.), m. p. and mixed m. p. 79—81°; the infrared spectrum was identical with that of an authentic sample. Elution with ether–methanol (5 : 1) afforded cholestane-2α : 3α-diol [19] (47 mg.), m. p. and mixed m. p. 209—213°.

Cholest-1-ene (17 mg.) in ethylamine was treated with lithium (50 mg.) for 35 min. (blue for 15 min.). The infrared spectrum of the product showed the presence of only a small percentage of starting material. After treatment of the total product with osmium tetroxide as described above, pure cholestane (9 mg.), m. p. and mixed m. p. 79—81°, was obtained. In a similar experiment with cholest-2-ene (31 mg.), cholestane (24 mg.) was obtained.

Reduction of Ergosta-8 : 22-*diene*-3β : 11β-*diol* (XI).—The diol was prepared by heating a solution of 3β-acetoxy-11-oxoergosta-8 : 22-diene (0·77 g.) and lithium aluminium hydride (0·3 g.) in ether (100 c.c.) under reflux for 1 hr. Excess of reagent was decomposed with water, and the precipitated hydroxides were washed repeatedly with ether. Evaporation of the dried ether solution gave material (0·68 g.) which on crystallisation from acetone afforded the pure *diol*, m. p. 161—163°, $[\alpha]_D$ +2° (Found : C, 80·95; H, 11·25. $C_{28}H_{46}O_2$ requires C, 81·1; H,

[18] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.
[19] Henbest and Smith, *J.*, 1957, 926.

11·2%). This compound showed no light absorption in the 2400—2500 Å region. Mild acetylation gave the 3β-*monoacetate* (plates from acetone), m. p. 173—184°, $[\alpha]_D$ +12° (Found: C, 79·0; H, 10·7. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Heating a solution of this compound in acetic acid–acetic anhydride at 100° for 1 hr. gave 3β-acetoxyergosta-7 : 9 : 22-triene.

For reduction, the 3 : 11-diol (1·31 g.) in ethylamine (25 c.c.) was treated with lithium (0·4 g.), the mixture being shaken until the blue colour disappeared. The product (1·05 g.) was twice crystallised from acetone to give *ergosta*-8 : 22-*dien*-3β-*ol* (XII) (0·76 g.), m. p. 166—169°, $[\alpha]_D$ +30° (Found: C, 84·0; H, 11·45. $C_{28}H_{46}O$ requires C, 84·35; H, 11·65%). The *acetate* had m. p. 167—169°, $[\alpha]_D$ +14° (Found: C, 81·85; H, 10·7. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). This acetate (0·59 g.) in ethyl acetate (50 c.c.) was shaken with hydrogen and Adams's catalyst for 2 hr. Isolation of the pure product yielded 3β-acetoxyergost-8-ene (0·39 g.), m. p. 156—158°, $[\alpha]_D$ +22° (lit. values [13] m. p. 156—157°, $[\alpha]_D$ +22°).

Ergost-8-*ene*-3β : 5α-*diol* (XIV).—3β-Acetoxy-5α : 8α-epidioxyergost-9-ene (XIII) (2 g.) dissolved in ethylamine (100 c.c.) was reduced by the general technique except that further quantities of lithium were added in order to preserve a blue colour during 4 hours' shaking. The product (1·7 g.) on crystallisation from ethyl acetate–methanol yielded the *diol*, m. p. 215—226°, $[\alpha]_D$ +34° (Found: C, 80·75; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). Experiments had shown that longer reduction was necessary in this case, samples of the crude product being heated in ethanol containing a little hydrochloric acid to determine unchanged 8α-hydroxy-Δ^9-compound as 7 : 9-diene, the reduction being assumed to proceed *via* the 5α : 8α-diol.

Acetylation of the diol at 20° afforded 3β-*acetoxyergost*-8-*en*-5α-*ol* (needles from methanol), m. p. 188—190°, $[\alpha]_D$ +20° (Found: C, 78·7; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Ultraviolet end absorption (in EtOH): $\varepsilon_{2100} = 4400$; $\varepsilon_{2150} = 3900$; $\varepsilon_{2200} = 3400$. Normal benzoylation gave 3β-*benzoyloxyergost*-8-*en*-5α-*ol*, m. p. 165—167°, $[\alpha]_D$ +30° (Found: C, 80·5; H, 10·2. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·1%).

The $[M]_D$ changes on acetylation and benzoylation are −50° and +14°, respectively, in good agreement with those given [13] for the 5α-hydrogen series, −46° and +15°, respectively.

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