690. *Some Grignard Reactions with Cholest-4-en-3-one.*

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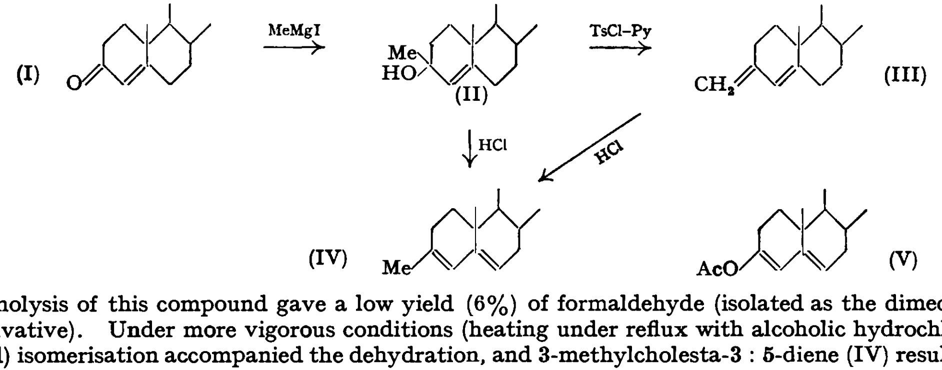
The reaction between cholest-4-en-3-one and methylmagnesium iodide gives 3-methylcholest-4-en-3-ol. In the presence of cuprous chloride 3-methylene-cholest-4-ene and 3-methylcholesta-3 : 5-diene are also formed; 1 : 4-addition to the αβ-unsaturated carbonyl system is not observed.

THE interaction of cholest-4-en-3-one (I) and methylmagnesium iodide has been found to give an αβ-unsaturated tertiary alcohol, $C_{28}H_{48}O$, which appears to be the product of normal addition to the carbonyl group. The alcohol is considered to be a molecular compound (II) of 3α-methyl-cholest-4-en-3β-ol and 3β-methylcholest-4-en-3α-ol, by analogy with the related compound (which it resembles closely in optical rotation; see table) formed by the epimeric cholest-4-en-3-ols obtained by the reduction of cholest-4-en-3-one with aluminium *iso*propoxide or lithium aluminium hydride (Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567; McKennis and Gaffney, *ibid.*, 1948, **175**, 217). The resolution of the 3-methylcholest-4-en-3-ol molecular compound was however not achieved. Although about half the material was precipitated by digitonin, the attempted isolation of the epimers according to McKennis and Gaffney's method (*loc. cit.*) failed to give pure materials. Thus treatment of the insoluble digitonide with pyridine resulted in dehydration to a diene, as shown by the brown colour developed with tetranitromethane, and crystallisation of the unprecipitated material did not afford a homogeneous specimen.

Treatment of 3-methylcholest-4-en-3-ol with toluene-*p*-sulphonyl chloride and pyridine (cf. Bann, Heilbron, and Spring, *J.*, 1936, 1274) afforded 3-methylenecholest-4-ene (III); ozonolysis of this compound gave a low yield (6%) of formaldehyde (isolated as the dimedone derivative). Under more vigorous conditions (heating under reflux with alcoholic hydrochloric acid) isomerisation accompanied the dehydration, and 3-methylcholesta-3 : 5-diene (IV) resulted, the m. p. and molecular rotation of which are similar to those of cholesta-3 : 5-diene (see table). Further support for structure (IV) is forthcoming from the optical-rotation dispersion curve



	M. p.	$[M]_D$.	$\lambda_{max.}$ (Å).	ε.
3-Methylcholest-4-en-3-ol molecular compound	115·5°	+304°	—	—
Cholest-4-en-3-ol molecular compound *	141	+324	—	—
3-Methylcholesta-3 : 5-diene	79·5	−493	2390	22,700
Cholesta-3 : 5-diene *	79	−453	2350	23,000

* Schoenheimer and Evans (*loc. cit.*).

which is similar to that of the enol-acetate of cholest-4-en-3-one (V) which also contains a $C_{(3)}$-substituted 3 : 5-diene system. The ready isomerisation of 3-methylenecholest-4-ene on treatment with hydrochloric acid is in agreement with Barton and Brooks's observations (*J.*, 1951, 268) concerning the stability of conjugated diene systems. Although the ultra-violet absorption spectra of these dienes are not entirely identical, both show maximum absorption at $\lambda = 2390$ Å, the value calculated by Woodward's method (Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold, New York, 1949, 185).

Kharasch (*J. Amer. Chem. Soc.*, 1941, **63**, 2308) found that the course of the reaction between methylmagnesium iodide and αβ-unsaturated ketones may be altered from 1 : 2- to 1 : 4-addition by catalytic amounts of cuprous chloride. When cuprous chloride was added to the Grignard reaction with cholest-4-en-3-one, considerable dehydration of the tertiary alcohol occurred with the formation of a mixture of the two dienes, which was partially separated by crystallisation.

EXPERIMENTAL.

3-*Methylcholest*-4-*en*-3-*ol*.—The Grignard reagent prepared from magnesium (0·81 g.), methyl iodide (4·7 g.), and dry ether (20 ml.) was cooled to 0° and a solution of cholest-4-en-3-one (10·6 g.) in dry ether (70 ml.) and dry benzene (5 ml.) was added during 30 minutes. The mixture was heated under reflux for 15 minutes, set aside for 30 minutes, and poured on crushed ice (80 g.) and ammonium chloride (8 g.). The ethereal extract was dried (Na_2SO_4) and evaporated. The residue on crystallisation from acetone–methanol gave 3-*methylcholest*-4-*en*-3-*ol* (7·73 g.) as needles, m. p. 114—115·5°, $[\alpha]_D^{19}$ +76° (*c*, 1 in benzene) [Found : (i) on a specimen dried at 56°/0·1 mm. for 1 hour : C, 82·3; H, 11·9. $C_{28}H_{48}O,\frac{1}{2}MeOH$ requires C, 82·1; H, 12·1%; (ii) on a specimen dried at 56°/0·1 mm. for 18 hours : C, 83·6; H, 12·1; active hydrogen, 0·26. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1; Active hydrogen, 0·25%]. The compound gave a pale yellow colour with tetranitromethane in chloroform, and a strong Rosenheim reaction.

The residual mother-liquors from the crystallisation afforded, on evaporation, cholest-4-en-3-one, m. p. 78—80°.

3-*Methylcholesta*-3 : 5-*diene*.—3-Methylcholest-4-en-3-ol (0·6 g.) was heated under reflux for 2 hours with N/30-ethanolic hydrochloric acid (50 ml.). After removal of the solvent the residual 3-*methylcholesta*-3 : 5-*diene* crystallised from methanol–acetone in laths, m. p. 79—79·5°, $[\alpha]_D^{19}$ −129° (*c*, 1 in chloroform). The diene gave a yellow-brown colour with tetranitromethane in chloroform, which faded rapidly when the solution was kept. Light absorption in *cyclo*hexane : Maxima at 2390 Å ($\varepsilon = 22{,}700$) and 2310 Å ($\varepsilon = 21{,}500$) (Found : C, 87·2; H, 12·2. $C_{28}H_{46}$ requires C, 87·9; H, 12·1%). This diene was also formed when 3-methylenecholest-4-ene was heated under reflux with ethanolic hydrochloric acid.

3-*Methylenecholest*-4-*ene*.—3-Methylcholest-4-en-3-ol (0·5 g.) was heated on the water-bath for 15 minutes with toluene-*p*-sulphonyl chloride (0·6 g.) and dry pyridine (5 ml.). The mixture was poured into N/2-hydrochloric acid, and the ether extract was washed successively with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. A solution of the residue in light petroleum (60—80°; 40 ml.) was filtered through a column of alumina (Brockmann Grade II; 1 × 10 cm.). The filtrate on evaporation afforded 3-*methylenecholest*-4-*ene* (0·45 g.) which crystallised from acetone–methanol in laths, m. p. 63—64°, $[\alpha]_D^{19}$ +50·5° (*c*, 1 in benzene) (Found : C, 87·6; H, 12·2. $C_{28}H_{46}$ requires C, 87·9; H, 12·1%). The diene gave a yellow-brown colour with tetranitromethane in chloroform which faded rapidly when the solution was kept. Light absorption in *cyclo*hexane : Maxima at 2390 Å ($\varepsilon = 17{,}260$) and 2330 Å ($\varepsilon = 16{,}230$).

Ozonolysis of 3-*Methylenecholest*-4-*ene*.—A stream of ozonised oxygen (*ca.* 4%) was passed through a solution of the diene (0·9 g.) in chloroform (20 ml.) until absorption was complete. After removal of the solvent under reduced pressure, the residue was boiled with water (20 ml.), acetic acid (5 ml.), and zinc dust (1 g.) for ¾ hour and then distilled into an ice-cold receiver. The aqueous distillate was added to a solution of dimedone (1 g.) in ethanol (15 ml.). After a while formaldehyde dimedone separated in long needles (43 mg., 6%) which, after being washed with water, had m. p. 186—188° and did not depress the m. p. of an authentic specimen.

The Catalysed Grignard Reaction.—Dry cuprous chloride (0·3 g.) was added to the Grignard reagent prepared from magnesium (0·24 g.), methyl iodide (1·6 g.), and dry ether (5 ml.). After this had been stirred at 0° for 30 minutes, a solution of cholest-4-en-3-one (2·56 g.) in dry ether (15 ml.) was added during 30 minutes. The reaction mixture was worked up as described above. A solution of the product in acetone–methanol slowly deposited crystals of 3-methylcholest-4-en-3-ol (0·21 g.). Careful concentration of the mother-liquors and addition of methanol resulted in the separation of crude 3-methylcholesta-3 : 5-diene {1·05 g., $[\alpha]_D^{19}$ −111·6° (*c*, 1 in chloroform)}, m. p. 77—78° after repeated crystallisation from acetone–methanol. Light absorption in *cyclo*hexane : Maxima at 2390 Å ($\varepsilon = 21{,}150$) and 2310 Å ($\varepsilon = 19{,}750$) (Found : C, 87·2; H, 12·2. Calc. for $C_{28}H_{46}$: C, 87·9; H, 12·1%). The optical rotation indicates the presence of 91% of 3-methylcholesta-3 : 5-diene and 9% of 3-methylenecholest-4-ene. The pure diene was obtained by heating the crude material with ethanolic hydrochloric acid whereupon the contaminant, 3-methylenecholest-4-ene, underwent isomerisation.

Evaporation of the remaining mother-liquors gave an oil which was dissolved in light petroleum (60—80°; 50 ml.) and filtered through a column of alumina (Brockmann Grade II; 2 × 20 cm.) which was washed with light petroleum (60—80°; 200 ml.) followed by benzene–methanol (49 : 1; 200 ml.). The light petroleum filtrate on evaporation afforded a solid which could not be obtained crystalline. This was purified by dissolving it in light petroleum (40—60°) and filtering it through a column of alumina (1 × 35 cm.). From the first fractions of the eluate, crude 3-methylenecholest-4-ene [260 mg.; m. p. 60—62°, $[\alpha]_D^{19}$ $-28{\cdot}9°$ (*c*, 1 in chloroform)] was obtained. The m. p. and optical rotation were unchanged by further chromatographic treatment (Found: C, 87·9; H, 12·1. Calc. for $C_{28}H_{46}$: C, 87·9; H, 12·1%). The optical rotation indicates the presence of 55% of 3-methylenecholest-4-ene and 45% of 3-methylcholesta-3 : 5-diene. Light absorption in *cyclo*hexane: Maxima at 2390 Å (ε = 19,150) and 2330 Å (ε = 18,500). The mixed m. p. with an authentic specimen of 3-methylenecholest-4-ene was 60—64°.

The benzene–methanol filtrate afforded cholest-4-en-3-one (0·9 g.; m. p. 76—78°).

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