428. 6β-*Acetylcholest*-4-*en*-3-*one and Some Derived* 6-*Substituted Steroids.*

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The enol acetate of cholest-4-en-3-one reacts with acetic anhydride–boron trifluoride to give 6β-acetylcholest-4-en-3-one. The structure of this product follows from its physical properties, and from reactions leading to 6-acetylcholest-4-ene, 6-acetylcholesta-3,5-diene, and 6-ethylidenecholest-4-en-3-one.

THE enol acetate (I) of cholest-4-en-3-one reacts rapidly (3 minutes at 20°) with acetic anhydride–boron trifluoride [1a] to give 6β-acetylcholest-4-en-3-one (IIa). Longer reaction times result in further complex changes, as shown by infrared spectroscopy. The formation of 6-acetyl-Δ^4-3-ketones in this way was reported recently by Mazur and his co-workers, though details of this work are not available.[1b]

6β-Acetylcholest-4-en-3-one was characterised by its ultraviolet ($\lambda_{max.}$ 247 mμ) and infrared spectra. It is strongly lævorotatory. Zderic and Limon [2] assigned the structure 6ξ-acetylprogesterone to a product with similar properties ($\lambda_{max.}$ 246 mμ; $[\alpha]_D$ −199°) obtained by hydration of 6β-ethynylprogesterone. The structure and stereochemistry of

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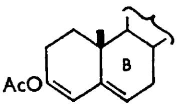
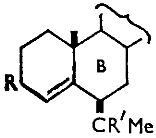
[1] (*a*) Young, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 3635; (b) Youssefyeh, Gorodetsky, Levy, and Mazur, I.U.P.A.C., 1963, Abstract A, p. 341.

[2] Zderic and Limon, *J. Amer. Chem. Soc.*, 1960, **82**, 2304.

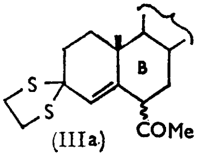
6β-acetylcholest-4-en-3-one are supported by its nuclear magnetic resonance (n.m.r.) spectrum. The spectrum showed the usual peaks for the cholestane skeleton, with additional peaks which are assigned to the acetyl methyl group (τ 7·85) and the C-2 methylene group (τ 7·65, 7·60). A doublet (τ 6·82, 6·72) is assigned to the allylic C-6 proton adjacent to a carbonyl group. The coupling constant (6 c./sec.) points to a flattening of ring B to relieve the 6β–19 steric compression; the dihedral angles between the C-7 protons and the 6α-proton are probably of the order of 30 and 90°.[3] A single sharp peak (τ 3·95), assigned to the C-4 olefinic proton, indicates the 6β-configuration for the acetyl group.[4]



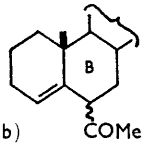
(I)



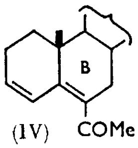
(II) a: R=R'=:O
b: R=α-H,β-OH; R'=:O
c: R = R'= H,OH
d: R=:O; R'= H,OH



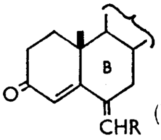
(IIIa)



(IIIb)



(IV)



(V) a: R = Me
b: R = H

Some chemical transformations of 6β-acetylcholestenone support this structural assignment. Acid-catalysed ketalisation with ethanediol gave, in 61% yield, 3,3-ethylenedioxycholest-5-ene.[5] Reaction with ethanedithiol–boron trifluoride,[6] in contrast, gave 6ξ-acetyl-3,3-ethylenedithiocholest-4-ene (IIIa), which still showed infrared bands arising from the non-conjugated acetyl group. The ethylenedithio-compound was desulphurised by Raney nickel in refluxing acetone, to give 6ξ-acetylcholest-4-ene (IIIb) as the major product. The structure was indicated by its ultraviolet and infrared spectra, and by n.m.r. peaks due to the C-6 proton (τ 7·10, 7·02), the acetyl methyl group (τ 7·85), and the C-4 olefinic proton (τ 4·30, 4·13). Like some other sterically hindered βγ-unsaturated acetyl compounds,[7,8] 6ξ-acetylcholest-4-ene was stable to acids and alkalis, with no appreciable isomerisation into the conjugated 5-ene. Two dimeric products isolated from the desulphurisation presumably arose from union of pairs of free-radical intermediates.[9] One of these products, believed to be the simple 3,3'-linked " dimer " of 6ξ-acetylcholest-4-ene, had infrared and n.m.r. spectra closely resembling those of the monomer. The other " dimer," although exhibiting the infrared bands characteristic of the non-conjugated acetyl group, had a complex ultraviolet spectrum, suggesting the presence of a triene or tetraene system. Its structure is unknown.

Sodium borohydride reduced 6β-acetylcholest-4-en-3-one to 6β-acetylcholest-4-en-3β-ol (IIb) and the diol (IIc). The infrared spectrum revealed the structure of 6β-acetylcholest-4-en-3β-ol, and oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone[10] converted it into 6β-acetylcholest-4-en-3-one. The 6β-acetyl-4-en-3β-ol was dehydrated by 10% methanolic hydrochloric acid, to give 6-acetylcholesta-3,5-diene (IV). The ultraviolet absorption of this dienone ($\lambda_{max.}$ 221 and 281 mμ) may be compared with that of the

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[3] Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

[4] Collins, Hobbs, and Sternhell, *Tetrahedron Letters*, 1963, 197; Wittstruck, Malhotra, and Ringold, *J. Amer. Chem. Soc.*, 1963, **85**, 1699.

[5] (*a*) Dauben, Löken, and Ringold, *J. Amer. Chem. Soc.*, 1954, **76**, 1359; (*b*) Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.

[6] Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.

[7] Meyer and Wolfe, *J. Org. Chem.*, 1962, **27**, 3263.

[8] Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403.

[9] Hauptmann and Wladislaw, *J. Amer. Chem. Soc.*, 1950, **72**, 707.

[10] Burn, Petrow, and Weston, *Tetrahedron Letters*, 1960, No. 9, 14.

structurally related 3-alkoxy-6-formyl-3,5-dienes[11] ($\lambda_{max.}$ 220 and 320 mμ), where the bathochromic shift of the long-wavelength band is probably due to participation of the 3-substituent. The predicted absorption maximum for 6-acetylcholesta-3,5-diene is at 290 mμ (Woodward rules). The hypsochromic shift to 281 mμ, the low extinction coefficient of this band (ε 6150), and the relatively stronger absorption (ε 9400) at 221 mμ suggest imperfect conjugation of the dienone system. This would indicate a conformation with the acetyl group forced out of the plane of the ring system by steric interference with adjacent groups.[12]

Optical rotatory dispersion data for 6-acetylcholest-4-ene derivatives.

	Extrema				Amplitude
Compound	[θ]	λ (mμ)	[θ]	λ (mμ)	*a*
(IIa)...........................	−44,500°	318	+105,000°	250	Large negative *
(IIb)	−27,500	315	+31,100	270	−586
(IIIa)	−38,400	315	+52,100	277·5	−905
(IIIb)	−24,000	317·5	+31,200 †	250	−552 †
3,3′-" Dimer " of (IIIb)	−61,800	315	+86,500	265	−741 ‡

* Two overlapping Cotton effects (negative *ca.* 300 mμ; positive *ca.* 240 mμ). † Turning point not reached. ‡ Value for " half molecule."

The diol (IIc) was oxidised selectively by dichlorodicyanobenzoquinone to give 6β-(1-hydroxyethyl)cholest-4-en-3-one (IId), the structure of which was indicated by its ultraviolet, infrared, and n.m.r. spectra. The C-4 olefinic proton again yielded only a sharp singlet (τ 4·23), indicating no coupling between the C-4 and C-6 protons. The configuration of the hydroxyethyl group is therefore defined as 6β, and oxidation of the hydroxyethyl compound with chromic acid–acetone gave 6β-acetylcholest-4-en-3-one, confirming this configuration.

Dehydration of the hydroxyethyl compound (IId) in methanolic hydrochloric acid (1%) gave 6-ethylidenecholest-4-en-3-one (Va) ($\lambda_{max.}$ 246 and 279 mμ), which, like 6-methylenecholest-4-en-3-one (Vb) (prepared from the 6-formyl enol ether[11]) is strongly dextrorotatory. The ultraviolet absorption of 6-methylenecholestenone ($\lambda_{max.}$ 260 mμ) appears to comprise two unresolved maxima, the lower near 245 mμ. The bathochromic shift of 19 mμ in the longer-wavelength absorption when the terminal methyl group is present is consistent with the Woodward rules. A product regarded[2] as 6-ethylideneprogesterone had $[\alpha]_D$ +435°, $\lambda_{max.}$ 244 and 278—280 mμ.

The optical rotatory dispersion curves for all the 6-acetyl-4-enes described above showed negative Cotton effects (see Table). The observed large amplitudes are characteristic of non-planar βγ-unsaturated carbonyl systems, and suggest that the acetyl group is constrained in a particular preferred conformation.[13]

A correlation was also noticed between the infrared spectra of the various 6-acetylcholest-4-enes, which showed a strong doublet at about 1170 and 1160 cm.$^{-1}$. This was absent from the spectra of compounds which lacked either the 6-acetyl group or the 4,5-double bond.

EXPERIMENTAL

Melting points were determined on a Kofler block and are corrected. Rotations were measured for chloroform solutions at room temperature, unless otherwise stated. Infrared spectra were recorded for carbon disulphide, and ultraviolet spectra for methanol solutions, except where otherwise stated. N.m.r. spectra were determined at 60 Mc. in deuterochloroform, with tetramethylsilane as internal standard. The alumina used for chromatography was Spence, Grade H; " deactivated alumina " refers to Grade H treated with 5% of 10% acetic acid. Light petroleum refers to the fraction of b. p. 50—70°.

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[11] Burn, Ellis, Feather, Kirk, and Petrow, *Chem. and Ind.*, 1962, 1908.

[12] Waight and Erskine, " Steric Effects in Conjugated Systems," ed. Gray, Butterworths, London, 1958, p. 73.

[13] Moscowitz, Mislow, Glass, and Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 1945.

6β-*Acetylcholest*-4-*en*-3-*one* (IIa).—3-Acetoxycholesta-3,5-diene (5 g.) in acetic anhydride (500 c.c.) was treated with freshly distilled boron trifluoride etherate (5 c.c.) at 20° for 3 min. The solution was poured into water (5 l.) and shaken vigorously to decompose the reagent. The yellow amorphous solid product, m. p. 95—107°, was dried, dissolved in boiling pentane, decolourised with charcoal, and the solution concentrated to 25 c.c., to give 6β-*acetylcholest*-4-*en*-3-*one* (2·1 g.) as needles, m. p. 141—142° (from anhydrous methanol), $[\alpha]_D$ −217° (*c* 0·64), $[\alpha]_D$ −200° (*c* 1·3 in ethanol), $\lambda_{max.}$ 247 mμ (ε 14,400), $\nu_{max.}$ 1717 and 1350 (COMe), 1681 and 866 cm.$^{-1}$ (4-en-3-one) (Found: C, 81·3; H, 11·1. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%).

Ketalisation of 6β-*Acetylcholest*-4-*en*-3-*one.*—A mixture of 6β-acetylcholest-4-en-3-one (1 g.), toluene-*p*-sulphonic acid (100 mg.), benzene (30 c.c.), and ethanediol (50 c.c.) was heated under reflux with a water separator for 10 hr. The product, isolated with ether, was filtered through alumina (10 g.) in light petroleum–benzene (5 : 1), and crystallised from ethanol, to give 3,3-ethylenedioxycholest-5-ene (680 mg.), m. p. 134—134·5°, $[\alpha]_D$ −20° (*c* 0·99) (lit.,[5a,b] m. p. 131—132°, $[\alpha]_D$ −22·8°; m. p. 134—134·5°, $[\alpha]_D$ −31·4°) (Found: C, 81·4; H, 11·3. Calc. for $C_{29}H_{48}O_2$: C, 81·25; H, 11·3%).

6ξ-*Acetyl*-3,3-*ethylenedithiocholest*-4-*ene* (IIIa).—Boron trifluoride etherate (2 c.c.) was added to a solution of 6β-acetylcholest-4-en-3-one (4 g.) in ethane-1,2-dithiol (10 c.c.). After 5 min. the paste which had formed was diluted with methanol (20 c.c.) and filtered. The *product* formed needles (3·5 g.) m. p. 207—208° (from ether–methanol), $[\alpha]_D$ −176° (*c* 0·66), $\nu_{max.}$ 1724 and 1355 cm.$^{-1}$ (COMe) (Found: C, 74·25; H, 9·9; S, 12·9. $C_{31}H_{50}OS_2$ requires C, 74·0; H, 10·0; S, 12·75%).

Desulphurisation of 6β-*Acetyl*-3,3-*ethylenedithiocholest*-4-*ene* (IIIa).—A suspension of the ethylenedithio-compound (2·5 g.) in acetone (100 c.c.) was added to Raney nickel (40 c.c. of settled sludge) in acetone (200 c.c.) which had been heated under reflux for 1 hr., and the mixture was heated under reflux, with stirring, for a further 5 hr. The hot mixture was filtered, the nickel was washed with hot ethanol, and the solvents were removed from the filtrate at 20 mm. The product, in light petroleum, was adsorbed on to deactivated alumina (230 g.). Elution with light petroleum gave 6ξ-*acetylcholest*-4-*ene* (IIIb) as prisms, m. p. 87·5—88° (from ether–methanol), $[\alpha]_D$ −140° (*c* 0·72), $\nu_{max.}$ 1721 and 1351 cm.$^{-1}$ (COMe) (Found: C, 84·6; H, 11·9. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%).

Elution with light petroleum–benzene (10 : 3) afforded a "*dimer*" (180 mg.), m. p. 244—248° (decomp.), $[\alpha]_D$ −399° (*c* 0·52), $\nu_{max.}$ 1722, 1352, and 872 cm.$^{-1}$, $\lambda_{max.}$ (light petroleum) 284 (ε 41,600), 294 (ε 48,400), 311 (ε 34,000), 318 (ε 36,000), and 328 mμ (ε 34,800) [Found: C, 84·7; H, 11·35%; *M*, 588 (decomp.; Rast). $C_{58}H_{92}O_2$ requires C, 84·8; H, 11·3%. *M*, 820]. Further elution with light petroleum–benzene (1 : 1) gave a product (190 mg.) regarded as the "3,3′-*dimer*" of 6ξ-acetylcholest-4-ene, m. p. 219—220°, $[\alpha]_D$ −112° (*c* 0·65), $\nu_{max.}$ 1722, 1352 (COMe), and 853 cm.$^{-1}$, no intense u.v. absorption [Found: C, 84·7; H, 11·5%; *M*, 720 (Rast). $C_{58}H_{94}O_2$ requires C, 84·6; H, 11·5%. *M*, 822].

Reduction of 6β-*Acetylcholest*-4-*en*-3-*one with Sodium Borohydride.*—Sodium borohydride (1·5 g.) was added with stirring, during 1 hr., to a solution of 6β-acetylcholest-4-en-3-one (3 g.) in methanol (240 c.c.). After being stirred for a further 3 hr. the solution was concentrated under a vacuum without heating, poured into dilute sulphuric acid, and the product isolated with benzene–ether (1 : 1). The resulting gum was adsorbed from light petroleum–benzene (2 : 1) on to deactivated alumina (100 g.). Elution with benzene–ether (100 : 1) gave 6β-*acetylcholest*-4-*en*-3β-*ol* (IIb) (840 mg.) as plates, m. p. 164·5—165° (from ether–light petroleum), $[\alpha]_D$ −163° (*c* 0·5), $\nu_{max.}$ 3636 (OH), 1721 and 1355 (COMe), and 1655 cm.$^{-1}$ (C:C·C:O) (Found: C, 81·05; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). Elution with ether–methanol (20 : 1) gave the diol (IIc) (1·9 g.) as a gum, $\nu_{max.}$ 3622 and 3390 cm.$^{-1}$ (OH).

Oxidation of 6β-*Acetylcholest*-4-*en*-3-*ol* (IIb).—6β-Acetylcholest-4-en-3β-ol (100 mg.) and dichlorodicyanobenzoquinone (80 mg.) were dissolved in dioxan (3 c.c.) and the solution was kept at 20° for 4 hr. The mixture was poured into 2% sodium carbonate solution, and the product was isolated with ether. Crystallisation from methanol gave 6β-acetylcholest-4-en-3-one, m. p. and mixed m. p. 141—142°, infrared spectrum identical with that of the pure material.

6-*Acetylcholesta*-3,5-*diene* (IV).—6β-Acetylcholest-4-en-3β-ol (150 mg.), in chloroform (3 c.c.) and methanol (10·5 c.c.), was treated with concentrated hydrochloric acid (1·5 c.c.) at 20° for 20 hr. The product, isolated with ether, was dissolved in light petroleum and adsorbed on to deactivated alumina (30 g.). Elution with light petroleum–benzene (100 : 3), and crystallisation from ethanol, gave 6-*acetylcholesta*-3,5-*diene* (94 mg.), m. p. 56—58°, $[\alpha]_D$ −159° (*c* 0·8), $\lambda_{max.}$ 221 (ϵ 9400) and 281 mμ (ϵ 6150), $\nu_{max.}$ 2994, 789, 759 (ethylenic CH), 1684, 1625 (dienone), and 1344 cm.$^{-1}$ (COMe) (Found: C, 84·9; H, 11·1. $C_{29}H_{46}O$ requires C, 84·8; H, 11·3%).

Oxidation of Diol (IIc).—A solution of the diol (1·5 g.) and dichlorodicyanobenzoquinone (1·2 g.) in dioxan (25 c.c.) was set aside for 6 hr., and poured into 2% sodium carbonate solution. The product, isolated with ether, was decolourised with charcoal, and crystallised from light petroleum, giving 6β-(1-*hydroxyethyl*)*cholest*-4-*en*-3-*one* (IId) (880 mg.) as needles, m. p. 168—168·5°, $[\alpha]_D$ +96° (*c* 0·61), $\lambda_{max.}$ 243—244 mμ (ϵ 14,000), $\nu_{max.}$ 3623, 3534, 1692, and 1672sh cm.$^{-1}$ (Found: C, 81·4; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%).

Oxidation of 6β-(1-*hydroxyethyl*)*cholest*-4-*en*-3-*one* (IId).—A solution of the hydroxyethyl compound (150 mg.) in acetone (12 c.c.) was treated dropwise with a slight excess of chromic acid–sulphuric acid reagent.[14] Water was added until the product crystallised. Recrystallisation from methanol gave 6β-acetylcholest-4-en-3-one (95 mg.), identical with previous samples.

6-*Ethylidenecholest*-4-*en*-3-*one* (Va).—The hydroxyethyl compound (IId) (165 mg.) was dissolved in methanol (25 c.c.) and concentrated hydrochloric acid (0·25 c.c.). After 4 hr. the solution was diluted with water. The *product*, extracted with ether and crystallised from methanol, formed needles, m. p. 81·5—82·5°, $[\alpha]_D$ +333° (*c* 0·63), $\lambda_{max.}$ 246 (ϵ 6300) and 279 mμ (ϵ 6740), $\nu_{max.}$ (Nujol) 2985, 877, 830 (ethylenic CH), 1672, 1645, and 1602 cm.$^{-1}$ (dienone) (Found: C, 84·7; H, 11·1. $C_{29}H_{46}O$ requires C, 84·8; H, 11·3%).

6-*Methylenecholest*-4-*en*-3-*one* (Vb).—This was prepared from 3-ethoxycholesta-3,5-diene by way of 3-ethoxy-6-formylcholesta-3,5-diene (amorphous, $\lambda_{max.}$ 220 and 320 mμ) by the method of Burn *et al.*,[11] and formed *prisms*, m. p. 119—121° (from methanol), $[\alpha]_D$ +253° (*c* 0·45), $\lambda_{max.}$ 260 mμ (ϵ 11,200) (Found: C, 84·5; H, 11·1. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

The authors thank Professor W. Klyne for the measurement of the optical rotatory dispersion curves, Mr. I. R. McDonald, at the Dominion Laboratory, Petone, for n.m.r. measurements, and Mr. B. W. Cox for the infrared spectra. Part of this work was carried out (by D. N. K.) in the Research Laboratories of British Drug Houses Limited, London.

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[*Received, July* 12*th*, 1963.]

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[14] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.