1100. *Aza-steroids. Part X.** *4-Aza-3-oxo-*A*-homo-5α-cholest-1-ene*

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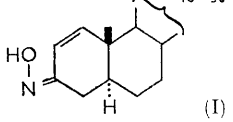
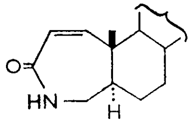
5α-Cholest-1-en-3-one oxime, m. p. 148—150°, obtained by recrystallisation from methanol, is the *anti*-isomer (III) and does not undergo the Beckmann rearrangement with thionyl chloride at 20°. The *syn*-component (I) of mixtures of the isomeric oximes, by Beckmann change with thionyl chloride at 20° gives the ε-lactam (II) in good yield.

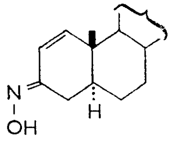
A SPECTROSCOPIC method, originated by Slomp and Wechter,[1] and used by Mazur,[2] Shoppee, Lack, and Newman,[3] and Shoppee, Akhtar, and Lack,[4] permits distinction between the *anti*- and *syn*-isomers of oximes of αβ-unsaturated cyclohexenones by examination of the chemical shift of the vinyl proton caused by the proximity of the hydroxyl group in the *syn*-isomer (*e.g.*, I).



(I)



(II)



(III)

5α-Cholest-1-en-3-one,[5,6] by oximation in refluxing methanol, furnishes a crude crystalline product whose n.m.r. spectrum shows it to contain about 16% of the *syn*-oxime (I)

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* Part IX, C. W. Shoppee and L. N. Mander, *J.*, 1965, 1971.

[1] G. Slomp and W. J. Wechter, *Chem. and Ind.*, 1962, 41.
[2] R. H. Mazur, *J. Org. Chem.*, 1963, **28**, 248.
[3] C. W. Shoppee, R. E. Lack, and B. C. Newman, *J.*, 1964, 3388.
[4] C. W. Shoppee, M. I. Akhtar, and R. E. Lack, *J.*, 1964, 3392.
[5] A. Butenandt, L. Mamoli, H. Dannenberg, L. W. Masch, and J. Paland, *Ber.*, 1939, **72**, 1617.
[6] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404.

and about 84% of the *anti*-oxime (III). Recrystallisation from methanol gives almost pure *anti*-oxime (III), m. p. 149—150°,[7] characterised as the acetate. The n.m.r. spectrum exhibits a doublet for one proton (H-1) centred at τ 3·58 ($J_{1,2} = 10$ c./sec.), a doublet for one proton (H-2) centred at τ 4·00 ($J_{2,1} = 10$ c./sec.), and signals of total intensity corresponding to two protons (H-4α, H-4β) between τ 6·9 and 7·5. Recrystallisation of the oximation product from methyl cyanide gives a mixture of the isomeric oximes, m. p. 133—135°, containing ~10% of the *syn*-oxime (I) and ~90% of the *anti*-oxime (III); in the n.m.r. spectrum the signal for the single proton (H-2) in (I) now appears as an ill-defined doublet centred at τ 3·44, overlapping the signal for the proton (H-1) in (I) and (III) at τ 3·58, whilst signals corresponding approximately to two protons (H-4α, H-4β) in (I) and (III) occur between τ 6·9 and 7·4. The signal for the hydroxylic proton is under the 4-methylene envelope since deuteration causes no apparent change in the spectrum; a new signal for the hydroxylic proton at τ 9·03 appears when the spectrum is taken at 80°. Examination of a Dreiding model of the *anti*-oxime (III) indicates some deshielding of both 4-protons by the oxygen atom of the oximino-group. The oxime mixture, m. p. 133—135°, was thermostable since the n.m.r. spectrum after melting and resolidification was completely unchanged.

Nuclear magnetic resonance data (τ units)

	1-H	2-H	$J_{1,2}$ (c./sec.)	C-18 Me	C-19 Me
5α-Cholest-1-en-3-one	2·89	4·15	10·0	9·31	8·98
syn-Oxime (I)	3·58	3·44	—	—	—
anti-Oxime (III)	3·58	4·0	10·0	9·32	9·13
anti-Oxime acetate	3·32	3·82	10·4	9·33	9·12

The *anti*-oxime (III) does not undergo the Beckmann rearrangement. The nearly pure *anti*-oxime (90% *anti*: 10% *syn*), by treatment with thionyl chloride at 20°, gave 83% of recovered *anti*-oxime, whose infrared spectrum was identical with that of the starting material. The pure *anti*-oxime similarly gave 78% of recovered *anti*-oxime, accompanied by 18% of 5α-cholest-1-en-3-one formed by hydrolysis during brief treatment of the reaction mixture with 4N-potassium hydroxide at 80°, and a trace of a substance, m. p. 250—252°, whose infrared spectrum was identical with that of 5α-cholest-1-en-3-one and which is possibly a dimer; no trace of the ε-lactam (II) could be detected.

The mother-liquors from the methanol recrystallisation of the *anti*-oxime yielded a mixture of the isomeric oximes, estimated by n.m.r. spectrometry to contain ~23% of the *syn*-oxime (I), which underwent Beckmann change with thionyl chloride at 20° to give 73% [based on (I)] of the ε-lactam (II), $\nu_{max.}$ 3585, 1660, 1605 cm.$^{-1}$, $\lambda_{max.}$ 219 mμ, by *trans*-interchange. The 4-aza-3-oxo-Δ^1-structure (II) is confirmed by the ultraviolet absorption maximum at 219 mμ, which may be compared with that at 220 mμ observed for 3-aza-4-oxo-A-homoandrost-4α-ene,[8] and that at 222 mμ observed for 3-aza-3-oxo-A-homocholest-4α-ene.[9]

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Ultraviolet spectra (in ethanol) and infrared spectra (in carbon tetrachloride), unless otherwise stated, were measured with Perkin-Elmer 4000 A and 221 spectrophotometers, respectively. N.m.r. spectra were measured on a Varian A60 instrument with deuterochloroform as solvent and tetramethylsilane as internal reference. Chromatography was on silica gel (Davison 40—200 mesh) or aluminium oxide (Spence type H, activity II).

5α-*Cholest*-1-*en*-3-*one*.—Prepared by dehydrobromination of 2α-bromo-5α-cholestan-3-one with calcium carbonate in refluxing dimethylacetamide,[10] the ketone had m. p. 100—101°, $\lambda_{max.}$ 230 mμ, $\nu_{max.}$ 1680, 785 cm.$^{-1}$; n.m.r. spectrum τ 2·87 (doublet, $J_{1,2} = 10$ c./sec.; H-1), τ 4·15 (doublet, $J_{2,1} = 10$ c./sec.; H-2), τ 7·5—7·85 (H-4α, H-4β).

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[7] S. K. Roy, Ph.D. Thesis, Sydney, 1961.

[8] C. W. Shoppee and G. Krüger, *J.*, 1961, 3641.

[9] C. W. Shoppee, G. Krüger, and R. N. Mirrington, *J.*, 1962, 1050.

[10] G. F. H. Green and A. G. Long, *J.*, 1961, 2532.

5α-*Cholest*-1-*en*-3-*one Oxime* (III).—5α-Cholest-1-en-3-one was oximated with hydroxylamine hydrochloride and sodium acetate trihydrate in refluxing methanol for 1 hr., and the product isolated in the usual way. Recrystallisation from methanol gave the anti-*oxime*, m. p. 149—150°, $\nu_{max.}$ 3270—3230 cm.$^{-1}$, no absorption in the range 1800—1650 cm.$^{-1}$, $\nu_{max.}$ (in Nujol) 3300, 1610, 980, 960, 940, 775, 760, 725 cm.$^{-1}$ [Found (after drying at 60°/0·1 mm. for 4 hr.): C, 81·0; H, 11·35. $C_{27}H_{45}NO$ requires C, 81·15; H, 11·35%]; the *acetate*, prepared using acetic anhydride–pyridine at 20° overnight, had m. p. 150—152°, $\nu_{max.}$ (in Nujol) 1750 cm.$^{-1}$, no absorption at 3500—3000 cm.$^{-1}$, after recrystallisation from acetone [Found (after drying at 60°/0·1 mm. for 4 hr.): C, 78·85; H, 10·75. $C_{29}H_{47}NO_2$ requires C, 78·5; H, 10·75%]. The crystalline material obtained by concentration of the methanol mother-liquor was a mixture (~77% *anti*, ~23% *syn*) of the isomeric oximes. Recrystallisation from methyl cyanide gave a mixture (~90% *anti*, ~10% *syn*) of the isomeric oximes, m. p. 133—135°, $\nu_{max.}$ 3270—3230 cm.$^{-1}$, with no selective absorption in the range 1800—1650 cm.$^{-1}$.

4-*Aza*-3-*oxo*-A-*homocholest*-1-*ene* (II).—(*a*) The nearly pure *anti*-oxime (90% III, 10% I), m. p. 133—135° (120 mg.), was dissolved in thionyl chloride (2 ml.), and after 1—2 min. at 20° the yellow solution was added slowly to 4N-potassium hydroxide (25 ml.), at 70°. The mixture was cooled immediately and extracted with chloroform (3 × 15 ml.). After the usual working up, the resultant oil was chromatographed on alumina (5 g.) in hexane. Elution with ether–hexane (1 : 1) and with ether yielded a colourless oil which slowly crystallised to give unchanged oxime (100 mg.) whose infrared spectrum was identical with that of the starting material.

(*b*) 5α-Cholest-1-en-3-one *anti*-oxime (III), m. p. 148—150° (450 mg.), was added to thionyl chloride (5 ml.) at 10° during 10 min., and the mixture allowed to stand for a further 10 min. before being poured into 4N-potassium hydroxide (50 ml.) at 80°. The suspension was cooled at once and extracted with chloroform, to give a product (435 mg.). This (300 mg.) was chromatographed on alumina (9 g.) in pentane. Elution with ether–pentane (1 : 1) (4 × 50 ml.) gave 5α-cholest-1-en-3-one (52 mg.), m. p. 100°, identified by mixed m. p., thin-layer chromatography on alumina in chloroform (R_F 0·8), and the infrared spectrum. Elution with ether gave unchanged *anti*-oxime (232 mg.), m. p. 148—149° (from methanol), identified by mixed m. p., thin-layer chromatography (R_F 0·27), and the infrared spectrum. Elution with chloroform gave a substance (13 mg.), m. p. 250—252°, whose infrared spectrum appeared to be identical with that of 5α-cholest-1-en-3-one, and which is possibly a dimer; no trace of 4-aza-3-oxo-A-homocholest-1-ene (II) could be detected. When the *anti*-oxime, m. p. 148—150° (153 mg.), was added to 4N-potassium hydroxide (30 ml.) at 80°, the cooled suspension by extraction with ether gave a product shown by thin-layer chromatography on alumina in chloroform to consist of *anti*-oxime (R_F 0·27) and 5α-cholest-1-en-3-one (R_F 0·8).

(*c*) The mixed oximes (23% I, 77% III) (538 mg.) were added to thionyl chloride (7 ml.) at 10° during 20 min.; the mixture was then poured into 4N-potassium hydroxide (50 ml.), at 80°, and the cooled suspension extracted with chloroform. The product (498 mg.) was chromatographed on alumina (45 g.), in hexane, and 138 fractions were collected. Elution with ether–hexane (1 : 1) (7 × 20 ml.) gave a semi-solid (15 mg.), which appeared to be a mixture of *anti*-oxime (III) and ε-lactam (II) from its infrared spectrum, $\nu_{max.}$ (in Nujol) 3330, 975, 955, 940, 775 cm.$^{-1}$ (*anti*-oxime), 1695, 1500, 1265, 1110, 1065, 1030, 745, 705 cm.$^{-1}$ (ε-lactam), but giving a positive Beilstein test. No material was eluted with ether, but use of chloroform–ether (1 : 5) (18 × 20 ml.) gave unchanged *anti*-oxime (89 mg.), m. p. and mixed m. p. 148—150° (from methanol). Elution with chloroform–ether (1 : 1) (5 × 20 ml.) and chloroform (5 × 20 ml.) gave only oils (probably impure oxime), but further use of chloroform (10 × 20 ml.) gave 4-*aza*-3-*oxo*-A-*homo*-5α-*cholest*-1-*ene* (90 mg.), double m. p. 253—255° and 276—278° (decomp.), $\lambda_{max.}$ 219 mμ (log ε 2·9], $\nu_{max.}$ (in $CHCl_3$) 3585 (NH), 1600 (CO·NH), 1605 cm.$^{-1}$ (C=C), $\nu_{max.}$ (in Nujol) 1700, 1650, 1600, 1260, 1110, 1065, 1030, 740 cm.$^{-1}$, after recrystallisation from methanol [Found (after drying at 100°/0·1 mm. for 2 hr.): C, 80·9; H, 11·1. $C_{27}H_{45}NO$ requires C, 81·15; H, 11·35%].

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