

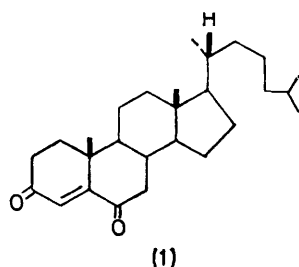
Steroids and Related Studies. Part XIX.¹ Products of the Schmidt Reaction with Cholest-4-ene-3,6-dione

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Treatment of cholest-4-ene-3,6-dione with an equimolar quantity of sodium azide in polyphosphoric acid yields 4-aza-A-homocholest-4a-ene-3,6-dione and 3-aza-A-homocholest-4a-ene-4,6-dione. The product obtained on treating 4-aza-A-homocholest-4a-ene-3,6-dione with 1 mol. equiv. of sodium azide or cholest-4-ene-3,6-dione with 2 mol. equiv. of sodium azide has been shown to be 4,6-diaza-AB-dihomocholest-4a-ene-3,7-dione.

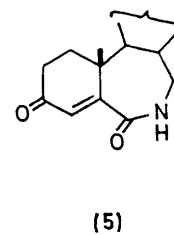
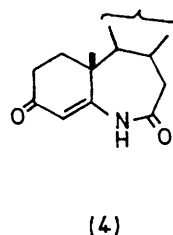
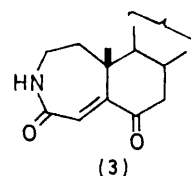
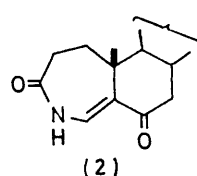
Of various procedures used for the synthesis of aza-steroids,² much use has been made of the Schmidt reaction with steroid ketones and of Beckmann rearrangements of the derived oximes.³ We describe here the Schmidt reaction with cholest-4-ene-3,6-dione (1).⁴



The dione (1) was prepared by oxidation of cholesterol with sodium dichromate.⁵ Treatment of the product with 1 mol. equiv. of hydroxylamine hydrochloride in pyridine, gave a mono-oxime, λ_{\max} 287 nm ($\log \epsilon$ 4.19), which we expected to be the 3-oxime in the light of the reported relative reactivity of 3- and 6-oxo-steroids.⁶ Coombes *et al.*⁷ later published the preparation of the same oxime from the dione (1) and from 6-ethoxycholesta-4,6-dien-3-one; they also obtained it as a product of photolysis of 6-nitrocholest-5-en-3 β -yl acetate. The oxime did not rearrange when treated with thionyl chloride in dioxan.

Treatment of the dione (1) with 1 mol. equiv. of sodium azide in polyphosphoric acid at 55–60° for 10 h gave two products (A), m.p. 259–261°, and (B), m.p. 200–204°. Elemental analysis and mass spectral studies indicated them to be isomeric monoaza-deriva-

tives of molecular formula $C_{27}H_{43}NO_2$. One would expect the 3-oxo-group to react preferentially, but the four isomeric mono-lactam structures (2)–(5) were all considered.



The n.m.r. spectrum of compound (A) displayed a one-proton doublet (J 7.0 Hz) centred at τ 3.45 and a broad one-proton doublet (J 7.0 Hz) centred at τ 2.40. On addition of deuterium oxide the former collapsed to a singlet and the latter disappeared; there were no noticeable changes in other regions of the spectrum. Therefore, the signals are assigned to an olefinic proton and to an NH group. The size of the coupling constant indicates that the two protons must be in a vicinal relationship. These observations favour the 4-aza-A-homocholest-4a-ene-3,6-dione structure (2) for product (A).

¹ Part XVIII, preceding paper.

² H. Singh, V. V. Parashar, S. Padmanabhan, and R. B. Mathur, *Indian J. Pharm. Educ.*, 1970, **4** (2), 2.

³ H. Singh, V. V. Parashar, and S. Padmanabhan, *J. Sci. Ind. Res. India*, 1966, **25**, 200.

⁴ Preliminary communication, H. Singh, S. Padmanabhan, A. K. Bose, and I. Kugajevsky, *Chem. and Ind.*, 1967, 118.

⁵ L. F. Fieser, *Org. Synth.*, 1963, Coll. Vol. 4, p. 189.

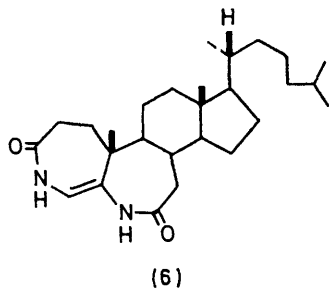
⁶ J. Décombe, R. Jacquemain, and J. Rabinovitch, *Bull. Soc. chim. France*, 1948, 447.

⁷ G. E. A. Coombes, J. M. Grady, and S. T. Reid, *Tetrahedron*, 1967, **23**, 1341.

The isomeric product (B) showed an n.m.r. spectrum similar to that of (A) except that the olefinic proton signal appeared as a doublet with J 1.5 Hz at τ 4.06 and the NH signal was very broad. On addition of deuterium oxide the NH signal disappeared, the olefinic doublet became a singlet, a complex two-proton signal at about τ 6.75 underwent an appreciable change in its contour. The small size of the coupling constant indicates long-range interaction between the NH and CH=C systems, and the signal at τ 6.75 must correspond to a methylene group adjacent to NH,^{8,9} as in structures (3) and (5). The long-range coupling is consistent with an **M** relationship¹⁰ as in structure (3). In structure (5) this relationship does not exist. Structure (3) is also preferable on the grounds that the 3-oxo-group is in general more reactive than a 6-oxo-group.

The assignment of structures (2) and (3) to compounds (A) and (B) is supported by their u.v. spectra. Similar chromophores occur in lactams derived during studies on lanostadienol.¹¹

When compound (A) was treated with 1 mol. equiv. of sodium azide or cholest-4-ene-3,6-dione (1) with 2 mol. equiv. of sodium azide, a product was obtained with λ_{\max} 250 nm ($\log \epsilon$ 4.17). Elemental analysis showed it to be a diaza-derivative. Its n.m.r. spectrum displayed two NH signals, a doublet (J 7.0 Hz) and a singlet near τ 2.20. A signal for one olefinic proton was displayed at



τ 4.06 (d, J 7.0 Hz). There was no signal at *ca.* τ 6.6,^{8,9} which would correspond to a CH_2NH system. Deuterium exchange produced no noticeable change at higher field but the olefinic doublet collapsed to a singlet and the NH signals vanished. This product can thus be formulated as 4,6-diaza-AB-dihomocholest-4a-ene-3,7-dione (6).

⁸ P. T. Lansbury, J. G. Colson, and N. R. Mancuso, *J. Amer. Chem. Soc.*, 1964, **86**, 5225.

EXPERIMENTAL

Schmidt Reaction with Cholest-4-ene-3,6-dione (1).—Compound (1) (2 g, 0.005 mol) was dissolved in polyphosphoric acid (50 g) with stirring at 55–60° (bath temp.). Sodium azide (0.4 g, 0.0062 mol) was added in small portions during 1 h. The mixture was stirred occasionally during 10 h at 55–60°. Crushed ice was added and the mixture was then neutralised with ice-cold 50% potassium hydroxide solution (50 ml) and extracted with chloroform (200 ml). The extract was washed repeatedly with water, dried (Na_2SO_4), and evaporated. The residue was washed with light petroleum (b.p. 40–60°; 50 ml) and crystallised from methanol (100 ml) to give 4-aza-A-homocholest-4a-ene-3,6-dione (2) (520 mg, 25%), m.p. 253–255°. Further crystallisation, from chloroform–methanol, gave a sample of m.p. 259–261°; λ_{\max} (EtOH) 279 nm ($\log \epsilon$ 4.19); λ_{\max} (0.1N-NaOH) 316 nm; ν_{\max} (Nujol) 3225, 3145, 1705, 1675, and 1605 cm^{-1} (Found: C, 78.0; H, 9.9; N, 3.15. $C_{27}H_{43}NO_2$ requires C, 78.4; H, 10.5; N, 3.4%).

The mother liquor remaining after removal of the lactam (2) was concentrated to *ca.* 40 ml; crystalline material (410 mg) of m.p. 227–230° separated out. The mother liquor from this crop on further concentration to 10–15 ml and cooling gave pale yellow needles of 3-aza-A-homocholest-4a-ene-3,6-dione (3) (310 mg, 15%), m.p. 200–204°; λ_{\max} (EtOH) 234 ($\log \epsilon$ 4.04) and 280sh nm (3.65); ν_{\max} (Nujol) 3225, 1695, 1653, and 1605 cm^{-1} (Found: C, 78.1; H, 10.1; N, 3.6%).

Schmidt Reaction with 4-Aza-A-homocholest-4a-ene-3,6-dione (2).—Sodium azide (65 mg, 0.001 mol) was added to a stirred mixture of the lactam (2) (400 mg, 0.001 mol) and polyphosphoric acid (10 g) at 55–60° during 1 h. The mixture was further stirred occasionally for 10 h at 55–60° and processed as just described. The residue crystallised from methanol to provide 4,6-diaza-AB-dihomocholest-4a-ene-3,7-dione (6) (200 mg, 48%), m.p. 290–296° (decomp.); λ_{\max} (EtOH), 250 nm ($\log \epsilon$ 4.17); ν_{\max} (Nujol) 3280, 1670, 1640, and 1590 cm^{-1} (Found: C, 76.05; H, 10.1; N, 6.35. $C_{27}H_{44}N_2O_2$ requires C, 75.65; H, 10.35; N, 6.55%).

The lactam (6) was also obtained when cholest-4-ene-3,6-dione (1) was treated with 2 mol. equiv. of sodium azide.

This research was supported part by a grant (to H. Singh) from the Council of Scientific and Industrial Research, New Delhi, India.

[1/2030 Received, 1st November, 1971]

⁹ G. S. Sidhu, G. Thyagarajan, and U. T. Bhalerao, *J. Chem. Soc. (C)*, 1966, 969.

¹⁰ N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy,' Holden-Day, San Francisco, 1964, p. 115.

¹¹ C. S. Barnes, D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 1952, 2339.