641. *Aza-steroids. Part VIII.** 7a-*Aza*-B-*homo*-5α-*cholestane* and 7a-*Aza*-B-*homocholest*-5-*ene*.

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The two 7a-aza-steroids named above have been prepared by Beckmann rearrangement of the oximes of 5α-cholestan-7-one and cholest-5-en-7-one and subsequent reduction of the resulting ε-lactams with lithium aluminium hydride.

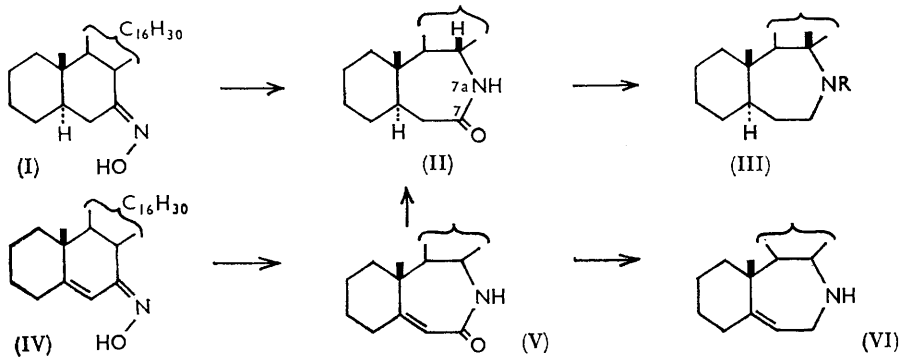
The preparation of 6-aza-B-homo-5α-cholestane was reported by Knof [1] and Shoppee, Roy, and Lack; [2] the B-homo-aza-steroid series is now extended by Beckmann rearrangement of the oxime (I) of 5α-cholestan-7-one and of the *syn*-oxime (IV) of cholest-5-en-7-one, to furnish the appropriate ε-lactams (II) and (V), which were reduced, respectively, to 7a-aza-B-homo-5α-cholestane (III; R = H) and 7a-aza-B-homocholest-5-ene (VI).

Few other B-homo-aza-steroids have been reported. Hara,[3] by treatment of methyl

* Part VII, preceding Paper.

[1] Knof, *Annalen*, 1961, **642**, 194.
[2] Shoppee, Roy, and Lack, *J.*, 1963, 3767.
[3] Hara, *J. Pharm. Soc. Japan*, 1958, **78**, 1030.

7-hydroxyimino-5β-cholanate with toluene-*p*-sulphonyl chloride–pyridine obtained methyl 7-oxo-7a-aza-B-homo-5β-cholanate, which was reduced by lithium aluminium hydride to 7a-aza-B-homo-5β-cholan-24-ol. This structure was assigned because the compound was different from 7-aza-B-homo-5β-cholan-24-ol, which was synthesised from the anhydride-ester methyl 6,7a-dioxo-7-oxa-B-homo-5β-cholanate by conversion with urea into the



corresponding 6,7a-dioxo-7-aza-steroid and reduction of this with lithium aluminium hydride. Knof [1] described the preparation of 3β-acetoxy- and 3β-hydroxy-6-aza-B-homo-5α-cholestane by two methods, one of which leads unambiguously to the 6-aza-structure assigned; Knof also described the preparation of the 3β-hydroxy-analogue of 7a-aza-B-homo-5α-cholestane (III; R = H).

5α-Cholestan-7-one [4,5] readily gave an oxime [6] (I), which appeared to be homogeneous and by treatment with thionyl chloride at −10° gave a single ε-lactam (II) [$\nu_{max.}$ 3200 (NH) 1670 cm.$^{-1}$ (CO·NH)]. The 7-oxo-7a-aza-structure (II) is established by the nuclear magnetic resonance spectrum, which shows (i) a complex signal at τ 4·5 for the proton in the NH-group, readily exchangeable for deuterium, and (ii) a multiplet at τ 6·76 of area corresponding to the single 8β-proton adjacent to the nitrogen atom. The alternative 7a-oxo-7-aza-structure would require the presence of a multiplet of area corresponding to the two 6α- and 6β-protons. Accordingly, we assign the formula (I) to 5α-cholestan-7-one oxime.

The ε-lactam (II), by reduction with lithium aluminium hydride, gave 7a-aza-B-homo-5α-cholestane (III; R = H), characterised as the *N*-acetyl derivative. The nuclear magnetic resonance spectrum of the *N*-acetyl-aza-steroid (III; R = Ac) shows (i) a sharp singlet at τ 7·93 for the three protons of the methyl group in the grouping N·COMe, (ii) a multiplet at τ 5·6 of area corresponding to the single 8β-proton adjacent to the >NAc group at C-7a, and (iii) a multiplet at τ 6·55 of area corresponding to the two 7a- and 7β-protons. The observations confirm structure (II) and indicate structure (III), because the alternative 7-aza-steroid structure would give rise to a signal of area corresponding to four protons (6α, 6β, 7aα, and 7aβ) adjacent to a >NAc group at C-7.

Cholest-5-en-7-one [7] furnished a single homogeneous oxime [8] whose formulation as the *syn*-isomer (IV) is proved by its nuclar magnetic resonance spectrum. Specimens recrystallised from methanol and from methyl cyanide showed identical spectra characterised by (i) a signal at τ 1·83 corresponding to the hydroxyimino-proton, readily exchangeable with deuterium, and (ii) a sharp peak at τ 3·45 corresponding to the vinylic proton at C-6. The vinylic proton in cholest-5-en-7-one appears at τ 4·32, and the chemical shift of 87 p.p.m. observed in the ketoxime indicates that it is the pure *syn*-isomer (IV).[cf. 9]

[4] Windaus, *Ber.*, 1920, **53**, 488.
[5] Cremlyn and Shoppee, *J.*, 1954, 3515.
[6] Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 2986.
[7] Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 3022.
[8] Tominaga, *Bull. Chem. Soc. Japan*, 1939, **14**, 486.
[9] Slomp and Wechter, *Chem. and Ind.*, 1962, 41.

It is consistent that Beckmann rearrangement of the oxime with thionyl chloride in dioxan or with thionyl chloride alone gave 78 and 88% yields, respectively, of the expected ε-lactam (V), $\nu_{max.}$ 3200 (NH), 1670 cm.$^{-1}$ (CO·NH), $\lambda_{max.}$ 221 mμ (log ε 4·2), which by hydrogenation with palladium–charcoal in ethanol afforded the saturated ε-lactam (II). Reduction of the unsaturated ε-lactam (V) with lithium aluminium hydride gave 7a-aza-B-homocholest-5-ene (VI), $\nu_{max.}$ 1670 cm.$^{-1}$ (NH) but no band at ~3200 cm.$^{-1}$

Experimental

For general experimental directions, see *J.*, 1958, 3458. $[\alpha]_D$'s are for chloroform solutions. Ultraviolet absorption spectra were measured for ethanol solutions in a Perkin-Elmer model 4000Å spectrophotometer, and infrared absorption spectra determined on an Infrachord as Nujol mulls or on a Perkin-Elmer model 221 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian D.P. 60 instrument at 60 Mc./sec. with deuteriochloroform as solvent and tetramethylsilane as internal reference.

5α-*Cholestan-7-one Oxime.*—Treatment of 5α-cholestan-7-one [4,5] (m. p. 115—117°; 2 g.) in ethanol (100 ml.) with hydroxylamine hydrochloride (5 g.) in the presence of sodium acetate trihydrate (7·5 g.) at 80° for 5 hr. gave the oxime (1·9 g.), prisms (from ether–methanol), m. p. 138—141° (lit.,[6] 134—135°), $[\alpha]_D$ −122° (*c* 1·27), $\nu_{max.}$ 3380, 1650 cm.$^{-1}$ (Found: C, 81·0; H, 11·9. Calc. for $C_{27}H_{47}NO$: C, 80·7; H, 11·8%).

7a-*Aza*-B-*homo*-5α-*cholestan-7-one.*—5α-Cholestan-7-one oxime (1 g.) was quickly dissolved, with swirling, in freshly purified thionyl chloride (20 ml.) at −10° (acetone + ice). The light yellow solution so obtained was slowly added to 4N-potassium hydroxide (200 ml.) at 90°. After cooling, the mixture was extracted with ether and washed with 3N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water. The crude product (950 mg.) was chromatographed on alumina (27 g.) in ether. Elution with ether gave unchanged oxime, (10 mg.), and elution with chloroform–ether (1 : 4) gave the required ε-*lactam* (930 mg.), needles (from methanol), double m. p. 90°/135—138°, $[\alpha]_D$ +9·5° (*c* 0·42), $\nu_{max.}$ 3200, 3120, 1670, 1650 cm.$^{-1}$ (Found: C, 80·6; H, 11·8. $C_{27}H_{47}NO$ requires C, 80·7; H, 11·8%).

N-*Acetyl*-7a-*aza*-B-*homo*-5α-*cholestane.*—7a-Aza-B-homo-5α-cholestan-7-one (200 mg.) in ether (25 ml.) was treated with lithium aluminium hydride (400 mg.) at 35° for 24 hr. Ice was added to destroy excess of lithium aluminium hydride, and the product was extracted with ether. The extract was washed with saturated sodium hydrogen carbonate solution and water. The oily product obtained after evaporation of the solvent was treated with acetic anhydride (3 ml.) in pyridine (7 ml.) at 20° for 24 hr. After the usual working up the crude product was chromatographed on alumina (6 g.). Elution with ether and chloroform–ether (1 : 1) gave N-*acetyl*-7a-*aza*-B-*homo*-5α-*cholestane* (190 mg.), needles (from aqueous acetone), m. p. 123—126°, $[\alpha]_D$ +95·5° (*c* 0·43), $\nu_{max.}$ 1630 cm.$^{-1}$ (Found: C, 81·2; H, 12·0. $C_{29}H_{51}NO$ requires C, 81·0; H, 12·0%).

Cholest-5-en-7-one Oxime.—(*a*) Cholest-5-en-7-one [7] (3·5 g.; m. p. 128—131°) in ethanol (200 ml.) was treated with hydroxylamine hydrochloride (9 g.) and sodium acetate trihydrate (14 g.) at 80° for 4 hr. After removal of ethanol (180 ml.), the mixture was diluted with water, extracted with ether, and worked up in the usual way, to give the oxime (3·2 g.), m. p. 177—180° (lit.,[8] 179—180°) (from ether–methanol), $[\alpha]_D$ −225° (*c* 1·0), $\lambda_{max.}$ 235 mμ (log ε 4·13), $\nu_{max.}$ 3400, 1650 cm.$^{-1}$ (Found: C, 81·3; H, 11·1. $C_{27}H_{45}ON$ requires C, 81·15; H, 11·3%).

(*b*) Cholest-5-en-7-one oxime (148 mg.; m. p. 177—180°) was dissolved in boiling methyl cyanide (20 ml.) and allowed to cool; within a few minutes crystals separated, which were filtered off and dried in a vacuum (120 mg.), m. p. and mixed m. p. 177—180°. The n.m.r. spectrum gave no indication of the presence of the stereoisomeric form.

7a-*Aza*-B-*homocholest-5-en-7-one.*—(*a*) Thionyl chloride (0·75 ml.) was slowly added, with swirling, to a solution of cholest-5-en-7-one oxime (313 mg.) in dioxan (10 ml.) at 10°, the temperature being kept below 15°. After 1·5 hr. at 20°, 2N-potassium hydrogen carbonate solution (15 ml.) was added in small portions, and the mixture extracted with ether and worked up in the usual way, to give a dark product which was chromatographed on alumina (10 g.). Elution with ether–benzene (1 : 4 and 1 : 1) furnished impure ε-lactam. Re-chromatography and crystallisation from chloroform–pentane afforded the 7a-*aza*-B-*homocholest-5-en-7-one* (277 mg.), m. p. 208—211°, $[\alpha]_D$ −109° (*c* 1·05), $\lambda_{max.}$ 221 mμ (log ε 4·2), $\nu_{max.}$ (CCl_4) 3415, 1660, 1610 cm.$^{-1}$ (Found: C, 81·1; H, 11·3. $C_{27}H_{45}NO$ requires C, 81·1; H, 11·35%).

(*b*) Cholest-5-en-7-one oxime (511 mg.) was dissolved in thionyl chloride (10 ml.) at −10°, and the resulting light yellow solution poured into 4N-potassium hydroxide (100 ml.) at 90°. The usual isolation procedure gave a dark product, which was twice chromatographed on alumina; elution with ether–benzene (1 : 4 and 1 : 1) gave ε-lactam (400 mg.), m. p. and mixed m. p. 208—211° (from chloroform–pentane), whose infrared spectrum was identical with that of the product obtained under (*a*).

7a-*Aza*-B-*homo*-5α-*cholestan*-7-*one*.—7a-Aza-B-homocholest-5-en-7-one (230 mg.) in ethanol (50 ml.) was shaken in hydrogen overnight with 10% palladium–charcoal (300 mg.). The catalyst was removed by filtration through Celite, and the filtrate worked up in the usual way, to yield 7a-aza-B-homo-5α-cholestan-7-one (212 mg.), m. p. and mixed m. p. 90°/135—138° (from methanol).

N-*Acetyl*-7a-*aza*-B-*homocholest*-5-*ene*.—7a-Aza-B-homocholest-5-en-7-one (250 mg.) was treated with lithium aluminium hydride (400 mg.) in ether (150 ml.) at 36° for 24 hr. The excess of lithium aluminium hydride was destroyed by adding ice, the ethereal layer decanted, the inorganic material extracted with ether, and the combined extracts were washed with sodium hydrogen carbonate and evaporated. The oil (245 mg.) (no C=O absorption in the infrared spectrum) was treated with acetic anhydride (3 ml.) in pyridine (10 ml.) at 20° for 24 hr. The usual isolation procedure afforded the *N*-acetyl derivative as an oil which did not crystallise, $\nu_{max.}$ (Nujol) 1670 cm.$^{-1}$.

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