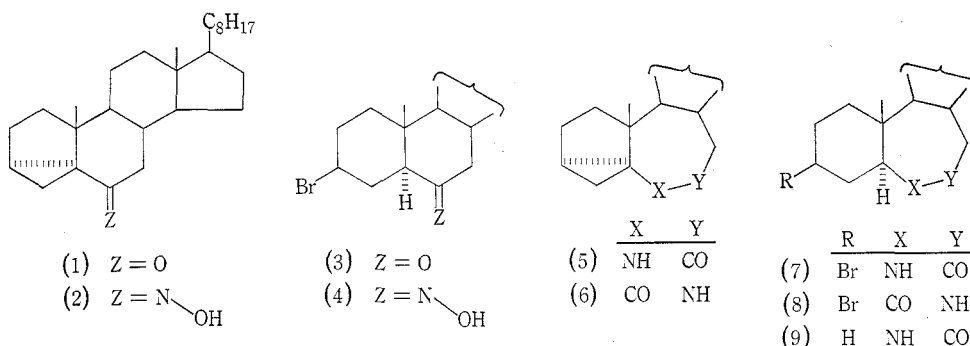


# AZASTEROIDS FROM 3 $\alpha$ ,5 $\alpha$ -CYCLOCHOLESTAN-6-ONE AND 3 $\beta$ -BROMO-5 $\alpha$ -CHOLESTAN-6-ONE

By M. S. AHMAD,\* SHAFIULLAH,\* and M. MUSHFIQ\*

[Manuscript received March 24, 1970]

A previous communication from this laboratory described the preparation of azasteroids from 3 $\beta$ -chloro-5 $\alpha$ -cholestan-6-one and 3 $\beta$ -acetoxycholest-4-en-6-one.<sup>1</sup> This paper is concerned with the Beckmann rearrangements of the oximes (2)<sup>2</sup> and (4), derived from 3 $\alpha$ ,5 $\alpha$ -cyclocholestan-6-one (1)<sup>3</sup> and 3 $\beta$ -bromo-5 $\alpha$ -cholestan-6-one (3),<sup>4</sup> respectively. The oxime (2) was shown to be homogeneous (t.l.c. and column chromatography<sup>5</sup>). This oxime on Beckmann rearrangement using *p*-toluenesulphonyl chloride in pyridine, followed by chromatography over alumina,<sup>6</sup> gave a single lactam, 6-aza-3 $\alpha$ ,5 $\alpha$ -cyclo-B-homocholestan-7-one (5).



Formulation of the lactam as (5), rather than its isomer 7-aza-3 $\alpha$ ,5 $\alpha$ -cyclo-B-homocholestan-6-one (6), was supported by spectral properties. The i.r. spectrum of the lactam showed peaks at 3200, 3080 (NH), 3036w (cyclopropane<sup>7</sup>), 1670s, 1658sh cm<sup>-1</sup> (CONH). The n.m.r. (100 MHz) spectrum of the lactam exhibited signals at  $\delta$  6.88 (s, NHCO), exchangeable with deuterium.<sup>8</sup> The sharpness of the

\* Department of Chemistry, Aligarh Muslim University, Aligarh, India.

<sup>1</sup> Ahmad, M. S., Shafiullah, and Siddiqui, A. H., *Indian J. Chem.*, 1969, **7**(11), 1167.

<sup>2</sup> Wallis, E. S., Fernholz, E., and Gephart, F. T., *J. Am. chem. Soc.*, 1937, **59**, 137.

<sup>3</sup> Heilbron, I. M., Hodges, J., and Spring, F. S., *J. chem. Soc.*, 1938, 759.

<sup>4</sup> Shoppee, C. W., and Summers, G. H. R., *J. chem. Soc.*, 1952, 1786.

<sup>5</sup> Hara, S., Oka, K., and Ike, Y., *Chem. Ind.*, 1967, 832.

<sup>6</sup> Craig, J. C., and Naik, A. R., *J. Am. chem. Soc.*, 1962, **84**, 3410.

<sup>7</sup> Cole, A. R. H., *J. chem. Soc.*, 1954, 3807.

<sup>8</sup> Shoppee, C. W., Akhtar, M. I., and Lack, R. E., *J. chem. Soc.*, 1964, 3392.

peak clearly indicated the absence of vicinal protons about NH, such as in (5). The absence of vinylic proton signals and the presence of complex signals in the region  $\delta$  0.68–0.4 were evidence of the presence of a cyclopropane system<sup>9</sup> in the lactam. Further the C7a methylene protons appeared centred at  $\delta$  2.3. The isomeric structure (6) was expected to exhibit a broad peak<sup>8</sup> for NH in the n.m.r. spectrum. The u.v. spectrum of the lactam was featureless.

3 $\alpha$ ,5 $\alpha$ -Cyclocholestan-6-one (1) with hydrogen bromide gave the bromo ketone (3)<sup>4</sup> ( $\nu_{\max}$  1710  $\text{cm}^{-1}$ ;  $\delta$  3.9,  $W_{\text{H}}$  25 Hz, axial H 3 $\alpha$ )<sup>10</sup> readily converted into the oxime (4) shown to be homogeneous by t.l.c. and column chromatography. Beckmann rearrangement of this oxime (4) with thionyl chloride gave a single lactam. This bromo lactam was assigned the structure (7) rather than the alternative structure (8) since sodium–isopentanol reduction gave the lactam (9), identical to that obtained by Beckmann rearrangement of 5 $\alpha$ -cholestan-6-one oxime.<sup>11</sup> The spectral properties of the bromo lactam are in agreement with structure (7).

The i.r. spectrum of (7) showed peaks at 3230, 3100 (NH), 1668  $\text{cm}^{-1}$  (CONH). The n.m.r. spectrum gave signals at  $\delta$  5.7 (br; H(C5)NH; exchangeable with deuterium), 3.84 (Br(C3)H;  $W_{\text{H}}$  24 Hz; axial H 3 $\alpha$ ),<sup>10</sup> 3.3 (br; 1H; H(C5)NHCO), 2.3 (unresolved; (C7a)H<sub>2</sub>). On addition of D<sub>2</sub>O, the peak at  $\delta$  3.3 collapsed to a doublet of doublets,  $J_{4\beta,5}$  12,  $J_{4\alpha,5}$  4 Hz.

### Experimental

All melting points are uncorrected. I.r. spectra were obtained with a Perkin–Elmer 237 spectrophotometer in KBr and u.v. spectra in 95% EtOH with a Beckman DB spectrophotometer. Rotations were determined in CHCl<sub>3</sub>. N.m.r. spectra were run in a Varian HA-100 instrument in CDCl<sub>3</sub> with TMS as the internal standard. The mass spectrum was measured at 70 eV on an A.E.I. MS-9 spectrometer. Light petroleum refers to the fraction b.p. 60–80°.

3 $\alpha$ ,5 $\alpha$ -Cyclocholestan-6-one (1) was prepared according to the procedure of Heilbron *et al.*,<sup>3</sup> m.p. 96–98°;  $\nu_{\max}$  3040w (cyclopropane), 1690  $\text{cm}^{-1}$ .

#### The Beckmann Rearrangement of the Oxime (2)

To a solution of the oxime (2) (1.3 g; m.p. 142–144°)<sup>2</sup> in pyridine (13 ml, freshly distilled over KOH) was added *p*-toluenesulphonyl chloride (1.3 g) and the reaction mixture was allowed to stand at room temperature (15–18°) for 15 hr. It was poured into crushed ice-water mixture and extracted with ether. The ether extract was washed with water, dil. H<sub>2</sub>SO<sub>4</sub>, water, and NaHCO<sub>3</sub> solution (5%), then dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent provided an oil (1.2 g). The crude material in light petroleum–benzene was allowed to stand over a column of alumina (30 g) for about 1 hr. Elution with benzene–ether (4 : 1 and 1 : 1) gave the lactam (5), recrystallized from light petroleum–ether (0.95 g), m.p. 198–200°,  $[\alpha]_{\text{D}}^{21} + 70^\circ$  (Found: C, 81.6; H, 11.3. C<sub>27</sub>H<sub>45</sub>NO requires C, 81.2; H, 11.3%). Mass:  $M^+$  399;  $\nu_{\max}$  3200, 3080 (NH), 3036 (cyclopropane), 1670, 1658  $\text{cm}^{-1}$  (CONH). N.m.r. (CDCl<sub>3</sub>):  $\delta$  6.88 (s; NHCO, exchangeable with deuterium), 2.3 (unresolved, (C7a)H<sub>2</sub>), 0.71 (18-Me), 1.02 (19-Me), 0.68–0.4 (complex; cyclopropyl protons).

#### 3 $\beta$ -Bromo-5 $\alpha$ -cholestan-6-one Oxime (4)

3 $\beta$ -Bromo-5 $\alpha$ -cholestan-6-one<sup>4</sup> (3) (0.7 g; m.p. 126°), hydroxylamine hydrochloride (1.8 g), sodium acetate trihydrate (2.8 g), methanol (40 ml), and water (2 ml) were heated under

<sup>9</sup> Tadanier, J., and Cole, W., *J. org. Chem.*, 1962, **27**, 4624.

<sup>10</sup> Bhacca, N. S., and Williams, D. H., "Applications of N.M.R. Spectroscopy in Organic Chemistry." (Holden-Day: San Francisco 1964.)

<sup>11</sup> Shoppee, C. W., Lack, R. E., and Roy, S. K., *J. chem. Soc.*, 1963, 3767.

reflux for 1 hr. The excess of the solvent was removed under reduced pressure and the residue was diluted with cold water. The *oxime* (4) was obtained as a solid and was recrystallized from methanol (0.48 g), m.p. 174–175°,  $[\alpha]_{\text{D}}^{21} + 83^\circ$  (Found: C, 67.7; H, 9.7.  $\text{C}_{27}\text{H}_{46}\text{BrNO}$  requires C, 67.5; H, 9.58%).  $\nu_{\text{max}}$  3280br (=N–OH), 1660m  $\text{cm}^{-1}$  (C=N–). Positive Beilstein test.

*The Beckmann Rearrangement of the Oxime (4)*

The *oxime* (4) (0.4 g) was added, as quickly as possible, with stirring to freshly purified thionyl chloride (5.5 ml) at 0° and the reaction mixture was poured immediately into 4N potassium hydroxide solution at 80°. A solid thus obtained was filtered, washed with water, and air-dried. Recrystallization from chloroform–ether gave the *bromo lactam* (7) (290 mg), m.p. 85°,  $[\alpha]_{\text{D}}^{21} + 27^\circ$  (Found: C, 67.9; H, 9.9.  $\text{C}_{27}\text{H}_{46}\text{BrNO}$  requires C, 67.5; H, 9.6%). Positive Beilstein test.  $\nu_{\text{max}}$  3230, 3100 (NH), 1668  $\text{cm}^{-1}$  (CONH). N.m.r. ( $\text{CDCl}_3$ ):  $\delta$  5.7 (br; H(C5)NHCO; exchangeable with deuterium), 3.84 (br; Br(C3)H; half-band with 24 Hz; axial<sup>10</sup>), 3.3 (br; H(C5)NHCO), 2.3 (unresolved; (C7a)H<sub>2</sub>), 0.67 (18-Me), 0.9 (19-Me).

*Sodium–Isopentanol Reduction of the Bromo Lactam (7)*

The *bromo lactam* (7) (0.25 g) was dissolved in hot isopentanol (7.5 ml) and sodium metal (1.5 g) was added with shaking. The reaction mixture was kept hot for 2 hr; all the metal dissolved. It was then poured into cold water, acidified with HCl, and extracted with ether. The ethereal solution was washed with water and  $\text{NaHCO}_3$  solution (5%) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed under reduced pressure; an oil (0.31 g; contaminated with traces of isopentanol) was obtained. The crude material was chromatographed over alumina (7.5 g). Elution with light petroleum–ether (1:1) and ether gave 6-aza-B-homo-5 $\alpha$ -cholestan-7-one (9), recrystallized from methanol (75 mg), m.p. and mixed m.p.<sup>11</sup> 173–174° (Found: C, 80.5; H, 11.5. Calc. for  $\text{C}_{27}\text{H}_{47}\text{NO}$ : C, 80.8; H, 11.7%).  $\nu_{\text{max}}$  3200 (NH), 1660  $\text{cm}^{-1}$  (CONH).

*Acknowledgments*

We are grateful to Dr S. M. F. Rahman for providing facilities, to C.S.I.R. and U.G.C. for financial support, and to Professor C. H. Hassall, University College, Swansea, for n.m.r. and mass spectra.