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STEROIDS AND RELATED STUDIES—XIII[1]

6-AZA-B-HOMO-5α-CHOLESTANE-3,7-DIONE AND SOME DERIVATIVES

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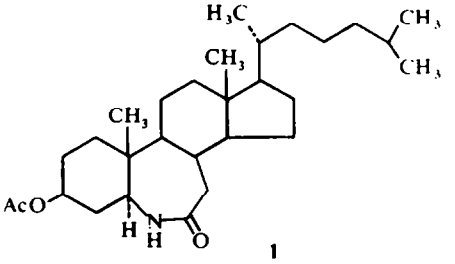
Abstract—The Schmidt reaction product from 3β-acetoxy-5α-cholestan-6-one has been shown to be 3β-acetoxy-6-aza-B-homo-5α-cholestan-7-one from spectral studies. The corresponding 3-keto-azasteroid was brominated with pyridinium hydrobromide perbromide when the 4-bromo derivative was obtained which reacted with N-phenylthiourea to give a thiazole. When the 3-keto-azasteroid was subjected to the Fischer indole synthesis, an indole (ring junction at C_2, C_3 of A ring) was formed.

IN RECENT years azasteroids[2] have attracted the attention of organic and medicinal chemists. They can be obtained by total synthesis and by the modification of natural steroids. For the latter approach Beckmann rearrangement and Schmidt reaction have proved to be convenient methods for introducing a N atom in the steroid ring system.[3]

3β-Acetoxy-6-aza-B-homo-5α-cholestan-7-one (1) has been prepared by Schmidt reaction on 3β-acetoxy-5α-cholestan-6-one (in PPA)[4] and by Beckmann rearrangement of the oxime of the 6-ketosteroid.[5] The location of the N atom in 1 was confirmed but the 5α-configuration was based on analogy.

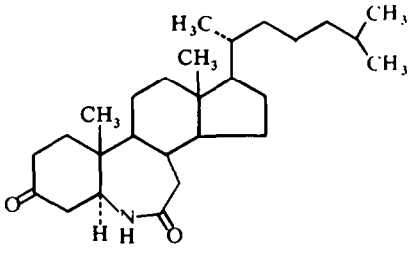


1

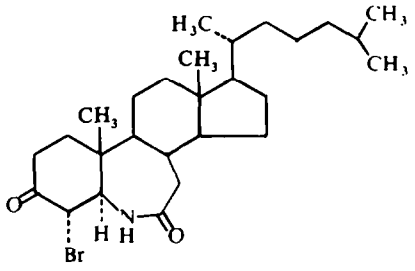
For further information on the structure and stereochemistry of 1, we have carried out spectral studies. The NMR spectrum of 1 in chloroform solution showed a doublet ($J=5$ c/s) at τ 3·92, and two broad peaks centred at τ 5·32 and 6·53 each corresponding to

single protons; other proton signals appeared at higher field (τ 7·6–9·3). After deuterium exchange by shaking with D_2O for a few minutes, the peak at τ 3·92 disappeared and the broad peak at τ 6·53 was transformed into a multiplet; obviously the former corresponds to N—H and the latter to 5-H. Had the N in **1** been at position -7, a two-proton signal coupled to N—H would have appeared.

The stereochemistry at the A/B ring junction in **1** can be deduced from the size of the coupling between 5-H and the adjacent methylene protons. However, such couplings could not be determined by a first order analysis of the 5-H signal in **1** because it was a part of an ABM system. The NMR spectrum of the 3-ketone (**2**) prepared from **1** by alkaline hydrolysis followed by chromic acid oxidation supported the conclusion about the location of the N but the signal of the 5-H proton was again a multiplet and too complex for first order interpretation. Treatment of **2** with pyridinium hydrobromide perbromide gave a monobromo derivative (**3**), the NMR spectrum of which was very informative: a one-proton doublet ($J = 11$ c/s) at τ 5·31 clearly indicated that **3** was a 4-bromo compound—the 2-bromo structure would have produced a quartet. The 5-H signal was a quartet ($J = 5$ and 11 c/s) which was simplified to a doublet (τ 6·20; $J = 11$ c/s) on deuterium exchange.

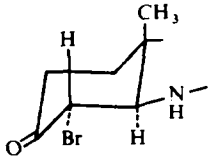


2



3

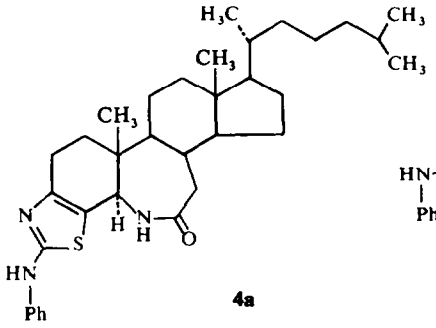
The size of the coupling between 4-H and 5-H corresponds to Jaa, therefore **3** must be 4α-bromo-6-aza-B-homo-5α-cholestane-3,7-dione and, **1** and **2** must belong to the 5α-cholestane series. The IR spectrum of **2** showed the CO absorption at 1730 cm^{-1} which was shifted to 1748 cm^{-1} in the bromo compound (**3**). This observation[6] indicating that the bromo substituent is equatorial is in agreement with the assignment of the 4α-position to the bromine in **3**.



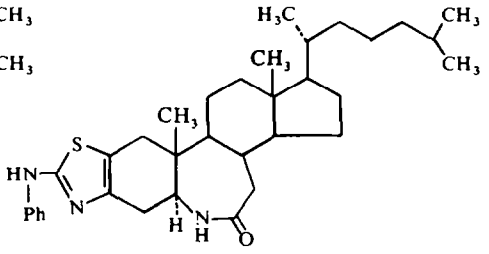
3

It may be noted that the bromination of 3-keto-5α-steroids[7] usually leads to the 2α-derivative. The preference for the 4α-position for the bromine in **3** must be due to the altered nature of the B ring in **2**.

The reaction of the bromoketone (**3**) with N-phenylthiourea gave a product **4** in 45% yield. The NMR spectrum of **4** showed two one-proton doublets ($J = 6$ c/s) at τ 3·9 and 5·58; on deuterium exchange the peak at the lower field due to the N—H signal disappeared and the other peak became a singlet. This derivative must therefore be assigned the angular structure **4a** instead of the alternative linear structure **4b**. Such an angular structure is to be expected since the precursor **3** has the bromine on C-4.

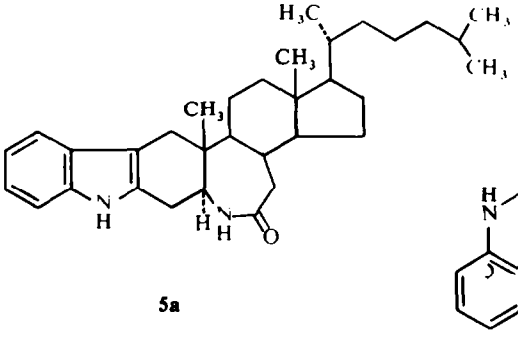


4a

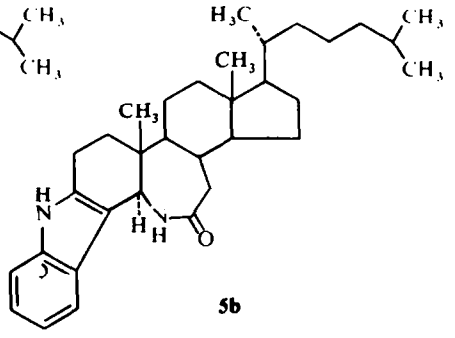


4b

The treatment of **2** with phenylhydrazine in acetic acid led to an indole for which the alternative structures **5a** and **5b** can be written. The NMR spectrum of this product showed the 5-H proton signal as a broad peak at τ 6·28 which became a complex multiplet after deuterium exchange. These observations establish the linear structure (**5a**) for the indole. Although during bromination the 4-methylene in **2** was found to be more reactive, the indole with the angular structure (**5b**) was not obtained in the Fischer synthesis.



5a



5b

EXPERIMENTAL

Optical rotations were measured in chloroform soln. The IR spectra were recorded in nujol on a Perkin-Elmer Infracord spectrophotometer. The NMR spectra were recorded with a Varian A-60 spectrometer operating at 60 Mc using TMS as an internal standard. The m.ps are uncorrected.

6-Aza-B-homo-5α-cholestane-3,7-dione (**2**). 3β-Hydroxy-6-aza-B-homo-5α-cholestan-7-one[8] (6 g) was dissolved in glacial AcOH (96 ml), to which was added a soln of CrO_3 (2·1 g) in water (4 ml). The mixture was allowed to stand for 18 hr at room temp. The excess CrO_3 was destroyed by adding MeOH. The mixture

was concentrated at reduced pressure, diluted with water, saturated with NaCl and extracted with chloroform. The extracts were washed with 2% Na_2CO_3 aq, water and dried over Na_2SO_4. The residue obtained by evaporating the solvent was chromatographed on alumina (100 g). Elutions with chloroform gave a crystalline material, which was further purified by crystallization from acetone. Compound **2** separated as needles, m.p. 236-237°, (58·6% yield), $[\alpha]_D$ +24·42° (*c*, 1·196); IR bands at 3425 (—NH—), 1730 (keto—C=O) and 1685 cm^{-1} (lactam—C=O). (Found: C, 77·73; H, 10·94; N, 3·46. $C_{27}H_{45}O_2N$ requires: C, 78·02; H, 10·91; N, 3·37%).

4α-Bromo-6-aza-B-homo-5α-cholestane-3,7-dione (**3**). Pyridinium hydrobromide perbromide reagent (0·2 g) was dissolved in glacial AcOH (2 ml); compd **2** (0·25 g) was added to it in parts with continuous stirring, when a clear soln resulted. It was poured into water, solid filtered and washed with water till free from acid, dried and crystallized from acetone. Repeated crystallizations gave **3**, needles, m.p. 187–189° (41·4% yield), $[\alpha]_D$ —20·83° (*c*, 0·960); IR bands at 3390 (—NH—), 1748 (—C=O) and 1670 cm^{-1} (lactam—C=O); (Found: C, 65·95; H, 9·20; N, 2·98; Br, 15·89. $C_{27}H_{44}O_2NBr$ requires: C, 65·56; H, 8·96; N, 2·83; Br, 16·15%).

2′-Phenylaminothiazolo[d-3,4]-*6-aza-B-homo-5α-cholestan-7-one* [**4a**]. A soln of **3** (0·3 g) and N-phenylthiourea (0·3 g) in 95% EtOH (20 ml) was refluxed for 5 hr. The soln was made alkaline with 1% methanolic KOH and concentrated under reduced pressure. The resulting yellow ppt was filtered off, washed with 95% EtOH and dried. Crystallization from $CHCl_3$-EtOH gave **4a**, m.p. 277–281°, (45·1% yield); IR band at 1660 cm^{-1} (lactam —C=O); (Found: C, 74·44; H, 8·94; N, 7·36; S, 5·73. $C_{34}H_{49}ON_3S$ requires: C, 74·54; H, 9·02; N, 7·67; S, 5·85%).

Indolo[b-3,2]-*6-aza-B-homo-5α-cholestan-7-one* (**5a**). Compd **2** (0·25 g) was dissolved in glacial AcOH (7·5 ml), phenylhydrazine (0·45 ml) added to it dropwise and the soln heated on a steam bath for 20 min and poured into cold water (200 ml). The ppt was filtered off, washed with water till free from acid, dried in air and crystallized from MeOH. Repeated crystallizations gave **5a**, m.p. > 300° (dec), (55·1% yield), $[\alpha]_D 0°$ (*c*, 0·505); IR bands at 3280 (—NH—) and 1655 cm^{-1} (lactam —C=O); (Found: N, 6·04. $C_{33}H_{48}ON_2$ requires: N, 5·73%).

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