Acknowledgment.—The authors are grateful to Dr. G. Ellis and his staff for the microanalyses, Dr. C. Hetzel for the nmr spectra, Mr. B. Hofmann for the infrared spectra, and Mr. L. E. McCardle for technical assistance.

The Conversion of Steroidal α-Bromo Ketones into Ketols by Means of Hydrazine[1]

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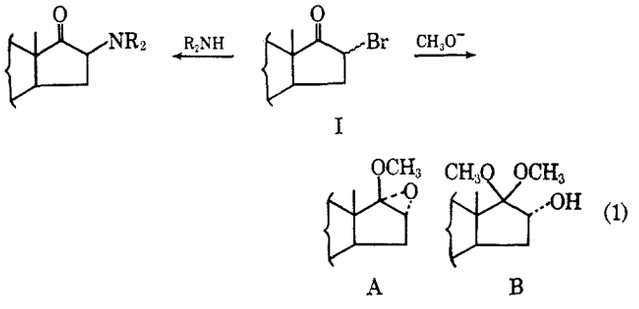
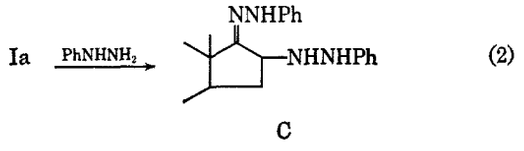
Received May 10, 1967

Recent studies on the chemistry of 16-bromo-17-keto steroids (I)[2] indicated that direct displacement of bromide by amines is possible in these α-bromo ketones. On the other hand, methoxide ions attacked at the carbonyl function with formation of ketal (B) *via* epoxide intermediates (A)[3] (eq 1).

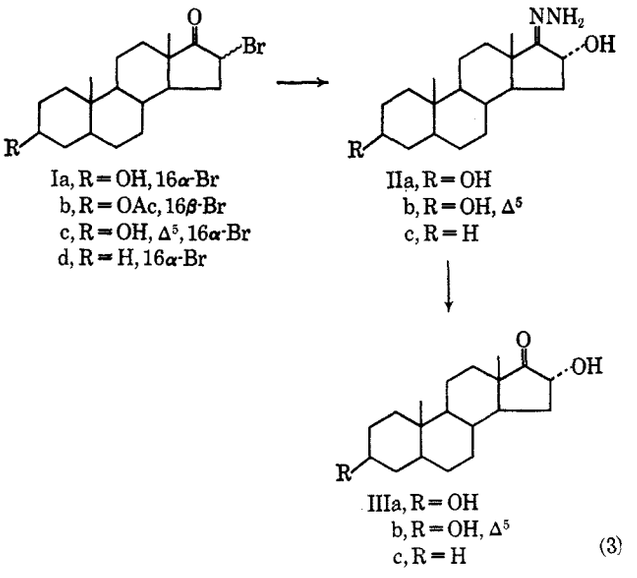


(1)

In conjunction with our investigation of the mechanism of osazone formation in the reaction of α-substituted ketones with phenylhydrazine,[4] we explored the reaction of steroidal α-bromo ketones with hydrazine itself. In contrast to the conversion of Ia into C with phenylhydrazine (eq 2)[4] treatment of 16α-bromoandrostan-3β-ol-17-one (Ia) with an excess of hydrazine hydrate in ethanol leads in 90% yield to 3β,16α-dihydroxyandrostan-17-one hydrazone (IIa). The structure of the latter was apparent from elemental analysis, infrared spectrum (ν_{max} 3400–3250 cm^{-1} (OH and NH), 1670 cm^{-1} (C=N)), and acid hydrolysis to the 17-keto-16α-ol (IIIa) (eq 3).

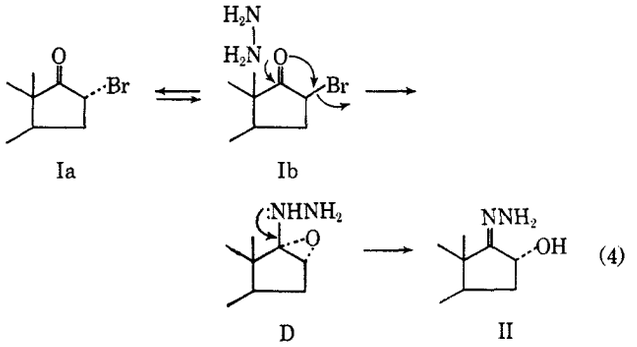


(2)

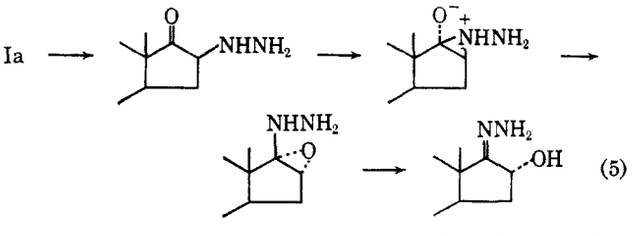


(3)

Ketols of type III are known to be stable under acid conditions although they are easily isomerized in basic medium.[3,5] Reduction of IIIa or IIIc with lithium aluminum hydride leads to 16α,17β-diols. Since the formation of II from I occurs with aqueous or anhydrous hydrazine, it can best be rationalized as in eq 4. This is analogous to the reaction of sodium methoxide with I which presumably proceeds through a similar epoxide intermediate (A). The 16α configuration of hydroxyl in II and III requires an α-epoxide intermediate (D) and hence the reaction should proceed *via* 16β-bromo 17-ketone (Ib). In fact, the 16β-bromo steroid Ib likewise gives II upon exposure to hydrazine. Another plausible mechanism consistent with our data has been suggested by the referee (eq 5).



(4)



(5)

The reaction of bromo ketones Ia or b with hydrazine constitutes a useful synthesis of 16α-hydroxy-17-ketoandrostanes and hence of 16α,17β-diols. In the same manner Ic and d were converted into IIIb and c, respectively.

(1) Stereochemistry. XXVI. For paper XXV, see A. Hassner and F. W. Fowler, *Tetrahedron Letters*, 1545 (1967).

(2) (a) C. L. Hewett and D. S. Savage, *J. Chem. Soc.*, 484 (1966); (b) A. Hassner and P. Catsoulacos, *J. Org. Chem.*, **32**, 549 (1967).

(3) A. Hassner and P. Catsoulacos, *ibid.*, **31**, 3149 (1966).

(4) A. Hassner and P. Catsoulacos, *Tetrahedron Letters*, 489 (1967); *Chem. Commun.*, 121 (1967).

(5) N. L. Leeds, O. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

Stevens and co-workers[6] observed similar results in the reaction of α-bromo ketones with liquid ammonia or ethylamine. Application of Stevens' method to steroidal α-bromo ketones I led only to isolation of starting material. On the other hand the reaction with hydrazine is applicable also to simpler α-bromo ketones. Thus α-bromoisobutyrophenone leads to α-hydroxyisobutyrophenone on treatment with hydrazine followed by hydrolysis.

Experimental Section[7]

General Procedure for the Reaction of Bromo Ketones I with Hydrazine Hydrate.—To 1 g of 16-bromo-17-keto steroid (I) in 20 ml of ethanol was added 10 ml of an aqueous 64% solution of hydrazine hydrate and the solution was heated under reflux for 90 min. After this time it was poured into ice water and the precipitate collected by filtration. The crystalline material was washed with water and dried to give an 90–94% yield of the hydrazone (II): ν_{max} 3400–3250 cm^{-1} (NH, OH), 1670–1675 cm^{-1} (C=N).

3β,16α-Dihydroxyandrostan-17-one Hydrazone (IIa). A. From 3β-Hydroxy-16α-bromoandrostan-17-one (Ia).—Compound IIa was crystallized from ethanol–water: mp 209–211°; $[\alpha]_D$ −45° ($CHCl_3$). *Anal.* Calcd for $C_{19}H_{32}N_2O_2$: C, 71.20; H, 10.07; N, 8.74. Found: C, 71.11; H, 10.26; N, 8.73.

B. **From 3β-Acetoxy-16β-bromoandrostan-17-one (Ib).**[8]—The infrared spectrum of this compound was identical with that of IIa prepared from the 16α-bromo ketone. Admixture melting point was undepressed.

3β,16α-Dihydroxy-5-androsten-17-one hydrazone (IIb) was prepared from 3β-hydroxy-16α-bromo-5-androsten-17-one, which in turn was obtained according to the method of Glazier[9] in 45% yield. The hydrazone IIb was purified by recrystallization from ethanol, mp 217–220°. *Anal.* Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.45; H, 9.70; N, 8.65.

16α-Hydroxyandrostan-17-one hydrazone (IIc) was prepared from the 16α-bromo 17-ketone Id which in turn was obtained according to the method of Fajkos.[10] Crystallization of IIc from ethanol gave product, mp 187–189°. *Anal.* Calcd for $C_{19}H_{32}N_2O \cdot 0.5H_2O$: C, 72.80; H, 10.54. Found: C, 72.45; H, 10.49.

General Procedure for the Hydrolysis of Hydrazones II.—Hydrazone II (0.5 g) was dissolved in 50 ml of methanol. To this solution was added 6 *N* sulfuric acid (5 ml) and the mixture was heated under reflux for 2 hr. After this time, the salt was removed by filtration and the filtrate was poured into water. After extraction with ether the organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was crystallized from appropriate solvents to yield ketols III.

3β,16α-Dihydroxyandrostan-17-one (IIIa).—Crystallization from methanol–water gave 255 mg (53%) of IIIa, mp 181–184°. An additional crystallization from acetone–Skellysolve F gave material of mp 185–187° (lit.[3] mp 184–186°), identical by infrared spectra with the ketol from the hydrolysis of 17,17-dimethoxyandrostane-3β,16α-diol.[3] Reduction of IIIa with lithium aluminum hydride in ether and acetylation yielded androstane-3β,16α,17β-triol triacetate, identical by infrared spectra with an authentic compound prepared according to Leeds and co-workers.[5]

3β,16α-Dihydroxy-5-androsten-17-one (IIIb).—Crystallization from methanol–water yielded 360 mg (75%) of IIIb, mp 183–187°; an additional crystallization from the same solvent gave mp 187–189° (lit.[11] mp 177–181°). Acetylation of diol IIIb gave 3β,16α-diacetoxy-5-androsten-17-one, mp 167–168° (lit.[11] 166–168°).

16α-Hydroxyandrostan-17-one (IIIc).—Crystallization from acetone–Skellysolve F gave 245 mg (53%) of IIIc, mp 161–163°. The analytical sample melted at 163–164°: ν_{max} 3450 (OH), 1760 cm^{-1} (C=O). *Anal.* Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.66; H, 10.46.

16α-17β-Dihydroxyandrostane.—16α-Hydroxyandrostan-17-one (IIIc) (90 mg) was dissolved in 20 ml of anhydrous ether and an excess of lithium aluminum hydride was added. The mixture was heated under reflux for 2.5 hr. Excess hydride was decomposed with dilute sulfuric acid. The diol was extracted with ether and the organic layer was washed with water and dried over $MgSO_4$. Crude product (80 mg) was obtained when the solvent was removed under reduced pressure. Crystallization from acetone–Skellysolve F gave pure diol: mp 217–218°; ν_{max} 3330 cm^{-1} (OH). *Anal.* Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.88; H, 11.25.

This compound was identical by infrared spectra with the compound prepared by reduction of 17β-acetoxy-16α,17α-oxidoandrostane with lithium aluminum hydride according to the method of Leeds and co-workers.[5]

Reaction of α-Bromoisobutyrophenone with Hydrazine.—The procedure described for the preparation of steroid hydrazones II was followed with α-bromoisobutyrophenone to give the hydrazone in 64% yield. Hydrolysis with 6 *N* sulfuric acid in methanol yielded 80% of crude α-hydroxyisobutyrophenone. The crude product was fractionated *in vacuo* to yield pure ketol, bp 85–87° (1.6 mm).

Registry No.—IIa, 13866-68-7; IIb, 13866-69-8; IIc, 13866-70-1; IIIc, 13866-71-2; 16α,17β-dihydroxyandrostane, 13866-72-3; hydrazine, 302-01-2.

Acknowledgment.—This investigation was supported by Public Health Service Grant CA-04474 from the National Cancer Institute.

(6) C. L. Stevens, P. Blumberg, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).

(7) All melting points are taken on Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined in the solid phase (KBr) on a Beckman IR-5 spectrophotometer. Elemental analyses were performed by A. Bernhardt, Mühlheim, and by MHW Laboratories, Mich.

(8) J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955).

(9) E. R. Glazier, *J. Org. Chem.*, **27**, 4397 (1962).

(10) J. Fajkos, *J. Chem. Soc.*, 3966 (1959).

(11) K. Fotherby, A. Colas, S. Atherden, and G. Marrian, *Biochem. J.*, **66**, 664 (1957).