17-Azasteroids. I[1]

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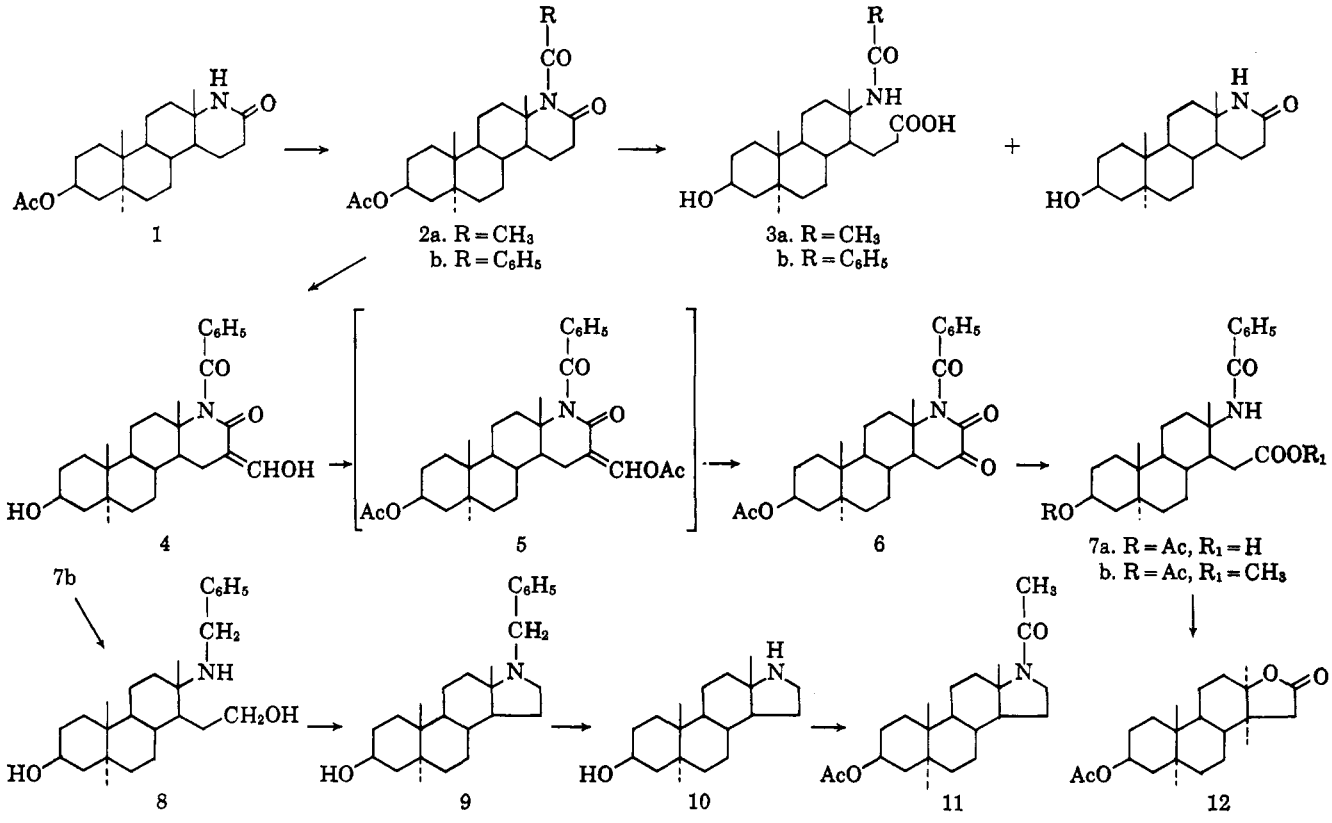
The elimination of C-17 from a known 17a-aza-D-homosteroid gave 13α-benzylamino-13,16-seco-5α-17-norandrostane-3β,16-diol which could be cyclized to produce a 17-azasteroid. This paper describes the synthesis of 3β-acetoxy-5α-17-azapregnan-20-one.

Structural modifications of naturally occurring steroids have produced changes in their biological activities which usually cannot be predicted. In this connection a recently published synthesis of 17-oxa-5α-androstan-3-one[2] noted that a modification of that procedure could lead to 17-azasteroids.

Although several publications[3-5] have appeared recently in which a total synthesis was used for the preparation of azasteroids, it was decided that a partial synthesis might yield the desired product more readily, and this paper describes the elimination of C-17 from a 17a-aza-D-homolactam, followed by reduction and ring closure to a five-membered amine. (See Chart I.)

CHART I



The known 3β-acetoxy-17a-aza-5α-D-homoandrostan-17-one[6] (1), prepared by the Beckmann rearrangement of the oxime of 3β-acetoxy-5α-androstan-17-one, served as starting material. The first step in the degradation of ring D was the introduction of a carbonyl function on C-16 which, by virtue of the α-dicarbonyl grouping, would make possible the elimination of C-17.

Originally, it was planned to formylate the six-membered lactam (in close analogy[7] to the formylation of the corresponding lactone), which then could be degraded to the desired α-keto lactam. Attempts employing conventional procedures for the formylation of C-16 failed. Acetylation or benzoylation of the lactam 1 rendered the 17-carbonyl of the resulting imide more "ketonic," evidenced by the preferential cleavage of the bond between the nitrogen and C-17 on alkaline treatment. This could be explained by the release of I-strain[8] or the generally greater reactivity of trigonal carbons (*e.g.*, >C=O) in a cyclohexyl *vs.* acyclic systems. This greater ketonic character led to preferential hydroxy methylation of the imides **2a** and **2b** in the 16 position. However, condensation also occurred on the methyl carbon of the acetate groups of **2a**. The

(1) This work was supported, in part, by a National Institutes of Health grant H-5266.

(2) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

(3) G. R. Clemo and L. K. Mishra, *J. Chem. Soc.*, 192 (1953).

(4) J. H. Burckhalter and H. Watanabe, Abstracts, 143rd National Meeting of the American Chemical Society, Cincinnati, Ohio, Jan., 1963, p. 14A.

(5) R. I. Meltzer, D. M. Lustgarten, R. J. Stanaback, and R. E. Brown, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 39M.

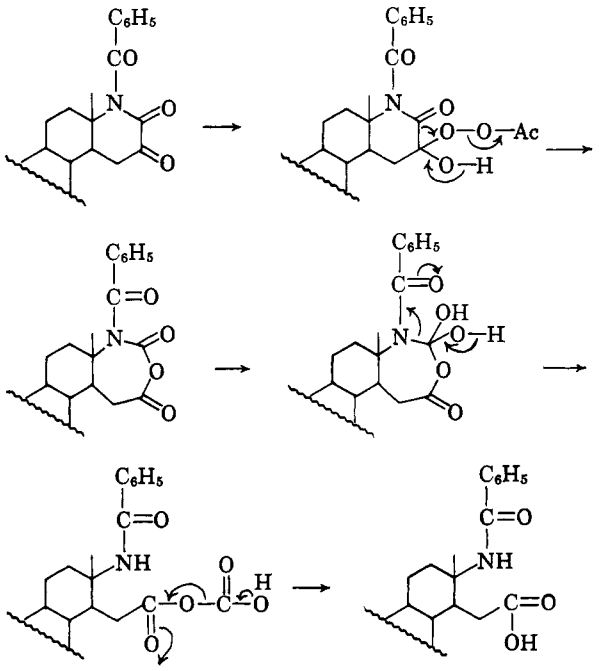
(6) R. Anliker, M. Müller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **38**, 1404 (1955).

(7) L. H. Knox, R. Villotti, F. A. Kincl, and H. J. Ringold, *J. Org. Chem.*, **26**, 501 (1961).

(8) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

imide **2b**, upon treatment with ethyl formate and sodium hydride in dry benzene, yielded in excellent yield the desired hydroxy methylene product **4**. Acetylation of **4** gave the diacetate **5**, which was directly ozonized without purification. The ozonolysis yielded a neutral product, which was identified as the desired 16-keto-N-benzoyl lactam, and as main product an acid which was first esterified with diazomethane, then acetylated, and finally chromatographed to give ester **7b** in excellent yield. The neutral α-keto benzoylamide (**6**) could be degraded to **7b** with peracetic acid. (See Chart II.)

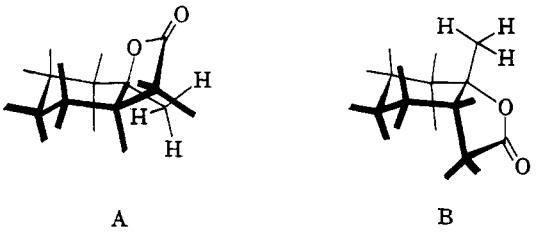
CHART II



A plausible mechanism for this degradation is a Baeyer–Villiger type attack on the carbonyl at C-16 followed by rearrangement to the anhydride. Hydration of the carbonyl at C-17 would then be followed by ring opening to a hydrogen carbonate which readily hydrolyzes with a concomitant loss of the original C-17. However, the same over-all change could have been effected by attack on the C-17 carbonyl. The over-all yield in the sequence from **1** to **7b** was approximately 37%. At this point, the first objective (the elimination of C-17) had been reached.

Possessing a satisfactory method for the preparation of a 17-nor compound, there remained for the completion of the synthesis the ring closure to the five-membered amine. The N-benzoyl ester (**7b**) was reduced with excess lithium aluminum hydride which gave the N-benzyl diol (**8**). The benzylamine (**9**) was obtained in good yield by treatment of **8** with thionyl chloride at room temperature. The hydrogenolysis of the N-benzyl compound (**9**) in ethanol containing a few drops of acetic acid over a platinum oxide catalyst gave a crystalline but very hygroscopic product (**10**), which was acetylated without any further purification to yield 3β-acetoxy-17-aza-5α-pregnan-20-one.[9]

Treatment of the acid **7a** with concentrated hydrochloric acid in acetic acid, instead of producing the desired five-membered lactam, yielded exclusively a nonnitrogenous compound identified as 3β-acetoxy-5α,13α-17-oxaandrostan-16-one (**12**). The structural assignment of **12** is based on its elemental analysis, its infrared absorption spectrum, its n.m.r spectrum,[10] and finally its nonidentity with the known 3β-acetoxy-17-oxa-5α-androstan-16-one.[2] This isolactone **12**, which has a C–D *cis* ring fusion, is the thermodynamically more stable product because it can be produced from 3β-acetoxy-17-oxa-5α-androstan-16-one under identical conditions. Inspection of models of the two possible isolactones **12** reveals that in the case of the 14β isomer (B) there are more severe 1,3-diaxial nonbonding interactions than in the case of the 13α isomer (A). A number of plausible mechanisms, *e.g.*, elimination of the benzamido group, formation of a carbonium ion at C-13, or assisted solvolysis, can be suggested to explain the over-all change.



A B

Experimental[12]

3β,N-Diacetoxy-17a-aza-5α-D-homoandrostan-17-one (2a$_{AB}$ from 1.—A solution of 900 mg. of the lactam **1** in 10 ml. of pyridine and 5 ml. of acetic anhydride was heated on a steam bath for 5 hr. The solution was cooled, the excess acetic anhydride was decomposed with methanol and then poured into ice–water. The resulting precipitate was collected, washed thoroughly with water, and dried to yield 1.05 g. of crude diacetate. Crystallization from ether gave 880 mg. of pure **2a**, m.p. 134–136°. A portion was recrystallized for analysis from ether–hexane, m.p. 136–138°; $[\alpha]_D$ −14° (*c* 0.8); infrared absorption, ν_{max} 1730 (3-acetoxy), 1650 (N-acetyl lactam), and 1250 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{35}NO_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 71.19; H, 9.01; N, 3.74.

3β-Hydroxy-13,17-seco-17α-acetylamino-5α-androstan-17-oic Acid (3a) from 2a.—To a solution of 360 mg. of the N-acetyl D-lactam (**2a**) in 50 ml. of methanol was added 200 mg. of potassium hydroxide in 5 ml. of water, and the mixture was refluxed for 2.5 hr., after which most of the methanol was removed *in vacuo*. Dilution with water was followed by extraction with ether. The ether layer was washed with 2 *N* potassium hydroxide and water, and then dried over sodium sulfate. Removal of solvent yielded 60 mg. of a neutral substance, m.p. 295–297°, which was identical in all respects with the known 3β-hydroxy-17a-aza-5α-D-homoandrostan-17-one.[6] The alkaline solution and the aqueous washings were mixed and acidified with 2 *N* hydrochloric acid to

(9) The conformation of the side chain is being investigated.

(10) In the case of the isolactone **12**, the C-15 protons are shifted downfield compared to the C-15 protons of the normal lactone,[2] probably owing to different stereochemical relationship with the rest of the molecule. They appear as two doublets centered at τ 7.17 (15α-H) and 7.79 (15β-H) with J_{AB} = 17 c.p.s., and are further split by the 15α proton with J_{AX} = 6 c.p.s. and J_{BX} ~ 0 c.p.s. (where A is 15α-H and B is 15β-H). The calculated values from the Karplus equation[11] are θ_1 (14α–15α) ~33° and θ_2 (14α–15β) ~87°. Inspection of a model of lactone **12** reveals that the dihedral angles between 14α and 15α is 30° and between 14α and 15β is 90°, comparing well with the values obtained from the Karplus equation.

(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(12) The microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points were taken on a Fisher-Jones hot stage and are corrected. Rotations were taken, unless noted otherwise, in chloroform. The infrared spectra were recorded from a pressed potassium bromide pellet on a Perkin-Elmer infracord spectrophotometer. Davison Type 923, 100–200-mesh silica gel was used for all chromatographic separations. The ultraviolet absorption spectrum was taken in methanol solution on a Cary 14 spectrophotometer. The n.m.r. spectra were recorded on a Varian V-4300B spectrometer using 20% solutions in deuteriochloroform and tetramethylsilane as an internal standard.

congo red. The flocculent precipitate was extracted with dichloromethane; the extract was washed with water, dried over sodium sulfate, and taken to dryness to give 290 mg. of acid **3a**, m.p. 223–226°. An analytical sample was prepared by recrystallization from acetone–hexane and had m.p. 226–227°; $[\alpha]_D$ +33° (*c* 0.85); ν_{max} 3350 (–OH), 3200 (N–H), 1698 (C=O of acid), 1630 (C=O of amide), and 1570 (N–H deformation and C–N stretching of amide) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.95; H, 9.61; N, 3.90.

3β-Acetoxy-N-benzoyl-17a-aza-5α-D-homoandrostan-17-one (2b) from 1.—To a solution of 1.42 g. of the lactam in 10 ml. of dichloromethane was added 60 ml. of a 15% aqueous solution of sodium hydroxide. The mixture was stirred vigorously with cooling (0–5°) while 7 ml. of benzoyl chloride in 10 ml. of dichloromethane was added within a period of 45 min. The mixture was stirred at room temperature for another 1 hr. Then the dichloromethane layer was separated and washed twice with a cold 2 *N* sodium hydroxide solution and then washed free of alkali with ice–water and dried over sodium sulfate. Removal of solvent yielded 1.52 g. of an oil which was crystallized from ether to give 1.25 g. of the N-benzoyl derivative (**2b**), m.p. 215–217°. The analytical sample was prepared by recrystallization from ether and had m.p. 216.5–217.5°; $[\alpha]$ +5° (*c* 0.75); infrared absorption maxima, ν_{max} 1740 (3-acetate), 1720 (N-benzoate), 1680 (C=O of lactam), 1625 (C=C aromatic), and 1250 (acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.16; H, 8.62; N, 3.17.

3β-Hydroxy-13,17-seco-13a-benzoylamino-5a-androstan-17-oic Acid (3b) from 2b.—Alkaline treatment of the N-benzoyl lactam (**2b**) according to the procedure described for the N-acetyl lactam gave in 70% yield the N-benzoyl seco acid (**3b**), m.p. 223–225°. The neutral material was identified as the known 3β-hydroxy-17a-aza-5α-D-homoandrostan-17-one.[6] An analytical sample of the acid was prepared by recrystallization from dichloromethane ether, m.p. 225–227°; $[\alpha]_D$ +10° (*c*, 1.0, methanol); infrared absorption maxima, ν_{max} 3350 (OH), 3250 (N–H), 1700 (C=O), 1680 (C=O of N benzoate), 1575 (C=C, aromatic), and 1550 (N–H deformation) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.18; H, 8.85; N, 3.51.

3β-Hydroxy-N-benzoyl-16-hydroxymethylene-17a-aza-5α-D-homoandrostan-17-one (4) from 2b.—To a solution of 2 g. of N-benzoyl lactam (**2b**) in 150 ml. of dry thiophene-free benzene was added 1.5 g. of sodium hydride. While the mixture was being stirred under nitrogen, 8 ml. of dry ethyl formate was added within 5 min., and the mixture was stirred for another 4.5 hr. at room temperature under nitrogen. The excess hydride carefully was decomposed by adding methanol and then water. The aqueous layer was separated, and the benzene layer was washed with water. The aqueous alkaline solution and the first washing were combined and acidified with cold hydrochloric acid, thereby precipitating the hydroxy methylene derivative (**4**). The precipitate was filtered off, washed thoroughly with water, and dried to give 2.1 g. of **4**. This product did not crystallize well and gave a poor analysis (probably due to some water of crystallization); it had m.p. 135–138°; $[\alpha]^{22}_D$ –49° (*c* 1.0, methanol); infrared absorption maxima, ν_{max} 3500 (–OH), 1690, 1650 (Ph–C(=O)–N–C(=O)–), and 1600 (hydroxymethylene C=C) cm.$^{-1}$; λ_{max} 245 mμ (log ε 3.90).

3β-Acetoxy-N-benzoyl-16-acetoxymethylene-17a-aza-5α-D-homoandrostan-17-one (5) from 4.—To a solution of 1.5 g. of the hydroxymethylene compound (**4**) in 10 ml. of pyridine, 5 ml. of acetic anhydride was added and stored at room temperature for 18 hr. Decomposition of excess acetic anhydride with methanol and usual work-up yielded 1.6 g. of oily diacetate **5** (no hydroxyl band in the infrared spectrum).

3β-Acetoxy-N-benzoyl-17a-aza-5α-D-homoandrostane-16,17-dione (6) and Methyl 3β-Acetoxy-13α-benzoylamino-13,16-seco-5α-17-norandrostan-16-oic Acid (7b) from 5.—A stream of ozone was passed through a solution cooled to –10° of 1.5 g. of the oily diacetate **5** in 60 ml. of a 1:1 mixture of ethyl acetate and acetic acid for 1 hr. After that, 10 ml. of 30% hydrogen peroxide and 10 ml. of water were added, and the mixture was stored at room temperature for 18 hr. After extraction with a large volume of ether, the ether solution was washed with water, then with five 50-ml. portions of cold 2 *N* sodium hydroxide solution, and then again with water. The solution was dried over sodium sulfate and the ether was evaporated, yielding 295 mg. of a neutral product—3β-acetoxy-N-benzoyl-17a-aza-5α-D-homoandrostane-16,17-dione (**6**), m.p. 212–215°. A sample was prepared for analysis by recrystallization from methanol–ether and had m.p. 216–218°; $[\alpha]^{22}_D$ +32° (*c* 0.85); ν_{max} 1745 (3-acetoxy), 1700 (N-benzoate and 16-ketone), 1675 (C=O lactam), 1625 (C=C aromatic), and 1245 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{35}NO_5$: C, 71.49; H, 7.78; N, 3.09. Found: C, 71.87; H, 7.43; N, 3.35.

The alkaline solution and the first aqueous washing were combined, acidified to congo blue with cold 2 *N* hydrochloric acid, and extracted with dichloromethane. The organic extract was washed several times with water and dried over sodium sulfate. Removal of solvent gave 1.05 g. of the oily acid **7a**. Since attempts to crystallize the acid failed, it was methylated in ethereal solution with diazomethane. Evaporation of the solvent left 1.18 g. of an oil, the infrared spectrum of which showed the presence of a small hydroxyl band and a low intensity acetoxy band. The oil then was acetylated in pyridine solution with acetic anhydride at 0° for 16 hr. Usual work-up yielded 1.12 g. of an oil which was chromatographed on a column of 100 g. of silica gel. Elution with ethyl acetate–benzene mixtures (8:92) yielded crystalline fractions melting between 124–128°, which were combined to give 850 mg. of the crystalline ester **7b**. Two recrystallizations from hexane yielded an analytical sample, m.p. 126–127°; $[\alpha]^{22}_D$ –7° (*c* 1.0); ν_{max} 3400 (N–H of amide), 1735 (3-acetate), 1675 (C=O of benzamide), 1600 (C=C aromatic), 1530 (N–H deformation of amide), and 1245 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{39}NO_5$: C, 71.61; H, 8.37; N, 2.98. Found: C, 71.73; H, 8.39; N, 3.07.

Methyl-3β-Acetoxy-13α-benzoylamino-13,16-seco-5α-17-norandrostan-16-oic Acid (7b) from 6.—To a solution of 150 mg. of the 16-keto-N-benzoyl lactam (**6**) in 5 ml. of acetic acid and 5 ml. of ethyl acetate was added 1 ml. of 40% peracetic acid, and the mixture was stored at room temperture for 24 hr. Then it was diluted with ethyl acetate and washed several times with water and then extracted with a cold 2 *N* sodium hydroxide solution and water. Drying over sodium sulfate and subsequent removal of the solvent yielded 5 mg. of a neutral product identified as starting material **6**. The alkaline extract was acidified with cold 2 *N* hydrochloric acid, and the acidic material was extracted with dichloromethane. The dichloromethane extract was washed with water and dried over sodium sulfate. Upon removal of the solvent, 120 mg. of an oily residue was left, which was esterified in ethereal solution with diazomethane to give 120 mg. of a crystalline ester, m.p. 125–127°, identical in all respects with the ester **7b** obtained previously.

13α-Benzylamino-13,16-seco-5α-17-norandrostane-3β,16-diol (8) from 7b.—To a slurry of 600 mg. of lithium aluminum hydride in 200 ml. of purified tetrahydrofuran was added a solution of 450 mg. of the ester **7b** in 20 ml. of absolute tetrahydrofuran, and the mixture was refluxed for 72 hr. After cooling, the excess reagent was decomposed with ethyl acetate and a saturated solution of sodium sulfate was added to coagulate the inorganic materials. The precipitate was filtered off and the residue was washed thoroughly with tetrahydrofuran. The washings and the filtrate were combined and dried over sodium sulfate. Removal of solvent *in vacuo* yielded 380 mg. of an oil, the infrared spectrum of which did not show any carbonyl band and which was chromatographed on a column of 40 g. of silica gel. Elution with ethyl acetate–benzene mixtures (35 to 50%) gave material melting between 150–155°. These fractions were combined to give 300 mg. of 13α-benzylamino-13,16-seco-5α-17-norandrostane-3β,16-diol (**8**). A sample was recrystallized from dichloromethane–hexane for analysis, m.p. 159–161°; $[\alpha]^{22}_D$ –26° (*c* 0.75); ν_{max} 3400 (OH), and 3200 (N–H) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.20; N, 3.63. Found: C, 77.64; H, 10.40; N, 3.50.

N-Benzyl-5α-17-azaandrostan-3β-ol (9) from 8.—To a solution of 400 mg. of the diol **8** in 15 ml. of dioxane, 1.0 ml. of freshly distilled thionyl chloride was added, and the solution was left at room temperature for 1 hr. Ice was added and the solution was neutralized with sodium hydrogen carbonate. The resulting precipitate was extracted with ethyl acetate, and the extract was washed several times with water and then dried over sodium sulfate. Removal of solvent yielded 370 mg. of an oil which was chromatographed on a column of 35 g. of silica gel. Elution with 25% ethyl acetate in benzene yielded 300 mg. of crystalline **9**,

m.p. 143–146°. A sample was recrystallized from ether–hexane for analysis and had m.p. 147–148°; $[\alpha]^{22}D$ +37° (*c* 1.0); ν_{max} 3450 (OH) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}NO$: C, 81.69; H, 10.15; N, 3.81. Found: C, 81.81; H, 10.15; N, 4.01.

3β-Acetoxy-5α-17-azapregnan-20-one (11) from 9.—The solution of 300 mg. of the N-benzyl compound (9) in 10 ml. of methanol containing a few drops of acetic acid was added to 50 mg. of platinum oxide, and the mixture was reduced with hydrogen for 18 hr. at 40 p.s.i. The catalyst was filtered off and washed with some ethanol. Evaporation of solvent gave 250 mg. of an oil which crystallized from ether. The crystals were too hygroscopic for isolation and the amine, therefore, was acetylated at room temperature with 2 ml. of acetic anhydride in 5 ml. of pyridine for 18 hr. Usual work-up yielded 270 mg. of an oil which was chromatographed on a silica gel column. Elution with 30–35% ethyl acetate in benzene yielded 200 mg. of crystalline 17-azapregnanolone acetate (11), m.p. 175–176°. A portion was recrystallized from ether for analysis and had m.p. 180–182°; $[\alpha]^{22}D$ +24° (*c* 0.63); ν_{max} 1740 (3-acetate), 1660 (C=O of N-acetate), and 1245 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.11; H, 9.82; H, 3.90.

3β-Acetoxy-5α,13α-17-oxaandrostan-16-one (12) from 7a.—To a solution of 200 mg. of benzamido acid (**7a**) in 10 ml. of glacial acetic acid was added 2.2 ml. of concentrated hydrochloric acid, and the mixture was refluxed under nitrogen for 20 hr. The acids were removed *in vacuo*, water was added, and the residue was extracted with dichloromethane. The extract was washed with a 2 *N* sodium carbonate solution and water and dried over sodium sulfate. Removal of solvent yielded 130 mg. of neutral material which was chromatographed on a column of 15 g. of silica gel. Elution with 5% ethyl acetate in benzene yielded 110 mg. of the lactone **12**, m.p. 140–143°. A portion of it was recrystallized from ether for analysis and had m.p. 145–146°; $[\alpha]^{22}D$ −23° (*c* 1.00 in dioxane); ν_{max} 1754 (γ-lactone), 1725 (3-acetate), and 1235 (3-acetate) cm.$^{-1}$; τ 7.17 (15α-H, $J_{15\alpha,15\beta}$ = 17 c.p.s. and $J_{15\alpha,14\alpha}$ = 6 c.p.s.), 7.79 (15β-H, $J_{15\beta,25\alpha}$ = 17 c.p.s. and $J_{15\beta,14\alpha}$ = 0 c.p.s.), 8.68 (18-CH_3), and 9.27 (19-CH_3).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.58; H, 9.04.

Acknowledgment.—Thanks are due to Mr. Thomas A. Wittstruck for the recording, calculation, and interpretation of the n.m.r. data.

The Ionization Constants of Some Imidazoles

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The basic and the acidic ionization constants of some imidazole derivatives have been determined spectrophotometrically or potentiometrically. For the nitroimidazoles, the spectrophotometric method has been used in concentrated sulfuric acid solutions for which the Hammett acidity function, H_0, has been adopted. Tautomeric equilibrium constants of the imidazoles containing an imino hydrogen have been calculated. The ionization constants have been correlated to the substituents and their position in the imidazole ring. The usefulness of pK_a measurements in assigning structures of these compounds is pointed out.

The chemistry of imidazoles has been studied[1] extensively and attention has been paid to their ionization constants. The pK_a values of some imidazoles have been determined[1,2] and useful observations have been made recently for some nitro derivatives, whose basicity is diminished strongly by the electronegative nitro group.[3] We then have considered of interest a further study of the basicity of the imidazole derivatives of this type. The potentiometric method was used for the derivatives whose basic dissociation constants were still measurable in this way. For the nitro derivatives we adopted the spectrophotometric method in concentrated acid solutions, which provides a suitable way for obtaining correct values. The acidic ionization constants also were determined potentiometrically. All the results obtained, together with data referred to in literature, have been correlated and evaluations useful for structure determination have been found.

Results and Discussion

The absorption spectra of the nitroimidazoles studied are reported in Table I. The introduction of a nitro group in the imidazole ring markedly changes the ultraviolet spectrum: the imidazole band at 207–208 mμ (ϵ_{mol} 5010)[4] is shifted to about 300 mμ in the nitro derivatives. This latter band is affected by the pH of the medium, and it shifts to longer wave lengths by acidic ionization and to shorter ones by protonation (see Table I). The ultraviolet absorption then allowed us to calculate the basic pK_a values of nitroimidazoles. The electron withdrawing effect of the nitro group strongly diminishes the basicity of the nitroimidazoles, and those containing an imino hydrogen behave as acids in water solution. The protonation takes place only in solutions of concentrated acids, and the pK_{BH^+} values become very low or even negative. The acidity of the solutions used was expressed with the Hammett function, H_0.[5] A number of solutions of sulfuric acid in water were prepared, and, from the tables reported by Paul and Long,[6] the corresponding H_0 values were derived, some of them having been confirmed using *p*-nitroaniline, *o*-nitroaniline, and 2,4-dinitroaniline as indicators.[7] The H_0 function already has been adopted for substituted imidazoles[3] even though these compounds are very different in structure from the aniline derivatives used in establishing the H_0 scale. The similarity in slopes found for the nitroimidazoles and the indicators indicates that the H_0 values of sulfuric acid solutions may be used for

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