AZA STEROIDS

IV. SYNTHESIS OF 11-AZA STEROIDS IN THE PREGNANE SERIES.[1]

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ABSTRACT

Lithium aluminum hydride reduction of 3β-hydroxy-11-aza-5α, 22β-spirost-8(9)-en -12-one (I) provides the enamine, II, which upon subsequent conversion to its iminium salt, IV, and borohydride reduction yields 11-aza-5α, 8ξ, 9α, 22β-spirostan-3β-ol (V). This reaction furnishes a convenient sequence for reduction of the 8,9-double bond in 11-aza steroid derivatives. Degradation of the sapogenin side chain then allows entry into 11-aza pregnane derivatives. The synthetic sequence provides the first examples of 11-aza steroid analogues in which ring C is six-membered and completely saturated.

In a previous paper in this series[2] we reported the first successful synthesis of an 11-aza steroid in the steroidal sapogenin series. It was felt at the time that this intermediate (I) may provide a convenient route to the pregnane and possibly to the adrenocortical class as well. We now report the preparation of some 11-aza pregnane derivatives.

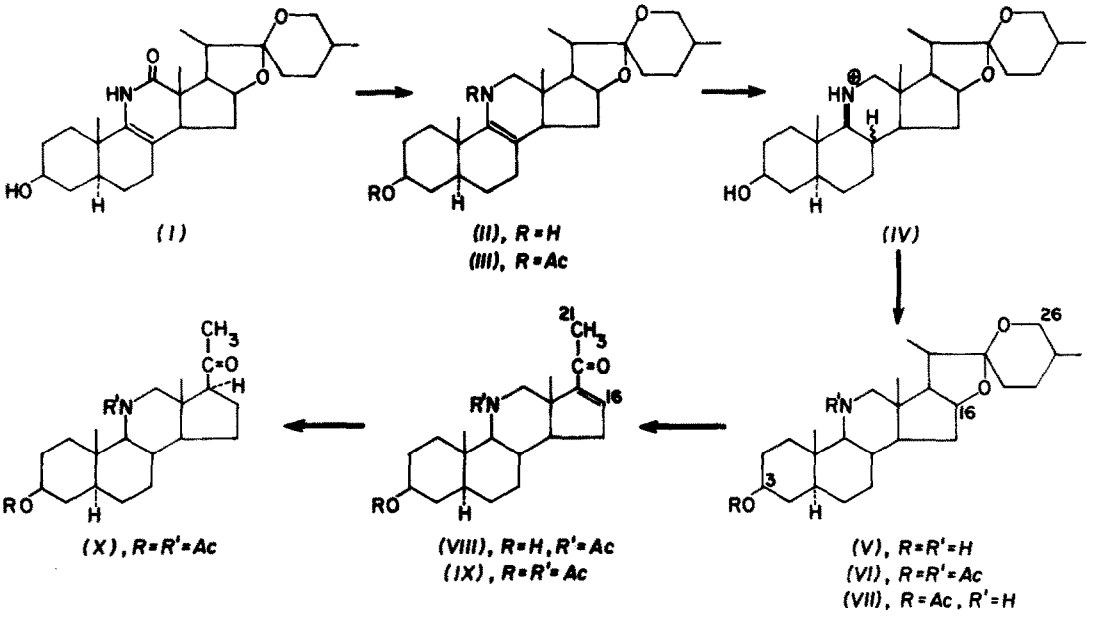
From previous results in our laboratory in the area of 6-aza steroids[3] and those of other workers[4] it was apparent that the hydride reduction of an enol lactam system could lead to either an enamine or

imine function. We decided to investigate this possibility in the case of the 11-aza intermediate, I. Reduction of I with lithium aluminum hydride in refluxing tetrahydrofuran provided a new reaction product and the spectral properties of this material quickly established that the lactam had been reduced. The strong lactam absorption present in the infrared spectrum of I had disappeared and instead, a weak absorption at 6.13μ (1632 cm^{-1}) characteristic of the enamine chromophore was now evident. The expected shift to 6.02μ (1660 cm^{-1}) was also observed in the infrared spectrum of the hydrochloride salt of II in good agreement with published work on α,β-unsaturated amines. Furthermore, the characteristic absorption in the ultraviolet spectrum of the enol lactam, I, (λ_{max} 255 mμ) was also absent in the ultraviolet spectrum of the reduction product but now a new absorption at 236 mμ was noted. This data was again in good agreement with the enamine chromophore which has been extensively investigated in the ultraviolet region by Leonard and co-workers.[6] This evidence excludes the imine chromophore since the $\geq$C=N- grouping would not exhibit these spectral properties and we assign structure II to this reduction product. In spite of numerous attempts to obtain this enamine crystalline we were unsuccessful and consequently characterized this compound as the acetate, III.

It should be noted at this point that Engel and Rakhit[7] have reported a similar reduction and also postulate an enamine grouping although no spectral data is presented for the product obtained directly from the reduction. They also encountered difficulties in obtaining a crystalline product and report spectral data on the crystalline acetate derivative of the enamine. These authors have

also reduced their enamine derivatives to the saturated 11-aza analogues.[8]

Having obtained the $\Delta^{8,9}$-11-aza hecogenin derivative, II, we then considered the reduction of the 8,9 double bond. It is well known from the normal steroid series that this double bond is particularly difficult to hydrogenate and the necessary conditions would almost certainly destroy the spiroketal system so that this method could not be seriously considered. It was felt that one way to eliminate this difficulty would be to convert the enamine, II, into the iminium system, IV, and then subsequently reduce the latter by means of a hydride reagent. The conversion, $\rangle C{=}C\text{-}N\langle \longrightarrow \rangle \underset{H}{C}\text{-}C{=}\overset{+}{N}\langle$, is well known from the work of Leonard on unsaturated amines[5,9] and strong support for the success of this reaction was already evident from the observed shift in the infrared spectrum of the salt derivative of II.



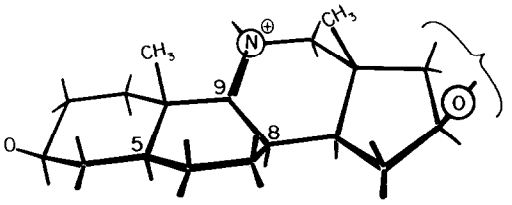
Indeed when the enamine, II, was first treated with anhydrous hydrogen chloride and the resulting crude product was subjected to reduction with sodium borohydride, we obtained after chromatographic purification, the desired reduction product, V, m.p. 211-212°C, as one of the crystalline substances from this reaction. Three other crystalline products were actually obtained from this reaction and the pertinent data is provided in the experimental portion although further work is necessary before complete structural assignments can be made in these instances. The reduction product, V, exhibited the expected spectral properties in agreement with the assigned structure. The compound no longer showed any absorption in the ultraviolet spectrum and the enamine absorption in the infrared region was also absent. The characteristic spiroketal bands[10,11] were still present in the fingerprint region of the infrared spectrum and therefore indicated that, as expected, the spiroketal system was still intact.

Nuclear magnetic resonance (NMR) spectroscopy also played an important role in providing confirmatory evidence for all the structures in this investigation. This was possible since in relation to another problem a detailed analysis of the NMR spectra of a large number of known steroidal sapogenins had been carried out[12,13] and pertinent regions of the NMR spectra could be now assigned with certainty. It is necessary at this point to discuss briefly some of the relevant features of the previous work as they apply to the present study. We had previously shown that in the instance of saturated sapogenins, the low field region of the NMR spectra indicated only two sets of signals. One set was observed as a broad multiplet which showed two main broad signals in the region 200-210 c.p.s.,[14] which was attributed

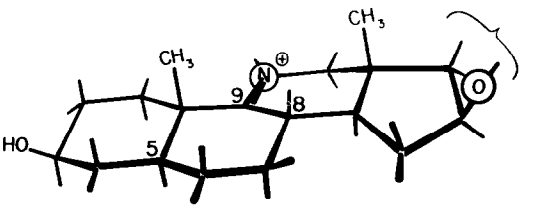
to the C_{26} protons of the spiroketal system and the other set at lower field (250-300 c.p.s.) was due to the one proton at C_{16} and the C_3 proton in the case of C_3-acetylated sapogenins. With this information on hand, one could readily analyze the low field region of the NMR spectrum of V. As expected the signals due to protons at C_3, C_{16} and C_{26} were clearly evident but in addition to these signals, new sets of lines appeared in the region, 130-185 c.p.s. and which corresponded in area to three additional protons. This region is normally completely devoid of any signals as shown by the spectra of numerous steroidal sapogenins and it was immediately obvious that these absorptions were due to protons on carbon atoms attached to the basic nitrogen atom (C_9 and C_{12}). This latter fact was confirmed when the NMR spectrum of the crystalline diacetate, VI, was analyzed. One would expect that the C_9 and C_{12} protons would now be shifted downfield and indeed this was the case. There was a general downfield shift of the signals in the 130-185 c.p.s. region and most importantly this region now constituted an area due to only two protons. A new one-proton signal now appeared as a broad doublet at lower field (220-245 c.p.s.) and was attributed to the C_9 proton. The presence of the O-acetyl and N-acetyl groupings in VI was confirmed by two spikes at 118 and 128 c.p.s. The proximity of the N-acetyl function to the C_{19} angular methyl group could also be recognized by analysis of the high field region in the NMR spectra of V and VI. In the former, the two angular methyl groups were barely separated and were observed as two sharp lines at 53 and 55 c.p.s. respectively, whereas in the latter a larger separation was noted (47 and 58 c.p.s.) and, as expected, the C_{19} signal now occurred at lower field. It was now clear that the sodium borohydride reduction

had been successful.

The stereochemistry of the newly created asymmetric centers (C_8 and C_9) in V deserves some comment. Although it is clear that the evidence presented here does not rigorously establish these asymmetric centers, consideration of the conformational expressions for the intermediates involved does allow tentative assignments. The initial process involving the conversion of the enamine, II, to the iminium intermediate, IV, generates an asymmetric carbon atom at C_8 and this should be considered presently. Conformational structures for both possibilities (8α and 8β) are shown in XI and XII respectively



(XI)



(XII)

since it is felt that approach of the hydrogen atom is probable from either side of the molecule. It is immediately obvious that in the 8α isomer, XI, ring B adopts the boat conformation and serious interactions exist between the "flagpole" hydrogen atoms at C_5 and C_8 and also between the 7β hydrogen atom and the C_{18} angular methyl group. On the other hand, in the 8β isomer, XII, ring B is not in a boat conformation and there are no severe interactions of the type encountered in XI. In fact the overall conformation of the molecule closely approximates that of the normal trans-anti-trans backbone of the natural steroids. If one is justified to consider that the conversion of II to IV is a process which leads to equilibration, then the 8β isomer, XII, is

certainly the preferred structure. Consideration of the next step, namely the borohydride reduction of the iminium intermediate to the final product, V, reveals that the approach of hydride from the 9α side in both the 8α and 8β isomers is very much preferred. In both XI and XII the two angular methyl groups prevent effective approach from the β side of the molecule.

The stereochemistry of sodium borohydride reductions of certain preformed iminium salts has been studied by Bohlmann.[15] In this work it was shown that attack of hydride occurred from the least hindered side of the molecule in its most stable conformer.

On the basis of our considerations and the above investigation, we postulate that the most likely stereochemistry at C_8 and C_9 in the reduction product, V, and in all subsequent substances reported below is 8β, 9α so that the normal steroid stereochemistry persists. Although this speculation does not provide absolute proof for these stereochemical centers, it is not possible to present any more rigorous data at this time since conclusive correlation to the conventional steroid system is not directly feasible.

Now that the enamine group had been reduced to a more stable system we then considered the well known degradation of the spiroketal side chain to Δ^{16}-20-keto-pregnane derivatives.[16] When the reduction product, V, was treated with acetic anhydride at 200° for ten hours, a brown oily product was obtained which, without further purification, was subjected to oxidation with chromium trioxide and the crude oily oxidation product was subjected to the action of aqueous potassium hydroxide at room temperature. The final crude product was

purified by chromatography on alumina to provide initially the expected 11-aza-pregn-16-en-20-one derivative, IX. The spectral properties of this crystalline material were in agreement with structure IX. The infrared spectrum indicated three strong absorptions of equal intensity at 5.78, 6.04 and 6.13 μ for the O-acetyl, Δ^{16}-20-keto and N-acetyl groupings. The conjugated ketone chromophore was further confirmed by the ultraviolet spectrum which showed an absorption at 235 mμ . Finally the NMR spectrum (Figure 1) was again very instructive and completely confirmed the structural assignment. A broad, one-proton signal centered at 403 c.p.s. indicated the presence of the C_{16} olefinic hydrogen atom and a very sharp line at 135 c.p.s. due to three protons was easily assigned to the C_{21} methyl group. Indeed comparison of these signals with those observed in the NMR spectrum of Δ^{16}-allopregnane-20-one which has the same system in ring D, showed excellent agreement.[17] The effect of the N-acetyl group on the two angular methyl protons was again clearly indicated since their signals are shifted to lower field (62 and 57 c.p.s.) relative to those observed in Δ^{16}-allopregnane-20-one (52 and 48 c.p.s.). Finally the region, 180-300 c.p.s., which is completely transparent in the spectrum of the allopregnane derivative indicates several sets of multiplets in the NMR spectrum of IX. The total area under these signals corresponds to four protons and apart from the lone proton at C_3 which normally shows a broad multiplet in the region, 270-300 c.p.s., the remaining signals are obviously due to the C_9 and C_{12} protons of this aza steroid derivative.

A second solid product was obtained in the later chromatographic fractions of the reaction mixture from the sapogenin side chain degradation. The spectral properties suggested immediately that it was

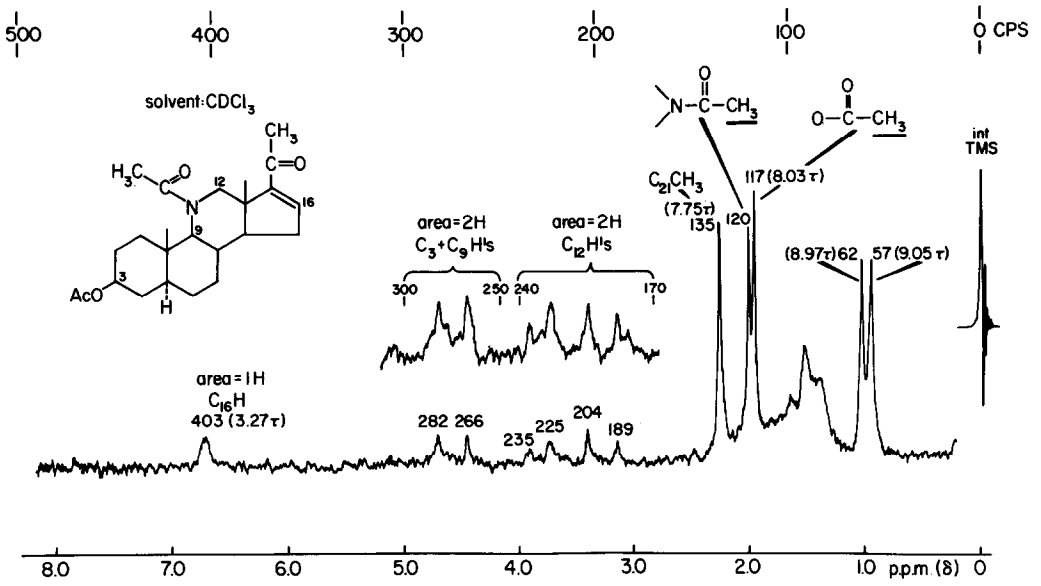


Figure I.

merely the 3β-hydroxy-11-N-acetyl derivative, VIII. The ultraviolet spectrum was identical with that observed for the diacetate, IX, but the infrared spectrum now indicated only two strong absorptions at 6.04 and 6.15 μ for the conjugated ketone and N-acetyl groups respectively. The structure, VIII, was conclusively established when acetylation of this compound provided the diacetate, IX.

The final step in this sequence, namely the reduction of the 16,17-double bond was readily accomplished by catalytic hydrogenation. This reduction product indicated no absorption in the ultraviolet region and the infrared spectrum now revealed three strong absorption bands at 5.79, 5.88 and 6.08 μ for the three carbonyl groups now present in the molecule. The NMR spectrum of this compound was also in agreement with the assigned structure, X.

This sequence now completes the synthesis of 11-aza steroids

possessing the acetyl side chain at C_{17}. We hope that these intermediates will also provide entry into the steroid hormones of the adrenocortical series.

EXPERIMENTAL

All melting points were determined on a Kofler apparatus and are uncorrected. The ultraviolet spectra were recorded in 95% ethyl alcohol on a Cary 14 recording spectrophotometer and the rotations were taken in 1% chloroform solutions. The infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. Analyses were performed by A. Bernhardt and his associates, Mulheim (Ruhr), Germany. The NMR spectra were taken in deuteriochloroform solutions on a Varian A60 instrument.

3β-Hydroxy-11-aza-5α,22β-spirost-8(9)-ene (II)

The enol lactam (I, 12.9 g) was dissolved in anhydrous tetrahydrofuran (1000 ml) and refluxed for 20 hours with lithium aluminum hydride (4 g) which was initially placed in a Soxhlet apparatus and gradually brought into the vessel by the refluxing solvent. The solvent was evaporated in vacuo and the residue decomposed cautiously by the addition of wet ethyl ether. The mixture was then treated with water, the ether layer separated and dried over anhydrous magnesium sulfate. Removal of the solvent provided a semi-solid product (10.6 g). This material was treated with ether (300 ml) and the white insoluble solid which remained undissolved was removed by filtration (5.5 g). Three recrystallizations of this material from ether provided a pure sample, m.p. 173-175° (block preheated to about 168°); $[\alpha]_D^{22}$ -30°; infrared

(KBr): 2.94 (broad), 6.11μ ; no ultraviolet absorption. This material is very difficult to analyze and its structure is still in question.

The ethereal filtrate was then concentrated to yield II as an oil (5 g) which resisted all attempts to crystallize; infrared (Nujol): 2.94 (broad), 6.13μ (1632 cm^{-1}, weak); infrared of HCl salt (Nujol): 6.02μ (1660 cm^{-1}, weak); ultraviolet: λ_{max} 236 mμ (alcohol); λ_{max} 272 mμ (alcohol solution containing a few drops of concentrated hydrochloric acid).

The aqueous layer was extracted exhaustively with ether in a continuous extraction apparatus (12 hrs). The ether extract was dried over anhydrous magnesium sulfate and then concentrated in vacuo, to yield a further 1.5 g of II.

3β-Acetoxy-N-acetyl-11-aza-5α,22β-spirost-8(9)-ene (III)

The oily enamine, II, (500 mg) was dissolved in pyridine (10 ml) and treated with acetic anhydride (20 ml). The mixture was allowed to stand at room temperature for 24 hours, after which time it was treated cautiously with water and extracted with ether. The ether extract was washed several times with water, then with 5% aqueous sodium bicarbonate solution and again with water. Filtration and removal of the solvent in vacuo provided an oily product (500 mg). This material was chromatographed on alumina (20 g, activity III). Elution with petroleum ether-benzene (1:3) and benzene yielded an oily material (200 mg). Final purification of this product was accomplished by preparative thin-layer chromatography (silica gel G, with chloroform - ethyl acetate (1:1) as developing medium, R_f=0.65) and the analytical sample (50 mg)

of III was obtained as an amorphous solid: $[\alpha]_D^{22}$ +56°; infrared ($CHCl_3$) 5.82, 6.15μ. Found: C, 71.81; H, 9.43; O, 16.41; N, 2.55. Calc. for $C_{30}H_{45}O_5N$: C, 72.11; H, 9.08; O, 16.01; N, 2.80.

Sodium Borohydride Reduction of Enamine

The enamine, II, (4.9 g) was dissolved in absolute methanol (500 ml) and hydrogen chloride gas was then passed through the solution until it was strongly acidic. The solvent was removed in vacuo and the reddish residue was taken up in absolute methanol (3000 ml). The resulting solution was treated with sodium borohydride (20 g) and the mixture then refluxed for five hours. The solvent was removed in vacuo and the residue dissolved in ether. The ether solution was first washed with water, then dried over anhydrous magnesium sulfate and finally concentrated in vacuo to provide a white solid (4.6 g). This material was dissolved in benzene and chromatographed on alumina (18 g, activity III). Elution with benzene-chloroform (9:1) provided a crystalline material (312 mg) which upon recrystallization from ether-hexane yielded an analytical sample, m.p. 167-170°; $[\alpha]_D^{22}$ -60°; infrared (KBr): 2.96μ ; no ultraviolet absorption. Found: C, 73.97; H, 10.31; O, 12.26; N, 3.57. Further work is required before a definite structure can be assigned to this compound.

The desired product (1.42 g) was eluted from the column with benzene-chloroform (3:1). Three recrystallizations from benzene provided an analytical sample (1.3 g) of 11-aza-5α,8ξ,9α,22β-spirostan-3β-ol (V), m.p. 211-212°; $[\alpha]_D^{22}$ -60°; infrared (KBr): 2.84 (sharp, NH), 2.94μ (broad, OH); no ultraviolet absorption, NMR: broad multiplet in region, 250-275 c.p.s. ($C_{16}H$), complex pattern in region, 130-230 c.p.s. (6 H,

C_3+C_9+C_{12}+C_{26}), 58, 55, 53, 49 and 44 c.p.s. (methyl signals and typical sapogenin C-methyl region).[12] Found: C, 74.56; H, 10.21; O, 11.40; N, 3.84. Calc. for $C_{26}H_{43}O_3N$: C, 74.77; H, 10.38; O, 11.49; N, 3.35.

Elution with benzene-chloroform (3:2) provided another crystalline compound (410 mg). Recrystallization from methylene chloride-hexane yielded an anlytical sample, m.p. 179-183°; $[\alpha]_D^{22}$ -100°; infrared (KBr): 5.90, 6.09μ; no ultraviolet absorption. Found: C, 69.61; H, 9.09; O, 17.72; N, 3.82. Further work is required before a definite structure can be deduced for this compound.

Elution with benzene-chloroform (1:3) and finally with chloroform yielded the fourth crystalline compound (1.83 g). Three recrystallizations from methylene chloride-hexane provided the analytical sample, m.p. 227-228°; $[\alpha]_D^{22}$ -109°; infrared (KBr): 2.84 (sharp, NH), 2.94μ (broad, OH); no ultraviolet absorption. Found: C, 70.58, 70.40; H, 9.98, 9.76; O, 15.82, 16.38; N, 3.29, 3.38.

Acetylation of V

The alcohol, V, (200 mg) was dissolved in pyridine (5 ml), treated with acetic anhydride (5 ml) and allowed to stand at room temperature for 24 hours. The reaction mixture was cautiously treated with water and then extracted with ether. The ether solution was washed several times with water, then with 5% aqueous hydrochloric acid, water, and finally with 5% aqueous sodium carbonate solution. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to provide an oily product (140 mg). This material was recrystallized twice from hexane to provide an analytical sample of the diacetate, VI, m.p. 195-

198°; $[\alpha]_D^{22}$ -14°; infrared (KBr): 5.79, 6.07μ; NMR: sharp signals at 118 and 129 c.p.s. (O- and N-acetyl) 58, 55, 48 (strongest signal) and 44 c.p.s. (methyl signals). Found: C, 71.59; H, 9.23; O, 15.32. Calc. for $C_{30}H_{47}O_5N$: C, 71.82; H, 9.44; O, 15.95.

The hydrochloric acid washings were made basic with 10% aqueous sodium hydroxide and the organic precipitate was extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo to provide a crystalline product (40 mg). Recrystallization of this compound from dichloromethane-hexane provided an analytical sample of the monoacetate, VII, m.p. 210-213°; $[\alpha]_D^{22}$ -59°; infrared (KBr): 5.78μ; NMR: sharp signal at 117 c.p.s. (O-acetyl), 59 (strongest signal), 55, 49 and 44 c.p.s. (methyl signals). Found: C, 73.50; H, 9.97; N, 3.66. Calc. for $C_{28}H_{45}O_4N$: C, 73.16; H, 9.87; N, 3.05.

Degradation of Sapogenin Side Chain

The procedure used here was essentially that of Wall[16] with slight modifications.

The alcohol, V, (4.2 g) was subjected to the action of acetic anhydride (60 ml) in a sealed tube at 200°C for 11 hours. The reaction mixture was treated with methanol to destroy the excess anhydride and the solution was concentrated in vacuo to yield a brownish oily residue. This residue was taken up in glacial acetic acid (100 ml) and the solution was cooled to 15°C. To this cold solution, a solution of chromium trioxide (2 g) in 80% acetic acid (16 ml) was added dropwise over a period of 20 minutes while the reaction temperature was kept at 15°C. The mixture was allowed to stand at 22°C for 15 hours, then treated with water to

allow the organic material to precipitate. This precipitate was extracted with ether and the ether extract was washed successively with water, aqueous potassium carbonate and finally with water. After drying over anhydrous magnesium sulfate, the solvent was removed to provide a white amorphous solid.

This material was dissolved in t-butyl alcohol (100 ml) and a solution of potassium hydroxide (1 g potassium hydroxide in 2 ml of H_2O) was added. This mixture was stirred vigorously for 2.5 hours at room temperature. The reaction mixture was treated with ether (500 ml) and the ethereal solution was washed several times with water. Removal of the solvent, after drying over anhydrous magnesium sulfate, yielded an amorphous product (2.7 g). This material was dissolved in a small amount of benzene and chromatographed on alumina (110 g, activity III). Elution with benzene-chloroform (4:1) yielded 3β,11-diacetoxy-11-aza-5α,8ξ,9α-pregn-16-en -20-one (IX, 850 mg), m.p. 185-188°; $[\alpha]_D^{22}$ +110°; infrared (KBr): 5.78, 6.04, 6.13μ; ultraviolet: λ_{max} 235 mμ (log ε 3.99); NMR: see Figure 1. Found: C, 71.98; H, 8.80; O, 15.35; N, 3.79. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; O, 15.94; N, 3.49.

Further elution with benzene-chloroform (2:3) provided a second product (1.1 g) which on two recrystallizations from ether yielded an analytical sample of the monoacetate, VIII, m.p. 191-194°; infrared (KBr): 2.90, 6.04, 6.13μ ; ultraviolet: λ_{max} 234 mμ (log ε 3.92); NMR: 119 (sharp, N-acetyl), 135 c.p.s. (sharp, C_{21} methyl). Found: C, 73.26; H, 9.42; N, 4.41. Calc. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; N, 3.90.

Acetylation of VIII

The alcohol, VIII, (50 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (1 ml). After allowing to stand at room temperature for 24 hours, the mixture was cautiously treated with water and extracted with ether. The ethereal solution was washed successively with water, 5% aqueous hydrochloric acid, 5% aqueous sodium carbonate and finally with water and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo provided a crystalline product (50 mg) which was shown to be identical in every respect with IX.

Catalytic Reduction of IX

The diacetate, IX, (70 mg) was dissolved in 95% ethanol (10 ml) and hydrogenated at room temperature and atmospheric pressure with 10% palladium on charcoal (30 mg). The catalyst was filtered and the ethanol was removed in vacuo to provide a crystalline product (70 mg). Three recrystallizations of this material from methylene chloride-hexane provided an analytical sample of 3β,11-diacetoxy-11-aza-5α,8ξ,9α-pregnan-20-one, (X), m.p. 188-192°; $[\alpha]_D^{22}$ +71°; infrared (KBr): 5.79, 5.88 and 6.08μ; NMR: sharp signals at 118, 128, and 130 c.p.s. (O- and N-acetyl and C_{21} methyl), 58 and 42 c.p.s. (angular methyl signals). Found: C, 71.55; H, 9.16; O, 15.23; N, 3.74. Calc. for $C_{24}H_{37}O_4N$: C, 71.43; H, 9.24; O, 15.86; N, 3.47.

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