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The Chemistry of 9β,19-Cyclo Steroid Derivatives[1,2]

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The 9β,19-cyclo-11-keto steroid system has been found to show a marked difference in reactivity from the corresponding triterpenoid derivatives. 11-Hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketals) **10** and **11** underwent ring opening in acid medium to give alcohol **15** and diene **17**, in contrast to the *Buxus* alkaloid **8**, which gave the conjugated diene **9**. No product of the conjugated diene type was detected under a variety of reaction conditions using the model cyclopropyl carbinol **11**. Hydride reduction of a series of steroidal 11-ketoamines also proceeded to a different extent from that of the triterpenoid alkaloids. These results are rationalized on the basis of significant differences in molecular conformations between the steroid and triterpenoid series.

In 1962, we reported the elucidation of the structure[4] and configuration[5] of cyclobuxine D (**1**), an alkaloid isolated from *Buxus sempervirens* L.[6] Cyclobuxine D was shown to be the prototype of a new class of steroidal alkaloids which contain the 9,19-cyclo-5α,9β-pregnane system **2** and has a substitution pattern at C-4 and C-14 which is intermediate in the biogenetic scheme between lanosterol- and cholesterol-type steroids. Subsequent studies have characterized many structurally related alkaloids.[7] In 1964, the isolation and characterization of buxenine G[8a] ("norbuxamine"[8b]) was reported, and this alkaloid was later proven to possess the novel structure and configuration **3**.[9] Several additional alkaloids possessing the unusual 9(10→19)*abeo*-5α-pregnane system (**4**) have been found.[8b,10-12]

In part XIII[1] of this series we reported that Huang-Minlon reduction of 9,19-cyclo-5α,9β-pregnane-3,11,20-trione 3,20-bis(ethylene ketal) (**5**)[13] proceeded in an unusual direction, to give a mixture of 9(10→19)-*abeo*-$\Delta^{9(11)}$-5α,10β-pregnene 3,20-bis(ethylene ketal) (**6**) and its C-10 isomer **7**, rather than the initially expected 11-deoxy compound. This provided a synthetic entry to the 9(10→19)*abeo*-5α-pregnane system (**4**) in the steroid series.

In a continuation of these studies on potential routes to B-homo steroid analogs of buxenine-G type alkaloids, we have examined the chemistry of some derivatives of the 9β,19-cyclo-11-keto steroid system **5**, including the synthesis of some amino steroids which are direct analogs of some of the *Buxus* alkaloids. In this paper we report the results of this work, which indicate a marked difference in reactivity between the 11-keto cyclopropyl system in the steroid model compounds and the triterpenoid alkaloids.

Goutarel has reported[14] the conversion of the cyclopropyl carbinol **8** (derived from cycloxobuxidine F by $LiAlH_4$ reduction, and of unspecified configuration at C-11) to the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene (**9**) by mild treatment with sulfuric acid. When the nonaminated steroidal cyclopropyl carbinols **10** and **11**, derived from **5** by metal hydride reduction, were treated with acid, quite different products were isolated.

Lithium aluminum hydride reduction of **5** gave a mixture which was homogeneous by tlc on silica layers, but which could be separated by chromatography on

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(8) (a) S. M. Kupchan and W. L. Asbun, *ibid.*, 3145 (1964); (b) D. Stauffacher, *Helv. Chim. Acta*, **47**, 968 (1964).

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(12) S. M. Kupchan, R. M. Kennedy, W. R. Schleigh, and G. Ohta, *Tetrahedron*, **23**, 4563 (1967).

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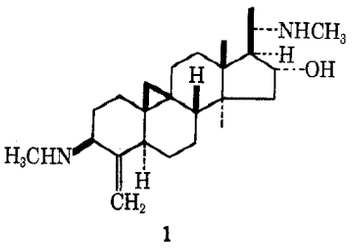
(14) D. Herlem, F. Khuong-Huu, and R. Goutarel, *C. R. Acad. Sci.*, **264**, 798 (1967).



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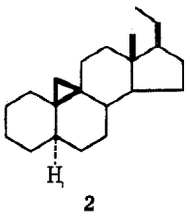

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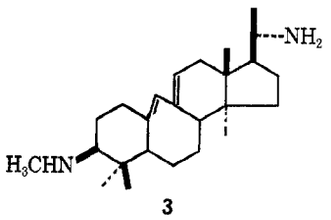

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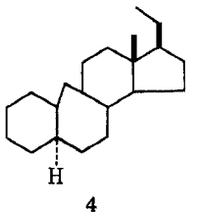

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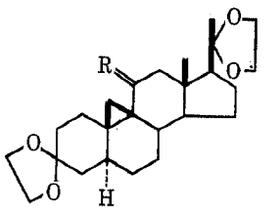
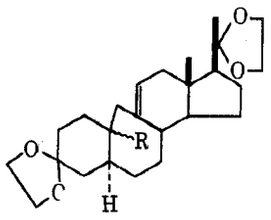
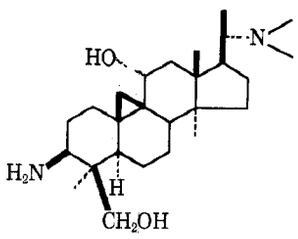


5, R = O
10, R = β-OH, α-H
11, R = α-OH, β-H
12, R = β-OAc, α-H
13, R = α-OAc, β-H



6, R = β-H
7, R = α-H



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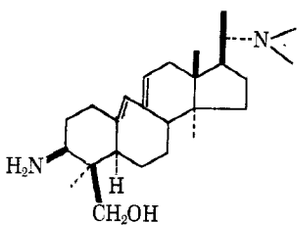

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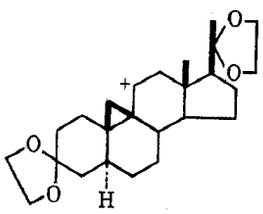

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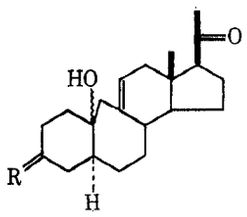
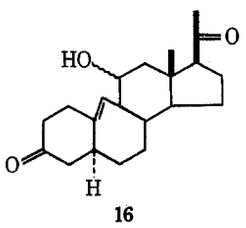


15, R = O
19, R = β-NEt2, α-H



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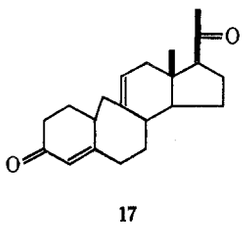

17

alumina to give 11β-hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketal) (**10**, 11%) and the corresponding 11α-hydroxy isomer (**11**, 65%). Inspection of Drieding models of ketone **5** has revealed that the 11-carbonyl group is appreciably less hindered than in the normal steroid nucleus.[1] Consequently, the major product of hydride reduction is the equatorial (11α) alcohol,[15] a result which has been found recently with a similar cyclopropyl ketone.[16] Zurcher's rules[17] predict that the hydroxyl groups in **10** and **11** should cause the C-18 methyl protons in **10** to resonate at approximately τ 0.2 lower field than that in **11**, all other ring C and D substituents being equal. In **10**, this resonance is at τ 8.95, while in **11** it occurs at τ 9.10, a difference of τ 0.15. The assignment was confirmed by examination of the nmr spectra of the respective C-11 acetates **12** and **13**, in which the C-18 methyl in the β-acetate should resonate at approximately τ 0.06 lower field than the α, under the conditions stated above.[17] Here the C-18 methyl in **12** resonated at τ 9.06, while in **13** the signal was at τ 9.10, a difference of τ 0.04. Reduction of ketone **5** did not proceed with sodium borohydride at room temperature, but in boiling isopropyl alcohol an increased amount of the 11β alcohol was formed, isolated yields being 21% of **10** and 31% of **11**. The increased steric accessibility of the 11 position in these compounds was emphasized by the ease of formation of the 11β-acetate compared to the analogous situation in normal steroids.[18]

On treatment with 30% v/v or 30% w/w sulfuric acid at room temperature for reaction times of 2–15 hr, both alcohols **10** and **11** gave very similar product mixtures, indicating that the dehydration reaction proceeds in both cases *via* a common intermediate, such as the carbonium ion **14**. In view of this, most of the subsequent work was done on the major alcohol (*i.e.*, **11**). Crystallization of the crude product from acid treatment gave the major product as a colorless solid in 70–82% yield, the amount of by-products increasing with longer reaction times. The major product has been assigned the homoallylic alcohol structure **15** on the basis of the following physical and chemical evidence. Elemental analysis supported assignment of an empirical molecular formula of $C_{21}H_{30}O_3$, and the mass spectrum confirmed the molecular weight as 330. A prominent peak in the mass spectrum at *m/e* 312, corresponding to loss of H_2O, indicated the presence of a hydroxyl group, while the absence of peaks at *m/e* 99 and 87 indicated that loss of the ketal groups had occurred at both C-3 and C-20. The ir spectrum showed bands at 5.85 and 5.90 (carbonyl) and 2.90 μ (hydroxyl), while the nmr spectrum indicated loss of the cyclopropyl ring (no signal at approximately τ 9.5). The absence of any new methyl resonance suggested that the cyclopropyl ring had opened to give a B-homo steroid. The presence of a new double bond was revealed by a broad singlet ($W_{1/2}$ = 9 Hz) at τ 4.57. No ketal resonance was present, and a three-proton singlet at τ 7.85 was attributed to the C-21 methyl group, while the C-18 methyl group resonated as a singlet at τ 9.32. The absence of a strongly absorbent chromophore in the uv spectrum showed that the double bond was not conjugated with a ketone nor with another double bond, as in the initially expected

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(16) T. Nakano, M. Alonso, and A. Martin, *Tetrahedron Lett.*, 4929 (1970).

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9(11),10(19)-diene (*cf.* ref 14). These data supported structures **15** or possibly **16** as likely. Structure **15** was preferred, since no signal corresponding to the C-11 methine proton of **16** could be found in the nmr spectrum, and no acetate ester was formed from the ring-opened product under normal conditions of acetylation of steroidal secondary alcohols. Treatment of the acetate **13** with sulfuric acid under similar conditions also gave the alcohol **15**. The minor product from the acid treatment of **11** was isolated as a gum (6% after 2 hr), and was also formed as the major product on further acid treatment of **15**. The uv spectrum [λ_{max} 237 nm (ϵ 22,410)] of this material indicated a conjugated π system other than the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene system.[14] Mass spectral measurements showed the compound to be a dehydration product of **15** (M^+ at *m/e* 312), while the nmr spectrum showed a singlet at τ 4.20 for one additional olefinic proton, three-proton singlets at τ 7.86 (C-21 Me) and 9.38 (C-18 Me), and a broad signal at τ 4.57 (C-11 H). The ir spectrum now had a band at 6.03 μ (α,β-unsaturated carbonyl) and no OH band. This evidence supported the structure **17** for the new diene dione. The formation of **17** from **15** can be readily rationalized mechanistically as dehydration to the 5(10)-olefin **18** (not isolated), followed by acid-catalyzed migration of the double bond into conjugation with the C-3 ketone. The latter reaction type is well documented.[19]

In an attempt to alter the direction of dehydration of **15** away from formation of conjugated ketone **17** and possibly toward a 9(11),10(19)-diene system, a C-3β-amino function was introduced by a Leuckart reduction.[20] Treatment of ketone **15** with formic acid and diethylamine in refluxing toluene gave 3β-diethylamino-9(10→19)*abeo*-$\Delta^{9(11)}$-5α-pregnan-10ε-ol-20-one (**19**) in good yield. Confirmation of the presence of the C-3 diethylamino group was obtained from the nmr spectrum (triplet at τ 8.97, J = 7 Hz, $>NCH_2CH_3$, quartet at τ 7.44, J = 7 Hz, $>NCH_2CH_3$) and from the mass spectral fragment ions at *m/e* 138 and 112, highly characteristic of a 3β-diethylamino-5α-pregnane.[21] However, the amine **19** was inert to dehydration under all but the most forcing conditions. The inertness of compound **19** to dehydration was also evident from its mass spectrum, in which the molecular ion (*m/e* 387) was of enhanced intensity relative to that of **15**, and the M − 18 peak was much weaker than in the spectrum of **15**.

When alcohols **10** or **11** were treated with acid under more vigorous conditions (50% sulfuric acid with heating on steam bath for 10 min), a complex mixture of products was produced. The major component (44%), isolated as a gum by preparative tlc, was shown to be dione **17**. Two other products of higher R_f value were also isolated, but these were less stable than compound **17**, and only partial spectral characterization was possible. The higher R_f compound had signals in the nmr spectrum at τ 9.42 (3 H, C-18 Me), 7.86 (3 H, C-21 Me), 4.59 and 4.48 (both 1 H, >C=CH), and bands in the ir spectrum at 5.87, 6.19, and 6.24 μ. No α,β-unsaturated ketone could be detected by ir or uv measurement. On the basis of this evidence, the high R_f compound is tentatively formulated as the diene **20**, which also could be formed by dehydration of **15**. The third material crystallized on standing, and appeared to be homogeneous in several tlc systems. However, nmr examination showed two closely overlapping peaks at τ 9.34 and 9.36 for the C-18 methyl resonance, suggesting that the apparently homogeneous material was a mixture of two very similar compounds. Signals also occurred at τ 7.83 (C-21 Me), 4.49 (broad s, >C=C< H), 4.06 (d, J = 10 Hz, >C=CH), and 3.17 (t, J_1 = 10 Hz, J_2 = 12.5 Hz, >C=CH). The ir spectrum showed a band for an α,β-unsaturated carbonyl group at 6.02 μ, different from that of **17**. From these data it is suggested that one compound present in this mixture is the diene **21**. Mass spectral examination revealed a peak at *m/e* 330 in addition to a stronger *m/e* 312 peak, indicating that the other component may be an alcohol corresponding to $C_{21}H_{30}O_3$.

Tosylation of alcohol **11** followed by elimination was next considered as a possible route to the 9(11),10(19)-diene. No tosylate could be isolated from treatment of **11** with *p*-toluenesulfonyl chloride in pyridine, elimination having occurred spontaneously to give a mixture (nmr spectrum) of olefins which was homogeneous by tlc. The uv spectrum of this mixture, when examined soon after isolation, exhibited absorbance at 248 nm, with shoulders at 238 and 255 nm, typical of the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene system, but the extinction coefficient at 248 nm suggested a maximum of 9–14% diene content. The olefin mixture proved quite unstable, but the main component was isolated by partition chromatography as a crystalline solid, and was shown to have the olefinic structure **22**. In the nmr spectrum of **22**, the C-11 proton resonated as a doublet (J = 10.5 Hz) at τ 3.67, while the C-12 proton was a doublet (J = 10.5 Hz) at τ 4.81. No other stable component of the olefin mixture was fully characterized, and no 9(11),10(19)-diene was isolated. Olefin **22** could not be converted to such a diene on treatment with acid. Alcohol **11** behaved in a similar way upon attempted mesylation.

In addition to the sulfuric acid mediated ring opening reactions described above, a wide variety of standard dehydration reagents, including $POCl_3$, PCl_5, and alumina/pyridine, were allowed to react with alcohols **10** and **11**. The alcohols were also subjected to glc treatment. In all cases complex and intractable mixtures of olefins resulted, having no uv absorption characteristic of the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene system.

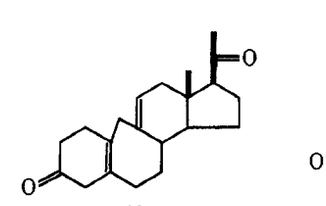
Although the vagaries of the chemistry of "bicyclobutonium" ions have been alluded to previously,[22] these are insufficient to explain the difference of our results from those of Goutarel.[14] At no stage was any of the 9(11),10(19)-diene isolated, and only in the product from attempted tosylation of **11** was it apparently detected. In general, the crude reaction mixtures in this work were found to decompose on standing (particularly the tosylation product), and it is conceivable that the desired steroidal diene, although

(19) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 586.

(20) R. R. Sauers, *J. Amer. Chem. Soc.*, **80**, 4721 (1958).

(21) (a) V. Cerný and F. Sorm in "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 305; (b) L. Dolejs, V. Hanus, V. Cerný, and F. Sorm, *Collect. Czech. Chem. Commun.*, **28**, 1584 (1963); (c) W. Vetter, P. Longevialle, F. Khuong-Huu-Laine, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1324 (1963).

(22) D. H. R. Barton, R. P. Budhiraja, and J. F. McGhie, *J. Chem. Soc. C*, 336 (1969).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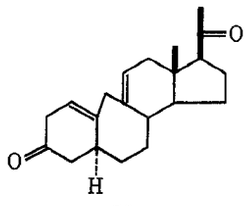
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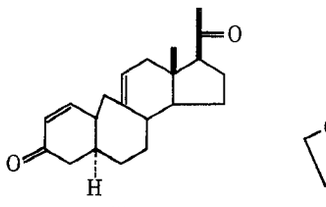
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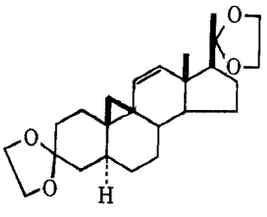
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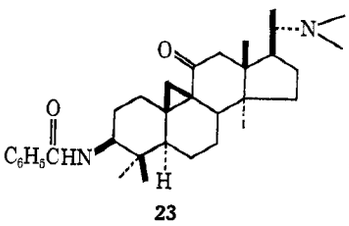
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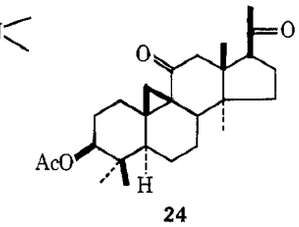
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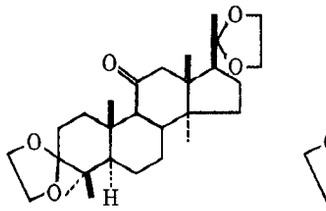
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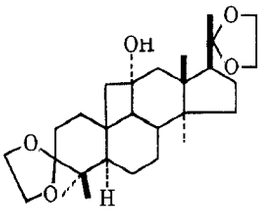
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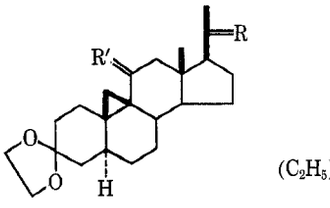
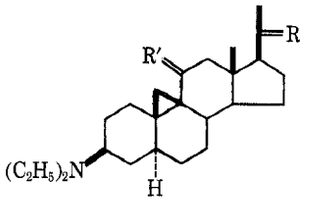




27, R = R′ = O
28, R = NOH; R′ = O
29, R = α-NH_2, β-H; R′ = O
30, R = β-NH_2, α-H; R′ = O
31, R = α-NH_2, β-H; R′ = α-OH, β-H
32, R = β-NH_2, α-H; R′ = α-OH, β-H
33, R = R′ = O
34, R = $(OCH_2)_2$; R′ = O
35, R = NOH; R′ = O
36, R = α-NMe_2, β-H; R′ = O
37, R = β-NMe_2, α-H; R′ = O

formed initially, was too unstable to isolate. The difference in reactivity of Goutarel's cyclopropyl alcohol **8** and the steroidal alcohols **10** and **11** may be due to the hydroxymethyl group at C-4 in **8** acting as a neighboring group in a directed ring-opening reaction. Hydrogen bonding between the OH group and one of the cyclopropyl protons would render such a proton more acidic and thus more easily removable in a directed process leading to the 9(11),10(19)-diene. However, a brief survey of some of the relevant literature, combined with our own results, indicates that the difference is more probably due to a fundamental difference in conformation of the triterpenoid *Buxus* alkaloid molecule and the unsubstituted steroid, which causes the 9β,19-cyclo-11-keto steroid to have different reactivity (or to give products of different stability). Thus we have shown recently[12] that *N*-benzoylcycloxobuxine-F (**23**) can be reduced to the 11-deoxy compound by vigorous reduction with $LiAlH_4$ in dioxane. The ketone **5** was only reduced to the corresponding alcohols **10** and **11** under these conditions. Nakano, *et al.*, have recently reported[16] that the triterpenoid cyclopropyl ketone **24** can be reduced, under similar conditions, to a 2:1 mixture of the 11-alcohol and 11-deoxy compound. A further anomaly between 11-ketones of the triterpene and steroid series is in their behavior upon irradiation. When photolyzed in ethanol, the diketal **25** gives none of the expected cyclobutanol[16] **26**, the triterpene analog of the main product of similar irradiation of 5α-pregnane-3,11,20-trione 3,20-bis(ethylene ketal).[13] Supporting evidence for a difference in molecular conformation of ketones **5** and **23** was obtained from the ORD curves of the two molecules. Both curves were positive, but widely different in amplitude, indicating a significant difference in conformation of the respective molecules.[12]

The possible effect of amino functions at C-3 and C-20 (*e.g.*, by intramolecular basic catalysis or as complexation agents) on the extent of reduction at C-11 was evaluated by the synthesis of 9β,19-cyclo 11-ketones possessing these groups. By brief treatment with warm aqueous acetic acid–methanol, diketal **5** was selectively hydrolyzed in high yield to the 3-monoketal **27**, which in turn was transformed to the oxime **28** by reaction with hydroxylamine hydrochloride in pyridine. Hydrogenation of this oxime at room temperature and atmospheric pressure in acetic acid over Adams catalyst afforded a mixture of isomeric 20-amino steroids, which was separated by partition chromatography[23] to give 20α-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal (**29**, 37%) and 20β-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal (**30**, 24%). The isomers could be distinguished by nmr spectroscopy. As well as the anticipated paramagnetic shift of the C-18 tertiary methyl protons in β isomer **30** (3.5 Hz) due to the deshielding effect of the neighboring C-20 nitrogen function,[17a,24] the C-21 methyl protons in **30** resonated at higher field (doublet, J = 6 Hz, at τ 8.97) than in **29** (doublet, J = 6 Hz, at τ 8.88). The C-12 methylene signal occurred at higher field in **29** (doublets, J = 14 Hz, at τ 7.22 and 7.90) than in **30** (doublets, J = 15 Hz, at τ 7.02 and 7.82). The preponderance of α isomer **29** over β isomer **30** is in accord with previous experimental findings on the hydrogenation of 20-oximino steroids.[25-28] Treatment of amino ketones **29** and **30** with $LiAlH_4$ in refluxing dioxane for 48 hr gave the corresponding 11-hydroxy compounds **31** and **32** as the predominant reaction products. The crystalline alcohols were assigned the 11α configuration by analogy with the hydride reductions of 9,19-cyclo-11-keto steroids discussed earlier. A minor product, having spectral data in agreement with the 11β-hydroxy epimer, was isolated as an oil from reduction of the 20α-amino steroid. The lack of formation of any 11-deoxy com-

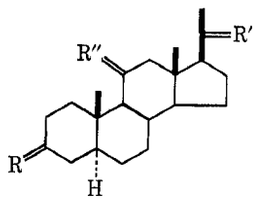
(23) K. S. Brown, Jr., and S. M. Kupchan, *J. Chromatogr.*, **9**, 71 (1962).
(24) A. Cohen and S. Rock, *Steroids*, **3**, 243 (1964).
(25) P.-L. Chien, W. E. McEwen, A. W. Burgstahler, and N. T. Iyer, *J. Org. Chem.*, **29**, 315 (1964).
(26) M.-M. Janot, F. Lainé, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 111 (1962).
(27) L. Nedelec, *ibid.*, 557 (1963).
(28) F. Ramirez and S. Stafiej, *J. Amer. Chem. Soc.*, **77**, 134 (1955).

pounds in these reductions indicates that a C-20 amino function has no effect on the extent of reduction of a C-11 ketone in these 9β,19-cyclo steroids, and that no intramolecular basic catalysis was operating. In separate experiments, it was also shown that the ketone **5** gave a very similar mixture of products when treated with $LiAlH_4$ as above in the presence of an externally added amine, *N*-methylbenzylamine, as when this base was absent. Thus, in the cyclopropyl steroid series of C-20 monoamines, no supporting evidence has been found for inter- or intramolecular basic catalysis as an explanation for the further reduction of the *Buxus* alkaloid **23** to the corresponding 11-deoxy compound.

Ketone **5** was completely deketalized by heating with methanol–acetic acid at 70–80° for 3 hr, and was then subjected to Leuckart reduction with formic acid and diethylamine to give, after partition chromatography, 3β-diethylamino-9,19-cyclo-5α,9β-pregnane-11,20-dione (**33**). The presence of the cyclopropyl ring reduced the intensity of the peaks at *m/e* 138 and 112 in the mass spectrum and gave rise to a new peak at *m/e* 99.[21] Attempted ketalization of **33** with a catalytic amount of *p*-toluenesulfonic acid in ethylene glycol–benzene gave only traces of the 20-ketal **34**. Use of 1.1 equiv of the acid for the same reaction time gave a main product as a gum which had M^+ at *m/e* 473 in the mass spectrum, indicating it to be an 11,20-diketal. This was confirmed by ir spectroscopy (no carbonyl band). The absence of any signal in the olefinic region of the nmr spectrum indicated that the compound possessed either a 9β,19-cyclo-11,20-bis(ethylene ketal) or a $\Delta^{5(10)}$-9(10→19)*abeo*-pregnene-11,20-bis(ethylene ketal) structure. This compound was not characterized further, and, to obtain a C-20-functionalized 3-amino 11-ketone, the synthesis of a 3,20-diamino-9β,19-cyclo-11-keto steroid was pursued.

The amine **33** was allowed to react with hydroxylamine hydrochloride in boiling ethanol–pyridine to yield the 20-oxime **35**. Hydrogenation of **35** in acetic acid with Adams catalyst gave a crude mixture of the 20-amines, which, upon N-methylation, gave the corresponding *N,N*-dimethylamines. By direct crystallization of the crude product a crystalline solid was isolated which appeared to be homogeneous by tlc, but which showed two singlets at τ 7.79 and 7.86 for $-NMe_2$ groups in the nmr spectrum. Although two such signals have been reported for a C-3-dimethylamino steroid,[29] later work with the 10-methyldiamines **45** and **46** suggested that the above product consisted of a mixture of 20α- and 20β-dimethylamines **36** and **37**. In view of the small amount of the mixture in hand, no attempt was made to separate the isomers, and the mixture *per se* was treated with excess $LiAlH_4$ in refluxing dioxane for 48 hr. Work-up gave a gum which again appeared homogeneous by tlc, but which probably represents a mixture of C-20 isomeric amines and 11α- and 11β-alcohols, with a predominance of the 11α isomer. Mass spectral analysis confirmed the addition of 2 H (M^+ at *m/e* 416), while the ir spectrum showed loss of cyclopropyl ketone and presence of hydroxyl. The latter was also confirmed by the presence of a multiplet at τ 5.74 (nmr spectrum) for the C-11 methine proton.

A final comparison of conformation *vs.* reactivity at the 11 position involved the reduction of the corresponding 3β,20α-diamine in the 10-methyl steroid series. 3β-Diethylamino-20α-dimethylamino-5α-pregnan-11-one (**45**) was chosen as a model diamine, possessing no 9β,19-cyclopropyl ring and no alkyl substituents likely to cause alterations in the known conformation[19] of the 11-keto-5α-pregnane skeleton. Leuckart reduction[20] of 5α-pregnane-3,11,20-trione (**38**) with diethylamine as the base gave the 3β-diethylamino-11,20-dione **39**, characterized as the hydrochloride **40**. Treatment of this amine with 1 equiv of hydroxylamine hydrochloride in refluxing dry pyridine–absolute ethanol for 30 min gave 3β-diethylamino-5α-pregnane-11,20-dione 20-oxime (**41**) as the sole product upon crystallization of the crude product from methanol. Reaction times of 3–4 hr and the use of excess hydroxylamine hydrochloride led to mixtures of **41** and the 11,20-dioxime **42**. Refluxing with a large excess of hydroxylamine hydrochloride for 18 hr gave dioxime **42** as the sole product. The 20-oxime **41** was hydrogenated over Adams catalyst at room temperature and atmospheric pressure to give a mixture of the C-20 epimeric primary amines. The major constituent (20α) was characterized as the dihydrochloride **43** and the acetamide **44**. N-methylation of the crude hydrogenation product with formic acid–formalin gave a mixture of the corresponding 20α- and 20β-dimethylamino compounds **45** and **46**. Although these isomers could not be distinguished by tlc, a combination of partition chromatography and careful fractional crystallization resulted in the isolation of the individual 20β- and 20α-dimethylamines (mp 203–205° and 147–148°, respectively) in yields of 18 and 33%, respectively. No appreciable paramagnetic shift of the C-18 methyl group in the nmr spectrum of the β isomer **46** relative to **45** was observed in this case. The isomers were most readily distinguished by the observed shift to lower field (τ 0.07) of the dimethylamino group and the C-21 methyl group in the 20α isomer relative to the 20β isomer.



38, R = R′ = R″ = O
39, R = β-NEt_2, α-H; R′ = R″ = O
40, R = β-NEt_2·HCl, α-H; R′ = R″ = O
41, R = β-NEt_2, α-H; R′ = NOH; R″ = O
42, R = β-NEt_2, α-H; R′ = R″ = NOH
43, R = β-NEt_2·HCl, α-H; R′ = α-NH_2·HCl, β-H; R″ = O
44, R = β-NEt_2, α-H; R′ = α-$NHCOCH_3$, β-H; R″ = O
45, R = β-NEt_2, α-H; R′ = α-NMe_2, β-H; R″ = O
46, R = β-NEt_2, α-H; R′ = β-NMe_2, α-H; R″ = O
47, R = β-NEt_2, α-H; R′ = α-NMe_2, β-H; R″ = β-OH, α-H
48, R = β-NEt_2, α-H; R′ = α-NMe_2, β-H; R″ = α-OH, β-H

Reduction of diamine **45** with $LiAlH_4$ in refluxing dioxane for 48 hr gave 3β-diethylamino-20α-dimethylamino-5α-pregnan-11β-ol (**47**) as the major product (58% yield). A second crystalline product, isolated in 13% yield, is probably the 11α-hydroxy isomer **48**, and a third band from the partition chromatographic purification yielded a colorless oil (13%), which was not investigated further. No evidence for the formation of any 11-deoxydiamine was found in the series.

(29) T. Nakano and Z. Votický, *J. Chem. Soc. C*, 590 (1970).

This result, when considered with those from similar reductions of the 9β,19-cyclopropyldiamines **36** and **37**, and the cyclopropyl monoamines **30** and **31** indicate that the presence of amino functions at C-3 and C-20 does not affect the degree of reactivity of the 11-ketone toward $LiAlH_4$ reduction, either in the presence of a conjugated cyclopropyl ring system or a normal 10-methyl steroid system.

The results of these hydride reductions enhance the proposals made above to account for the differences in reactivity of cyclopropyl carbinols **8** and **11** towards acid media. Only in the case of alkyl-substituted *Buxus* alkaloids was any 11-deoxy compound isolated from $LiAlH_4$ reduction of the 11-ketones. In all other cases, C-11 alcohols were formed as the predominant products, thus providing strong support for the proposal that there is a significant difference in molecular conformation between the 9β,19-cyclotriterpenes and 9β,19-cyclo and 10-methyl steroids.[30]

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus or on a Mettler FP2 apparatus. Infrared spectra were determined as KBr pellets or chloroform solutions on a Beckman IR-5A or Perkin-Elmer 257 recording spectrophotometer. Ultraviolet absorption spectra were measured in ethanol on a Beckman DK-2A ratio recording spectrophotometer. Optical rotations were measured, in chloroform solutions unless otherwise stated, on a Zeiss-Winkel polarimeter or a Perkin-Elmer 141 polarimeter, and are approximated to the nearest degree. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60A or a Hitachi Perkin-Elmer R20 recording spectrometer at 60 MHz unless otherwise stated. Chemical shifts have been recorded in τ values. Low-resolution mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer. High-resolution mass spectra were determined on an AEI MS-902 spectrometer. Thin layer chromatography employed silica gel GF254 unless otherwise stated. Spots were located by spraying with $Ce(SO_4)_2$ (3%) in H_2SO_4 (3 *N*) followed by heating until colored spots appeared. The solvent system (A) used for partition chromatography was a mixture of Skellysolve B, ethylene dichloride, methanol, and water (10:1:2:0.16), unless otherwise indicated. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Solvent evaporations were carried out under reduced pressure below 40°. All solutions were dried over anhydrous magnesium sulfate, unless otherwise stated.

Lithium Aluminum Hydride Reduction of Ketone 5.[12]—A solution of **5** (100 mg) in anhydrous ether (35 ml) was treated with lithium aluminum hydride (35 mg). After 1 hr at room temperature, the excess hydride was destroyed by careful addition of methanol. Water (30 ml) was added, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 30 ml), and the combined ethereal layers were washed with water and dried. Removal of solvent left a colorless solid (98 mg) which was homogeneous by tlc on silica gel, but showed two well-separated spots on alumina tlc (Merck type T) using chloroform as eluent. The product was chromatographed on neutral Woelm grade IV alumina (50 g). Elution with benzene–chloroform (6:4, 55 ml) gave 11β-hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketal) (**10**) as a colorless gum (11 mg): ir λ_{max} 2.85, 6.96, 7.25, 8.10, 8.65, 9.22, and 10.40 μ; nmr τ 6.04 (8 H, C-3, C-20 ketal H), 6.30 (1 H, m, C-11 H), 8.71 (3 H, s, C-21 CH_3), 8.95 (3 H, s, C-18 CH_3), and 9.79 (1 H, d, J = 5 Hz, C-19 H).

Anal. Calcd for $C_{25}H_{38}O_5$: mol wt, 418.2770. Found (high resolution mass spectrum): mol wt, 418.2720.

Further elution with the same solvents (20 ml) gave a mixture of **10** and **11** (9 mg). Continued elution with this solvent mixture (30 ml) followed by chloroform (100 ml) gave pure 11α-hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketal) (65 mg). Recrystallization from methanol–Skellysolve B gave colorless needles of alcohol **11**: mp 179–180°; $[\alpha]^{26}D$ +15° (*c* 1.10); ir λ_{max} 2.91, 6.82, 6.93, 7.17, 7.30, 8.18, 8.68, 8.92, 9.33, and 10.57 μ; nmr τ 6.01 (8 H, C-3, C-20 ketal H), 6.41 (1 H, m, C-11 H), 8.68 (3 H, s, C-21 CH_3), 9.10 (3 H, s, C-18 CH_3), and 9.47 (2 H, C-19 H); mass spectrum *m/e* 418 (M^+), 403, 400, 385, 373, 356, 338, 99, 91, and 87. This material was identical (melting point, mixture melting point, and tlc) to a previously isolated sample of unassigned configuration.[12]

Sodium Borohydride Reduction of Ketone 5.—A solution of **5** (100 mg) in isopropyl alcohol (40 ml) was heated under reflux with sodium borohydride (250 mg) for 17 hr. After removal of solvent, the residue was partitioned between chloroform (50 ml) and water (50 ml). The aqueous phase was extracted with chloroform (2 × 30 ml). After drying, the combined chloroform layers gave a colorless gum (98 mg). Chromatography on neutral Woelm grade IV alumina gave four fractions. The first fraction, eluted with benzene (40 ml), gave a mixture of ketone **5** and alcohol **10** (11 mg); the second fraction, eluted with chloroform–benzene (1:9, 21 ml) gave alcohol **10** (21 mg); the third fraction, eluted with chloroform–benzene (1:9, 24 ml) gave a mixture of **10** and **11** (32 mg); the fourth fraction, eluted with chloroform–benzene (1:9, 24 ml) and chloroform–benzene (1:1, 52 ml), gave alcohol **11** (31 mg).

11β-Acetoxy-9,19-cyclo-5α,9β-pregnane-3,20-dione Bis(ethylene ketal) (12).—A solution of alcohol **10** (12 mg) in pyridine (0.3 ml) and acetic anhydride (0.3 ml) was allowed to stand at room temperature overnight. The solution was then diluted with saturated sodium bicarbonate and extracted with chloroform. After drying the solution, removal of solvent left a residue which was taken up in chloroform and filtered through silica gel (1 g) to yield **12** as a colorless gum (12 mg): ir λ_{max} 5.84, 6.95, 7.30, 7.94, 8.83, 9.30, 9.51, 9.63, 9.76, 10.39, and 10.57 μ; nmr τ 5.05 (1 H, m, C-11 H), 6.01 (8 H, C-3, C-20 ketal H), 7.92 (3 H, s, C-11 $COCH_3$), 8.69 (3 H, s, C-21 CH_3), and 9.73 (1 H, d, J = 5 Hz, C-19 H); mass spectrum *m/e* 400 ($M^+ - CH_3CO_2H$), 356, 279, 149, 99, 87, 71, 69, 57 and 55.

11α-Acetoxy-9,19-cyclo-5α,9β-pregnane-3,20-dione Bis(ethylene ketal) (13).—Acetylation of **11** was carried out as for **10**. Crystallization of the product from Skellysolve B gave colorless prisms of the acetate **13**: mp 178–180°; $[\alpha]^{26}D$ +10° (*c* 1.10); ir λ_{max} 5.83, 6.93, 7.30, 7.72, 7.94, 8.68, 9.10, 9.28, 9.86, 10.57, 11.60, and 12.40 μ; nmr τ 5.38 (1 H, m, C-11 H), 6.03 (8 H, C-3, C-20 ketal H), 8.00 (3 H, s, C-11 $COCH_3$), 8.72 (3 H, s, C-21 CH_3), 9.10 (3 H, s, C-18 CH_3), and 9.48 (2 H, C-19 H); mass spectrum *m/e* 460 (M^+), 400.2600 ($M - CH_3CO_2H$) (calcd for $C_{25}H_{36}O_4$: 400.2613), 356, 99, 91, and 87.

Mild Acid Treatment of Alcohol 11.—A solution of alcohol **11** (48 mg) in dry dioxane (3.5 ml) was stirred with 30% (v/v) sulfuric acid (1 ml) for 20 hr at room temperature. The reaction mixture was then poured into saturated sodium chloride solution (50 ml) and extracted with ethyl acetate (3 × 25 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and water, and then dried. Removal of solvent left a dull white solid, which, on crystallization from benzene–ether, gave colorless needles of alcohol **15** (27 mg); mp 186–188°; $[\alpha]^{26}D$ +32° (*c* 0.34); ir λ_{max} 2.90, 5.85, 6.90, 7.05, 7.21, 7.34, 8.59, 8.80, 9.25, and 10.40 μ; nmr τ 4.57 (1 H, broad s, $W_{1/2}$ = 9 Hz, C-11 H), 7.85 (3 H, s, C-21 CH_3), and 9.32 (3 H, s, C-18 CH_3); mass spectrum *m/e* 330 (M^+), 312, 269, 105, 91, 86, 81, 79, 55, and 43.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.29; H, 8.93.

Chromatography of the crystallization mother liquors on neutral Woelm grade IV alumina (2.5 g) gave, on elution with benzene (30 ml), dione **17** (4.3 mg), identical (ir, uv, tlc) with the main product of vigorous acid treatment of ketone **5**.

3β,Diethylamino-10ε-hydroxy-9(10→19)*abeo*-Δ$^{9(11)}$-5α-pregnen-20-one (19).—A solution of dione **15** (27 mg) in dry toluene (3 ml) was added to a mixture of diethylamine (90 mg) and formic acid (97% solution, 19 mg). The mixture was refluxed in a preheated oil bath for 2 hr, then diluted with ether (30 ml) and extracted with 2 *N* hydrochloric acid (2 × 30 ml). The combined acidic extracts were basified with aqueous sodium hydroxide solution (2 *N*) and extracted with $CHCl_3$ (2 × 50 ml). The chloroform layer was washed with water (20 ml), dried, and evaporated to leave a crystalline residue (28 mg), mp 155–158°. Recrystallization from benzene–Skellysolve B gave pure amine

(30) F. Khuong-Huu, D. Herlem, and J. J. H. Simes [*Bull. Soc. Chim. Fr.*, 258 (1969)] have reported that the course of Wolff–Kishner reduction of the 9β,19-cyclo-11-keto steroid system in triterpenoid *Buxus* alkaloids differs from that of reduction of **5** (*cf.* part XIII[1]).

19 (16.5 mg): mp 161–162°; $[\alpha]^{25}D$ +11° (c 0.21); ir λ_{max} 3.00, 5.91, 6.82, 6.93, 7.25, 7.38, 7.74, 8.15, 8.40, 8.65, 9.30, 9.98, 10.27, and 10.87 μ; nmr τ 4.65 (1 H, broad s, C-11 H), 7.43 (4 H, q, J = 12 Hz, C-3 NCH_2CH_3), 7.77 (3 H, s, C-18 CH_3), 8.97 (6 H, t, J = 12 Hz, C-3 NCH_2CH_3), and 9.34 (3 H, s, C-18 CH_3); mass spectrum m/e 387 (M^+), 372, 369, 359, 330, 138, 112, 99.

Anal. Calcd for $C_{25}H_{41}NO_2$: M, 387.3137. Found (high resolution mass spectrum): M, 387.3128.

Mild Acid Treatment of Acetate 13.—A solution of acetate **13** (8 mg) in dioxane (1.5 ml) was treated with 30% v/v sulfuric acid (12 drops) overnight at room temperature. The solution was diluted with water, and extracted with chloroform (3 × 30 ml). The combined chloroform layers were extracted with saturated sodium bicarbonate (15 ml) and water (15 ml), and dried. Removal of solvent left a semicrystalline residue (6 mg) which was identical (ir, nmr, and tlc) with the alcohol **15**.

Vigorous Acid Treatment of Alcohol 11.—A solution of alcohol **11** (425 mg) in dioxane (40 ml) was heated with 50% v/v sulfuric acid (12 ml) on the steam bath for 15 min. The solution was diluted with water and extracted with chloroform (3 × 50 ml). The organic layers were extracted with saturated sodium bicarbonate solution and water, and then dried. Removal of solvent left a yellow-brown gum (340 mg) which exhibited no conjugated diene absorption in the uv spectrum.[14] This product was separated into three bands, by preparative tlc, using chloroform as developing solvent. Elution of band 1 (most polar) gave ketone **17** as a colorless gum (140 mg): $[\alpha]^{25}D$ +39° (c 0.54); uv λ_{max}^{EtOH} 237 nm (ε 22,410); ir λ_{max} 5.90, 6.03, 6.20, 6.92, 7.06, 7.37, 7.95, 8.20, 8.59, 8.85, 10.18, 11.01, 11.15, and 11.64 μ; nmr τ 4.20 (1 H, s, C-4 H), 4.51 (1 H, broad s, C-11 H), 7.86 (3 H, s, C-21 CH_3), and 9.38 (3 H, s, C-18 CH_3); mass spectrum m/e 312 (M^+), 269, 242, 227, 157, 91, 85, 83, 69, 43, and 41.

Anal. Calcd for $C_{21}H_{28}O_2$: M, 312.2089. Found (high resolution mass spectrum): M, 312.2094.

Band 2 gave a colorless gum (58 mg): ir λ_{max} 5.90, 5.98, 6.20, 6.93, 7.06, 7.22, 7.37, 7.60, 7.90, 8.12, 8.60, 8.80, 9.13, and 11.10 μ; nmr τ 3.19 (1 H, broad t, J = 10, J′ = 12.5 Hz, C-1 H), 4.06 (1 H, d, J = 10 Hz, C-2 H), 4.49 (1 H, broad s, C-11 H), 7.83 (3 H, s, C-21 CH_3), 9.34 (3 H, s, C-18 CH_3), and 9.36 (3 H, s, C-18 CH_3). One of the components of this band is suggested to be the Δ^1-3-ketone **21**.

Band 3 gave a colorless gum (42 mg): ir λ_{max} 5.88, 6.19, 6.25, 6.92, 7.05, 7.25, 7.37, 7.90, 8.14, 8.54, and 9.98 μ; nmr τ 4.37–4.75 (2 H, m, C-11 H, and C-1 H), 7.86 (3 H, s, C-21 CH_3), and 9.42 (3 H, s, C-18 CH_3). The $\Delta^{1(10),9(11)}$-3-keto-*B*-homodiene structure **20** is suggested as a possible structure for this compound.

Conversion of Alcohol 15 to Diene 17.—A solution of alcohol **15** (5 mg) in dioxane (1 ml) was heated under reflux with 30% w/w sulfuric acid (1 ml) for 6 hr. The mixture was worked up as previously described to give a colorless gum (4.5 mg), which was separated by tlc in the system benzene–ethyl acetate (2:1) to give diene **17** (2.2 mg) and a trace of higher R_f material.

Attempted Tosylation of Alcohol 11.—Alcohol **11** (220 mg) in pyridine (40 ml) was heated with *p*-toluenesulfonyl chloride (1 g) on the steam bath for 2 hr. The solvent was removed, and the residue was filtered through a short column of silica gel (Merck, 0.05–0.2 mm, 20 g) eluting with chloroform. Removal of solvent left a yellow gum (201 mg), which contained no starting material (tlc), but showed uv absorption as follows: λ_{max}^{EtOH} 246 (238 sh, 255 sh) nm (ε 1700–2550 in successive experiments). Assuming a value of ε of 21,900 for the $\Delta^{9(11),10(19)}$-diene,[14] this indicates that the crude product contained approximately 9–14% of the desired conjugated diene. A partition chromatography column was set up by impregnating Celite 545 (350 g) with 170 ml of the lower phase of the solvent system, cyclohexane–dimethylformamide–ethyl acetate–water (10:4:2.5:0.3). This was dry-packed in several increments into a column of suitable size (column volume 650 ml), and the upper phase of the solvent system was allowed to pass through the column for 20 hr. A portion of the crude product (125 mg) was applied to the column in 3 ml of the upper phase, and elution continued with the upper phase. The first 620 ml eluted no material; the next 30 ml gave crystals (44 mg) of olefin **22**. Recrystallization from methanol gave colorless needles: mp 94–95°; $[\alpha]^{25}D$ +54° (c 0.53); ir λ_{max} 6.18, 6.95, 7.31, 7.73, 8.12, 8.54, 8.67, 8.78, 8.92, 9.32, 9.65, and 10.53 μ; nmr τ 3.65 (1 H, d, J = 10 Hz, C-12 H), 4.81 (1 H, d, J = 10 Hz, C-11 H), 6.03 (8 H, C-3, C-20 ketal H), 8.63 (3 H, s, C-21 CH_3), 9.09 (3 H, s, C-18 CH_3), and 9.65 (1 H, d, J = 4.5 Hz, C-19 H); mass spectrum m/e 400 (M^+), 356, 313, 311, 294, 286, 257, 99, and 87.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.26; H, 9.04.

Further elution gave several fractions which were shown (by nmr) to be mixtures.

9,19-Cyclo-5α,9β-pregnane-3,11,20-trione 3-Ethylene Ketal (27).—A mixture of diketal **5** (200 mg), glacial acetic acid (1 ml), methanol (4 ml), and water (4 ml) was heated at 55° for 10 min to dissolve the steroid. Heating at this temperature was continued for a further 10 min, then ice water was added to the cooled solution, followed by solid sodium bicarbonate until the mixture was alkaline. The aqueous mixture was extracted with methylene chloride, the organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. An ethereal solution of the residue was filtered through alumina (Woelm, basic, grade III, 8 g) to yield a colorless oil (190 mg) which crystallized from Skellysolve B to give the monoketal **27** (149 mg): mp 126–128°; $[\alpha]^{28}D$ +141° (c 0.46); ir λ_{max} 5.86, 5.98, 7.35, and 10.55 μ; nmr τ 6.05 (4 H, s, C-3 ketal H), 7.12 (1 H, d, part of AB d, J = 14 Hz, C-12 H), 7.87 (3 H, s, C-21 CH_3), 9.18 (1 H, d, part of AB d, J = 4 Hz, C-19 H), and 9.32 (3 H, s, C-18 CH_3); mass spectrum m/e 372 (M^+), 357, 344, 328, 310, 286, and 99.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.00; H, 8.50.

9,19-Cyclo-5α,9β-pregnane-3,11,20-trione 3-Ethylene Ketal 20-Oxime (28).—Hydroxylamine hydrochloride (34 mg) was added to a solution of the monoketal **27** (136 mg) in pyridine (4 ml), and the resulting solution was allowed to stand at room temperature for 18 hr. The solution was poured into water and extracted with ether. The combined ether extracts were washed several times with water, dried over anhydrous Na_2SO_4, and concentrated. Tlc of the residue revealed one major and two minor components. Separation of the major band by thick layer chromatography gave a white foam which crystallized from ether–Skellysolve A to afford the oxime **28** (118 mg): mp 177–178°; $[\alpha]^{28}D$ +82° (c 0.56); ir λ_{max} 2.79, 3.05, 6.00, and 10.55 μ; nmr τ 1.77 (1 H, m, =NOH), 6.05 (4 H, C-3 ketal H), 7.23 and 7.79 (2 H, AB d, J = 14.5 Hz, C-12 H), 8.12 (3 H, s, C-21 CH_3), 9.19 (1 H, d, part of AB d, J = 4 Hz, C-19 H), and 9.31 (3 H, s, C-18 CH_3); mass spectrum m/e 387 (M^+), 371, 356, 342, 325, 308, 301, 99, 87, and 57.

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.20; H, 8.70; N, 3.71.

Catalytic Hydrogenation of Oxime 28.—A solution of oxime **28** (1.55 g) in glacial acetic acid (40 ml) was added to prereduced Adams catayst (500 mg) in glacial acetic acid (20 ml). Hydrogenation was carried out at atmospheric pressure and room temperature. After 10 hr, the hydrogenation was stopped. The reaction mixture was filtered, basified by addition of ammonium hydroxide, and extracted with ether. The combined ether extracts were washed with water, dried, and concentrated to yield a colorless oil (1.560 g). Partition chromatography[23] of the oil gave two large red bands on the column. Fractions collected before either band was eluted gave, on evaporation, the starting oxime (191.5 mg). The first red band (band 1) was eluted, and the solvent was removed to give a mixture of starting oxime and the 20β-amine **30** (352.4 mg) as shown by tlc. Chromatography of this mixture on alumina (Woelm, neutral, grade IV, 20 g) gave, on elution with benzene (25 ml), the starting oxime **28** (64.2 mg) with traces of the amine **30**. Further elution with benzene (50 ml) afforded isomer **30** (276.4 mg) which crystallized from ether–Skelly B to give 20β-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal **30** (248.5 mg): mp 123–124°; $[\alpha]^{29}D$ +82° (c 1.02); ir λ_{max} 2.82, 2.90, 6.00, 6.31, 7.01, and 10.55 μ; nmr τ 6.02 (4 H, C-3 ketal H), 7.02, and 7.82 (2 H, AB d, J = 15 Hz, C-12 H), 8.97 (3 H, d, J = 6 Hz, C-21 CH_3), and 9.22 (3 H, s, C-18 CH_3); mass spectrum m/e 373 (M^+), 356, 330, 314, 311, 287, 233, 99, and 44.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.74. Found: C, 73.76; H, 9.32; N, 3.63.

The second red band from the partition column gave a mixture of the starting oxime **28** and the 20α-amine **29** (703 mg). Chromatography of this mixture on alumina (Woelm, neutral, grade III, 50 g), on elution with benzene (775 ml) and benzene–ether (9:1, 400 ml) gave oxime **28** (219 mg). Elution with ether (100 ml) gave a mixture of the oxime and the 20α-amine (32.5 mg). Elution with ether (100 ml), 2% methanol in ether (400 ml), and finally methanol (500 ml) gave pure isomer **29** (399

mg). Crystallization from ether–Skellysolve B gave 20α-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal (384.4 mg): mp 121–123°; $[\alpha]^{29}D$ +85° (*c* 0.91); ir λ_{max} 2.86, 2.96, 6.00, 6.32, 7.02, and 10.55 μ; nmr τ 6.05 (4 H, C-3 ketal H), 7.22, and 7.90 (2 H, AB d, *J* = 14 Hz, C-12 H), 8.88 (3 H, d, *J* = 6 Hz, C-21 CH_3), and 9.27 (3 H, s, C-18 CH_3); mass spectrum *m/e* 373 (M^+), 356, 330, 311, 205, 99, 85, and 83.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.74. Found: C, 73.98; H, 9.35; N, 3.74.

20α-Amino-11α-hydroxy-9,19-cyclo-5α,9β-pregnan-3-one Ethylene Ketal (31).—A solution of the amine **29** (100 mg) in dry dioxane (15 ml) was added to a suspension of lithium aluminum hydride (215 mg) in dry dioxane (5 ml). The reaction mixture was heated under reflux for 48 hr and cooled, and the excess hydride was destroyed by careful addition of ether saturated with water. After filtration, the inorganic precipitates were thoroughly washed with methylene chloride, and the filtrate was dried. Removal of solvent left an oil (96 mg). Partition chromatography gave four clearly separated red bands which were collected separately. Bands 1 and 2 gave noncrystalline materials (16 and 4 mg, respectively) which were shown to be mixtures (tlc).

Band 3 gave an oil which did not crystallize, but appeared to be homogeneous by tlc (16 mg); ir λ_{max} 2.72, 2.79, 3.00, 5.90, 6.30, and 10.55 μ; nmr τ 6.01 (4 H, C-3 ketal H), 6.42 (1 H, m, C-11 H), 8.93 (3 H, d, *J* = 6 Hz, C-21 CH_3), 9.15 (3 H, s, C-18 CH_3), and 9.48 (2 H, C-19 H).

Band 4 gave a solid (59 mg), homogeneous by tlc. Crystallization from ether–Skellysolve B gave the alcohol **31**: mp 140–142°; $[\alpha]^{28}D$ +3° (*c* 0.82); ir λ_{max} 2.72, 2.78, 3.00, 6.30, and 10.55 μ; nmr τ 6.02 (4 H, C-3 ketal H), 6.42 (1 H, m, C-11 H), 8.95 (3 H, d, *J* = 6 Hz, C-21 CH_3), 9.22 (3 H, C-18 CH_3), and 9.50 (2 H, C-19 H); mass spectrum *m/e* 375 (M^+), 357, 340, 332, 314, 299, 252, 99, 69, and 44.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.38; H, 10.04; N, 3.69.

20β-Amino-11α-hydroxy-9,19-cyclo-5α,9β-pregnan-3-one Ethylene Ketal (32).—The ketone **30** (100 mg) was treated with lithium aluminum hydride (215 mg) in dioxane (20 ml) as described above for ketone **29**. The crude product (101 mg of an oil) was chromatographed on a partition column as above, giving three bands. Band 1 gave an oil (21 mg) which appeared to be homogeneous by tlc, but apparently was still a mixture by examination of its nmr spectrum.

Band 2 yielded an oil (8 mg) which was a mixture of two compounds (tlc).

Band 3 gave a crystalline material (68 mg), mp 141–143°, which appeared to be homogeneous (tlc). Crystallization from ether–Skellysolve B afforded the alcohol **32**: mp 145°; $[\alpha]^{28}D$ −4° (*c* 0.61); ir λ_{max} 2.78, 2.96, 6.31, and 10.55 μ; nmr τ 6.03 (4 H, C-3 ketal H), 6.37 (1 H, m, C-11 H), 7.18 (1 H, diffuse m, C-20 H), 8.97 (3 H, d, *J* = 6 Hz, C-21 CH_3), 9.16 (3 H, s, C-18 CH_3), and 9.49 (1 H, C-19 H); mass spectrum *m/e* 375 (M^+), 357, 340, 332, 314, 299, 99, 83, 57, and 44.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.52; H, 10.04; N, 3.68.

3β-Diethylamino-9,19-cyclo-5α,9β-pregnane-11,20-dione (33).—A solution of 9,19-cyclo-5α,9β-pregnane-3,11,20-trione (650 mg) in dry toluene (42 ml) was heated under reflux with diethylamine (940 mg) and 97% formic acid (195 mg) for 3.5 hr. The reaction mixture was cooled, diluted with ether (80 ml), and extracted with 2 *N* hydrochloric acid (3 × 30 ml). The organic layer was washed with water and dried. Removal of solvent left unreacted trione (110 mg). This material was recycled in the amination reaction. The combined acid extracts were basified with aqueous sodium hydroxide solution, and extracted with methylene chloride (4 × 40 ml). The organic layer was washed with water and dried. Removal of solvent left the crude product as a transparent oil (610 mg). Partition chromatography[23] of a portion (250 mg) of this product on Celite 545 using solvent system A gave one major and two minor bands. The first and third bands gave mixtures (tlc). The second, major band gave amine **33** as a colorless gum (208 mg): ir λ_{max}^{film} 5.86, 5.97, 6.90, 7.01, 7.23, 7.36, 7.86, 8.08, 8.62, 9.03, 10.82, and 11.85 μ; nmr (100 MHz[31]) τ 7.28 (4 H, q, *J* = 7 Hz, NCH_2CH_3), 7.81 (3 H, s, C-21 CH_3), 8.85 (6 H, t, *J* = 7 Hz, NCH_2CH_3), and 9.24 (3 H, s, C-18 CH_3); mass spectrum *m/e* 385 (M^+), 370, 356, 342, 328, 312, 138, 112, 99, and 86. For analytical characterization, this compound was converted to the C-20 oxime (*vide infra*).

Attempted Formation of C-20 Ketal 34 from Amine 33. A. Using a Catalytic Amount of *p*-Toluenesulfonic Acid.—A solution of amine **33** (400 mg) in dry benzene (10 ml) was heated under reflux with ethylene glycol (2.5 ml) for 2 hr. *p*-Toluenesulfonic acid (40 mg) was added, and the mixture was heated under reflux for a further 24 hr. After cooling, solid sodium bicarbonate (0.1 g) was added to the mixture, followed by water (5 ml) and ammonium hydroxide (5 ml). Extraction with chloroform, followed by washing and drying of the organic extract, gave a pale yellow gum (370 mg). Tlc indicated a small amount of material of slightly higher R_f than the starting amine. Partition chromatography gave three bands, only partly separated. Band 1 gave an oil (41 mg), which was shown to be a mixture by tlc; the mass spectrum showed that one of the components of the mixture was probably the desired monoketal (peak at *m/e* 429).

Band 2 also gave an oil (40 mg) which was shown to be a mixture by tlc. Band 3 gave the starting amine as a gum (281 mg).

B. Using 1.16 Equiv of *p*-Toluenesulfonic Acid.—The reaction was carried out as described above, using **33** (270 mg) and *p*-toluenesulfonic acid (147.5 mg). The usual work-up gave the product as a pale yellow gum (285 mg), which was chromatographed on alumina (Woelm, basic, grade II, 20 g). Elution with benzene (120 ml) gave nonpolar oily impurities (15 mg). Further elution with the same solvent (265 ml) and benzene–chloroform (4:1; 125 ml) gave the diketal fraction as a colorless gum (110.4 mg), homogeneous by tlc (R_f higher than that of **33**): ir λ_{max} 6.94, 7.30, 8.23, 9.17, 9.55, 10.55, and 13.25 μ; nmr (100 MHz) τ 6.09 (8 H, C-11, C-20 ketal H), 7.36 (4 H, q, *J* = 7 Hz, C-3 NCH_2CH_3), 8.68 (3 H, s, C-21 CH_3), 8.85 (6 H, t, *J* = 7 Hz, C-3 NCH_2CH_3), and 9.03 (3 H, s, C-18 CH_3); mass spectrum *m/e* 473 (M^+), 458, 445, 428, 400, 386, 372, 359, 112, 99, 87, 85, and 83.

Further elution with benzene–chloroform (4:1, 110 ml), benzene–chloroform (6:4, 175 ml), and benzene–chloroform (4:6; 85 ml) gave a mixture of the diketal and starting amine (119 mg).

Elution with benzene–chloroform (1:4, 100 ml) and chloroform (200 ml) gave starting amine (9.8 mg).

3β-Diethylamino-9,19-cyclo-5α,9β-pregnane-11,20-dione 20-Oxime (35).—A solution of amine **33** (100 mg) and hydroxylamine hydrochloride (30 mg) in absolute ethanol (2 ml) and dry pyridine (2 ml) was heated under reflux for 3 hr. The solution was cooled and treated with saturated aqueous sodium bicarbonate solution followed by excess ammonium hydroxide. The mixture was extracted with chloroform (3 × 30 ml), and the combined organic layers were washed with water and dried. Removal of solvent gave the oxime **35** as a colorless gum (94 mg) which crystallized on standing. Two recrystallizations from benzene–Skellysolve B gave colorless crystals: mp 199–201°; $[\alpha]^{26}D$ +63° (*c* 0.59); ir λ_{max} 5.99, 6.82, 6.91, 7.24, 7.93, 8.08, 8.43, 8.56, 9.01, 9.13, 10.39, and 11.30 μ; mass spectrum *m/e* 400 (M^+), 385, 371, 369, 138, 112, 99, and 86.

Anal. Calcd for $C_{25}H_{40}N_2O_2$: C, 74.96; H, 10.06; N, 6.99. Found: C, 74.82; H, 9.99; N, 6.89.

3β-Diethylamino-20α-dimethylamino-9,19-cyclo-5α,9β-pregnan-11-one (36) and 3β-Diethylamino-20β-dimethylamino-9,19-cyclo-5α,9β-pregnan-11-one (37).—A solution of oxime **35** (100 mg) in glacial acetic acid (10 ml) was hydrogenated at room temperature and atmospheric pressure over platinum oxide (10 mg). After stirring overnight, uptake of hydrogen had stopped, with consumption of 13.8 ml (2.5 equiv). Removal of solvent left a mixture of 20-aminosteroids as a colorless gum (102 mg). This was not purified, but treated immediately with formic acid (3 ml) and 40% formaldehyde solution (3 ml) on the steam bath under a nitrogen atmosphere for 6 hr. The mixture was cooled, diluted with aqueous ammonium hydroxide, and stored in the refrigerator overnight. Filtration gave a pale brown solid (84 mg), which crystallized from aqueous ethanol to give a mixture of diamines **36** and **37** as colorless prisms (27 mg): mp 101–103°; $[\alpha]^{26}D$ +26° (*c* 1.30); ir λ_{max} 5.96, 6.88, 7.24, 7.90, 8.36, 8.68, 9.00, 9.15, 9.90, and 10.83 μ; nmr (100 MHz) τ 6.87 (1 H, d, *J* = 14 Hz, C-12 H), 7.42 (4 H, q, *J* = 7 Hz, C-3 NCH_2CH_3), 7.79 and 7.86 [6 H, 2 s, $N(CH_3)_2$], 8.91 (6 H, t, *J* = 7 Hz, C-3 NCH_2CH_3), 9.08 (3 H, d, *J* = 7 Hz, C-21 CH_3), and 9.22 (3 H, s, C-18 CH_3); mass spectrum *m/e* 414 (M^+), 399, 385, 112, 99, 86, and 72.

(31) 100-MHz spectra were recorded on a Varian HA-100 recording spectrometer.

Anal. Calcd for $C_{27}H_{46}N_2O$: M, 414.3609. Found (high resolution mass spectrum): M, 414.3597.

Further crops of material obtained from the liquors of the crystallization were shown to be mixtures by tlc.

Lithium Aluminum Hydride Reduction of Ketones 36 and 37.—A mixture of ketones **36** and **37** (23 mg) in dioxane (0.75 ml) was added to a suspension of $LiAlH_4$ in dioxane (0.75 ml), and the mixture was heated under reflux for 48 hr. After the usual work-up, the organic product was isolated as a colorless gum (21 mg). Two consecutive purifications by tlc, each developed twice in the top phase of the solvent system *n*-butyl alcohol–acetic acid–water (4:1:5), gave only one major band as a colorless gum (9 mg): ir λ_{max} 2.94, 6.85, 7.28, 7.94, 8.74, 9.08, and 9.90 μ; nmr (100 MHz) τ 5.74 (1 H, broad s, C-11 H), 6.25 (1 H, m, C-20 H), 7.17 (1 H, d, J = 7 Hz, C-12 H), 7.41 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.83 and 7.87 [6 H, 2 s, $N(CH_3)_2$], 8.93 (6 H, t, J = 7 Hz, NCH_2CH_3), 8.96 (3 H, s, C-18 CH_3), and 9.12 (3 H, d, J = 6.5 Hz, C-21 CH_3); mass spectrum m/e 416 (M^+), 401, 399, 114, 113, 112, 99, 83, 72, 69, 57, 55, 45, 43, and 41. This material decomposed on standing, with production of base line tlc material.

3β-Diethylamino-5α,pregnane-11,20-dione (39).—A solution of 5α-pregnane-3,11,20-trione (1.6 g), 97% formic acid (0.49 g), and diethylamine (2.32 g) in dry toluene (105 ml) was heated under reflux for 4 hr. After cooling, the solution was diluted with ether (200 ml) and extracted with 2 *N* hydrochloric acid (5 × 150 ml). The organic layer was washed with water and dried, and the solvent was removed to leave unreacted starting material as a colorless solid (0.314 g). This material was recycled in the reductive amination, to leave less than 0.05 g of brown gum in the neutral layer. The combined acid layers were basified with aqueous sodium hydroxide solution and extracted with methylene chloride (5 × 150 ml). The organic layers were washed with water, dried, and evaporated *in vacuo* to yield amine **39** as a transparent gum (1.65 g) which partially crystallized on standing. Purification *via* hydrochloride **40** gave, after regeneration by basification and crystallization from aqueous ethanol, a colorless solid: mp 89–92°; $[\alpha]^{24}D$ +70° (*c* 0.92); ir λ_{max} 5.88, 6.95, 7.35, 7.40, 7.89, 8.31, 8.50, 8.68, and 9.50 μ; nmr τ 7.42 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.88 (3 H, s, C-21 CH_3), 8.97 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.00 (3 H, s, C-19 CH_3), and 9.43 (3 H, s, C-18 CH_3); mass spectrum m/e 387 (M^+), 372, 358, 344, 330, 223, 215, 139, 138, 113, 112, 105, 99, 84, 57, 56, 55, 43, and 41. For final characterization the amine was converted to the hydrochloride **40**, which crystallized as colorless needles from methanol: mp 278° dec; $[\alpha]^{25}D$ +53° (*c* 1.02, MeOH); ir λ_{max} 2.77, 2.93, 3.79, 4.02, 5.98, 6.92, 7.25, 7.38, 7.88, 8.22, 8.46, 8.63, and 9.72 μ; mass spectrum m/e 387 (M^+ − HCl), 372, 358, 344, 330, 139, 138, 113, 112, 99, 84, 71, 69, 57, 56, 55, 43, and 41.

Anal. Calcd for $C_{25}H_{42}ClNO_2$: C, 70.81; H, 9.98; Cl, 8.34; N, 3.30. Found: C, 70.66; H, 9.87; Cl, 8.42; N, 3.26.

3β-Diethylamino-5α-pregnane-11,20-dione 20-Oxime (41).—A solution of amine **39** (1.5 g, crude) and hydroxylamine hydrochloride (272 mg) in absolute ethanol (30 ml) and dry pyridine (30 ml) was heated under reflux for 25 min. The solvents were removed *in vacuo* and saturated aqueous sodium bicarbonate solution was added to the residue, followed by concentrated ammonium hydroxide. The mixture was stored in the refrigerator overnight, and the precipitate was then filtered, washed thoroughly with water, and dried in a vacuum desiccator over KOH overnight. Crystallization from methanol gave **41** as colorless needles (875 mg): mp 196–197.5°; two recrystallizations from the same solvent raised the melting point to 198–199°: $[\alpha]^{24}D$ +50° (*c* 1.16); ir λ_{max} 3.17 and 3.27 (broad), 5.88, 6.87, 7.25, 7.35, 8.20, 8.65, 10.33, 11.02, 13.32, and 14.28 μ; nmr τ 7.45 (4 H, q, J = 7.5 Hz, NCH_2CH_3), 8.23 (3H, s, C-21 CH_3), 8.97 (6 H, t, J = 7.5 Hz, NCH_2CH_3), 9.02 (3 H, s, C-19 CH_3), and 9.44 (3 H, s, C-18 CH_3); mass spectrum m/e 402 (M^+), 387, 371, 345, 331, 330, 329, 315, 138, and 112.

Anal. Calcd for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.51; N, 6.96. Found: C, 74.66; H, 10.66; N, 6.94.

3β-Diethylamino-5α-pregnane-11,20-dione Dioxime (42).—A solution of dione **39** (40 mg) in dry pyridine (4 ml) and absolute ethanol (4 ml) was heated under reflux with hydroxylamine hydrochloride (40 mg) for 18 hr. Work-up as described above gave a colorless precipitate which crystallized from methanol to give **42** as colorless needles (34 mg): mp 265–269°, raised after two recrystallizations from methanol to 271–273°; $[\alpha]^{24}D$ +64°[32] (*c* 0.25, MeOH); ir λ_{max} 3.08 and 3.17 (broad), 6.14, 6.93, 7.32, 9.66, 10.35, 11.30, 12.80, and 14.18 μ; mass spectrum m/e 417 (M^+), 402, 401, 400, 385, 384, 370, 368, 138, 112, 84, 57, 56, and 41.

Anal. Calcd for $C_{25}H_{43}N_3O_2$: C, 71.90; H, 10.38; N, 10.06. Found: C, 71.81; H, 10.53; N, 9.98.

Hydrogenation of Oxime 41.—A solution of **41** (1.1 g) was hydrogenated at room temperature and atmospheric pressure in the presence of pre-reduced Adams catalyst (130 mg). The hydrogenation was stopped when the oxime **41** was consumed (tlc). This required approximately 25 hr. The mixture was filtered and the filtrate was basified with ammonium hydroxide and extracted with chloroform. The organic extract was washed with water, dried, and evaporated to leave a mixture of the epimeric C-20 primary amino steroids as a clear oil (1.15 g). The dihydrochloride **43** crystallized from methanol–acetone as colorless prisms: mp 297° dec; three recrystallizations from the same solvents raised the melting point to 328° dec; $[\alpha]^{23}D$ +19° (*c* 1.17, MeOH); ir λ_{max} 2.91, 3.77, 4.01, 5.88, 6.23, 6.88, 7.20, 7.88, 8.30, 9.65, and 9.93 μ; mass spectrum m/e 389, 388 (M^+ − 2 HCl), 374, 373, 357, 331, 139, 138, 113, 112, 99, 84, 71, 56, 44, and 41.

Anal. Calcd for $C_{25}H_{46}Cl_2N_2O$: Cl, 15.36; N, 6.07. Found: Cl, 15.18; N, 5.97.

20α-Acetamido-3β-diethylamino-5α-pregnan-11-one (44).—A solution of the crude product (150 mg) from the above hydrogenation in dry pyridine (3 ml) and acetic anhydride (0.3 ml) was allowed to stand at room temperature overnight. The solution was diluted with water (230 ml) and ammonia (23 ml) and extracted with chloroform. The organic extract was washed with 2 *N* sodium hydroxide and water and dried. Removal of solvent left a colorless oil (152 mg). Trituration with Skellysolve B gave **44** as a colorless solid: mp 198–205°, raised by two recrystallizations from Skellysolve B–benzene to 221–223° dec; $[\alpha]^{23}D$ +41° (*c* 1.22); ir λ_{max} 2.98, 3.23, 5.85, 6.08, 6.45, 6.90, 7.26, 7.79, 8.28, 8.80, 9.45, and 10.25 μ; nmr τ 4.17 (1 H, m, NH-$COCH_3$), 6.01 (1 H, m, C-20 H), 7.33 (4 H, q, J = 7.5 Hz, NCH_2CH_3), 8.04 (3 H, s, $COCH_3$), 8.91 (6 H, t, J = 7.5 Hz, NCH_2CH_3), and 9.32 (3 H, s, C-18 CH_3); mass spectrum m/e 430 (M^+), 415, 138, 112, 57, 56, and 41.

Anal. Calcd for $C_{27}H_{46}N_2O_2$: C, 75.30; H, 10.77; N, 6.50. Found: C, 75.21; H, 10.73; N, 6.43.

3β-Diethylamino-20α-dimethylamino-5α-pregnan-11-one (45) and 3β-Diethylamino-20β-dimethylamino-5α-pregnan-11-one (46).—A solution of the crude diamine mixture (1.15 g), obtained by hydrogenation of oxime **41**, in 37% formaldehyde solution (24 ml) and 97% formic acid (24 ml) was heated on the steam bath for 7 hr, then allowed to stand overnight at room temperature. Ice water was added, followed by ammonium hydroxide, and the precipitated material was extracted with chloroform. The organic extract was washed (water), dried, and evaporated *in vacuo* to afford a colorless, crystalline solid (1.51 g). On addition of a small volume of the top phase of solvent system A to the residue, some solid (*ca.* 330 mg) remained insoluble.[33] Partition chromatography[23] of the filtrate after removal of this material gave rise to only one, rather diffuse, red band. This band was collected in nine fractions.

Fractions 1 and 2 were combined and evaporated to give 158 mg of a colorless, crystalline solid. Recrystallization from methanol gave the 20β-amine **46** as plates (98 mg): mp 197–199°, raised to 202–204° after two further recrystallizations from methanol; $[\alpha]^{24}D$ +39° (*c* 0.82); ir λ_{max} 5.91, 6.93, 7.28, 7.93, 8.30, 8.62, 9.29, and 10.80 μ; nmr (100 MHz) 6.38 (1 H, m, C-20 H), 7.25 (1 H, d, J = 12 Hz, C-12 H), 7.51 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.97 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.03 (3 H, s, C-19 CH_3), 9.27 (3 H, d, J = 6.5 Hz, C-21 CH_3), and 9.40 (3 H, s, C-18 CH_3); mass spectrum m/e 416 (M^+), 415, 402, 401, 359, 139, 138, 112, 99, 84, 72, 56, and 41.

Anal. Calcd. for $C_{27}H_{48}N_2O$: C, 77.83; H, 11.61; N, 6.72. Found: C, 77.90; H, 11.64; N, 6.75.

Fractions 3–7 gave a colorless, crystalline solid (695 mg), which was separated by repeated fractional recrystallization from methanol into the 20β-amine **46** (113 mg) and the 20α-amine **45**

(32) Owing to the insolubility of **42**, this value is approximate.

(33) On recrystallization from methanol or acetone, this compound formed small, shiny prisms, subliming at 282°. Combustion and mass spectral analysis supported a $C_7H_{12}N_4$ formula; the compound was not investigated further.

(379 mg): mp 147–148°; $[\alpha]^{23}D$ +48° (c 0.95); ir λ_{max} 5.88, 6.85, 6.94, 7.24, 7.29, 7.91, 8.30, 8.38, 8.67, 9.40, and 10.80 μ; nmr (100 MHz) τ 6.36 (1 H, m, C-20 H), 7.50 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.90 [6 H, s, $N(CH_3)_2$], 9.01 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.03 (3 H, s, C-19 CH_3), 9.20 (3 H, d, J = 7 Hz, C-21 CH_3), and 9.40 (3 H, s, C-18 CH_3); mass spectrum m/e 416 (M^+), 402, 401, 139, 138, 113, 112, 99, 84, 73, 72, 71, 58, and 56.

Anal. Calcd for $C_{27}H_{48}N_2O$: C, 77.83; H, 11.61; N, 6.72. Found: C, 77.62; H, 11.58; N, 6.70.

Fractions 8 and 9 gave colorless gums (22 and 2 mg, respectively) which did not crystallize.

Lithium Aluminum Hydride Reduction of Diamine 45.—A solution of **45** (180 mg) in dioxane (20 ml) was added to a suspension of $LiAlH_4$ (275 mg) in dioxane (15 ml). The mixture was heated under reflux for 48 hr, cooled, and treated with ether saturated with water. The suspension was filtered, and the inorganic precipitate was washed with boiling dichloromethane (2 × 30 ml). The combined filtrates were dried and concentrated to leave a colorless, crystalline solid (164 mg). Partition chromatography separated this residue into three bands.

Band 1 (highest R_f) gave a colorless solid (44 mg), mp 130–133°, which was shown by nmr to be a mixture of two compounds. Repeated partition chromatography of this material gave two red bands. Removal of solvent from the first band gave a colorless oil (24 mg) which crystallized from methanol to give 11α-hydroxydiamine **48** as colorless plates: mp 165–167°; $[\alpha]^{24}D$ +21° (c 0.50); ir λ_{max} 2.93, 6.88, 6.94, 7.29, 7.36, 8.39, 8.66, 9.15, 9.31 9.51, and 10.80 μ; nmr (100 MHz) τ 5.83 (1 H, m, C-11 H), 6.46 (1 H, m, C-20 H), 7.50 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.94 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3, and 3 H, s, C-19 CH_3), 9.13 (3 H, s, C-18 CH_3), and 9.28 (3 H, d, J = 6 Hz, C-21 CH_3); mass spectrum m/e 418 (M^+), 417, 403, 347, 138, 113, 112, 99, 98, 86, 84, 81, 73, 72, 71, 69, 57, 56, 55, 43, and 41.

Anal. Calcd for $C_{27}H_{50}N_2O$: C, 77.45; H, 12.04; N, 6.69. Found: C, 77.32; H, 11.88; N, 6.59.

The second band gave **47** as a colorless solid (11 mg), identical with the product obtained from band 2 of the first chromatography.

Band 2 gave 3β-diethylamino-20α-dimethylamino-5α-pregnan-11β-ol (**47**) as a colorless solid (94 mg) which crystallized from methanol as colorless plates: mp 178–179°; $[\alpha]^{24}D$ +30° (c 0.69); ir λ_{max} 2.94, 6.92, 7.36, 8.38, 8.68, 9.43, 9.53, and 10.85 μ; nmr (100 MHz) τ 5.80 (1 H, m, C-11 H), 6.38 (1 H, m, C-20 H), 7.49 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.89 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3, and 3 H, s, C-19 CH_3), 9.15 (3 H, s, C-18 CH_3), and 9.16 (3 H, d, J = 6 Hz, C-21 CH_3); mass spectrum m/e 418 (M^+), 417, 403, 348, 347, 138, 113, 112, 84, 73, 72, 57, 56, 55, and 41.

Anal. Calcd for $C_{27}H_{50}N_2O$: C, 77.45; H, 12.04; N, 6.69. Found: C, 77.25; H, 12.04; N, 6.66.

Band 3 gave a colorless oil (24 mg) which was shown to be a mixture of at least two compounds (tlc). It showed bands at 5.77, 6.88, 7.26, and 7.94 μ in the ir spectrum.

Registry No.—**10**, 34599-35-4; **11**, 34564-99-3; **12**, 34565-00-9; **13**, 34608-93-0; **15**, 34565-01-0; **17**, 34599-36-5; **19**, 34565-02-1; **21**, 34565-03-2; **22**, 34599-37-6; **27**, 34599-38-7; **28**, 34565-04-3; **29**, 34565-05-4; **30**, 34565-06-5; **31**, 34565-07-6; **32**, 34565-08-7; **33**, 34565-09-8; **35**, 34565-10-1; **36**, 34565-11-2; **37**, 34565-12-3; **39**, 34599-39-8; **40**, 34565-13-4; **41**, 34565-14-5; **42**, 34565-15-6; **43**, 34565-16-7; **44**, 34565-17-8; **45**, 34565-18-9; **46**, 34599-40-1; **47**, 34565-19-0; **48**, 34565-20-3.

Berlandin and Subacaulin, Two New Guaianolides from *Berlandiera Subacaulis*[1]

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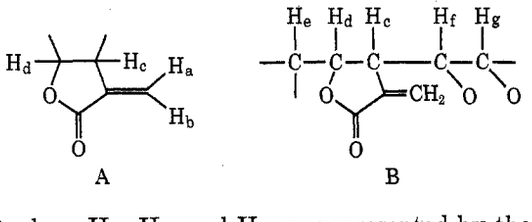
Two new guaianolides, berlandin and subacaulin, have been isolated from *Berlandiera subacaulis* (Nutt.) Nutt. Structure **2a** has been deduced for subacaulin. Berlandin is either **1a** or differs from acetylsubacaulin (**2b**) in configuration of the epoxide ring.

In the course of our investigations of subtribe Melampodiinae, tribe Heliantheae, family Compositae,[2] we are studying constituents of the North American genus *Berlandiera*.[3] The isolation and structure determination from *Berlandiera subacaulis* (Nutt.) Nutt. of two new guaianolides, which we have named berlandin and subacaulin, is reported herewith.

Berlandin (**1**), $C_{22}H_{26}O_7$ (high-resolution mass spectrum), mp 183–185°, $[\alpha]D$ +110.9°, was a conjugated γ lactone (ir bands at 1780 and 1670 cm^{-1}, very strong uv end absorption). The nmr spectrum (Table I) exhibited the characteristic doublets of H_a and H_b in partial structure A at 6.13 and 5.43 ppm. These signals were replaced by a new methyl doublet in the nmr spectrum of the tetrahydro derivative **3**. Irradiation at the frequencies of H_a and H_b established the location of H_c at 3.33 ppm in the usual fashion,[4] but the location of H_d, one of three protons in the region 3.6–5.8 ppm, could not be established unambiguously at this stage. Irradiation at the frequency of H_c did not affect a broad doublet at 5.59 ppm, but collapsed a triplet at 5.21 ppm to a doublet. The appearance of the broad doublet and the triplet suggested that the protons responsible for them were coupled to each other. Since the chemical shift of the signal at 5.21 ppm was too low for a proton under a lactone ether oxygen and since the nmr spectrum contained a doublet of doublets at 3.71 ppm,[5] it appeared very likely that A should be expanded



to B where H_d, H_f, and H_g are represented by the signals at 3.71, 5.21, and 5.59 ppm, respectively.

The ir spectrum of berlandin showed the presence of two additional carbonyl groups (bands at 1744 and 1722 cm^{-1}) which were attributed to ester functions,

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(2) The original impetus for these studies is given by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(3) D. J. Pinkava, *Brittonia*, **19**, 285 (1967).

(4) W. Herz, S. Rajappa, M. V. Lakshmikantham, and J. J. Schmid, *Tetrahedron*, **22**, 693 (1966).

(5) This partially overlapped the H_c resonance and could therefore not be decoupled satisfactorily.