at 0.1 mm. (bath temperature 250°) gave a yellow liquid. The infrared spectra before and after the distillation were identical; λ_{max}^{EtOH} 220 mμ (log ε 4.47), 256 mμ (4.12), inflection at 2.93 mμ (3.40).

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.94; H, 7.13; N, 4.00.

Conversion to the corresponding dicarboxylic acid [VIII; R = COOH; R_1 = H; R_2 = $(CH_2)_2$COOH].—*Cf.* above.

Reaction of 2,6-Di-*t*-butyl-4-cyanophenoxyl with 3-(*p*-Hydroxyphenyl)propionic Acid (Phloretic Acid).—In this reaction the free radical was prepared *in situ* by dissociation of its dimer. To a solution of 200 mg. (1.22 mmoles) of phloretic acid[28] in 10 ml. of ethyl acetate 0.56 mg. (1.2 mmoles) of the dimer[32] of the free radical was added in small portions with stirring. The solvent was then evaporated *in vacuo* and a solution of the crystalline residue in benzene chromatographed on a column of 30 g. of silica gel. Elution with benzene gave 4-hydroxy-3,5-di-*t*-butylbenzonitrile.[19] Elution with ether yielded a liquid which crystallized on treatment with petroleum ether. Recrystallization from benzene–petroleum ether gave 0.20 g. (42%) of 3-[4-(2-hydroxy-3-*t*-butyl-5-cyanophenoxy)phenylpropionic acid [VIII; R = CN; R_1 = H; R_2 = $(CH_2)_2$COOH] as colorless plates, m.p. 151–153°; λ_{max}^{EtOH} 220 mμ (log ε 4.51), 256 mμ (4.17), inflection at 294 mμ (3.36). Infrared bands (Nujol) at 3435 (hydroxyl), 2225 (nitrile), 1716 (carboxyl) 1602, 1587, and 1509 cm.$^{-1}$ (aromatic double bond).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 71.11; H, 6.55; N, 4.06.

Conversion to the Corresponding Dicarboxylic Acid [VIII; R = COOH; R_1 = H; R_2 = $(CH_2)_2$COOH].—*Cf.* above.

Acknowledgment.—This work was supported in part by Grant A-3706 from the National Institutes of Health, U.S. Public Health Service. The authors thank Prof. T. Kubota for his interest in this work, Dr. E. D. Becker and Mr. R. B. Bradley for determining and interpreting the proton n.m.r. spectra, and Dr. J. Axelrod for helpful advice concerning the catechol O-methyltransferase test.

(32) E. Müller and K. Ley, *Chem. Ber.*, **92**, 2278 (1959).

The Synthesis of C-18 Functionalized Steroid Hormone Analogs. II. Preparation and Some Reactions of 18-Chloro Steroids[1a]

JAMES F. KERWIN, MANFRED E. WOLFF,[1b] FRANKLIN F. OWINGS, BARBARA B. LEWIS, BENJAMIN BLANK, A. MAGNANI, C. KARASH, AND V. GEORGIAN[1c]

Smith Kline and French Laboratories, Philadelphia, Pennsylvania, and The Julian Laboratories, Inc., Franklin Park, Illinois

Received May 21, 1962

A number of 20-methylamino steroids have been prepared by reductive amination of the corresponding 20-keto steroids. Irradiation of the *N*-chloro derivatives of these amines in trifluoroacetic acid produced 18-chloro-20-methylamino steroids which were isolated as their trifluoroacetate salts. Treatment of the salts with base caused ring closure to conanines. However, when an 11-keto function was present, alkali treatment resulted in formation of 12,18-cyclo steroids in addition to 11-ketoconanines. The interconvertibility of 11-keto-12,18-cyclo steroids and 11-ketoconanines was demonstrated by conversion of 3β-hydroxy-20α-methylamino-12,18-cyclo-5α-pregnane-11-one (XVIII) into 3β-hydroxyconanine-11-one (XVIIb) and transformation of the latter compound into 3β-hydroxy-12,18-cyclo-5α-pregn-20-ene-11-one (XXII).

The presence of a 13-aldehyde group in aldosterone has focused attention on methods for preparing 18-functionalized steroids. The solution to this problem was originally approached by methods involving total synthesis, by partial syntheses from *Holarrhena* alkaloids and by way of 13,17-seco steroids.[2]

A fundamentally different type of synthetic route was made available when methods were found for the direct introduction of substituents at the C-18 methyl group of intact steroids. Functionalization by means of the Hofmann–Loeffler–Freytag reaction with formation of a carbon–nitrogen bond at C-18 was the first method reported.[3,4] Other methods for direct attack on the angular methyl group followed in rapid succession: thermal decomposition of a 21-diazo-20-ketone to form an 18,21-cyclo steroid,[5] irradiation of 20-keto steroids to form 18,20-cyclo-20-ols,[6] lead tetraacetate treatment of 20-hydroxy steroids to yield 18,20-epoxides[7] or, with iodine added, to form 18-iodo-18,20-epoxides,[8] photochemical rearrangement of 11β- or 20-nitrite esters to 18-oximes,[9]

(1) (a) Previous paper, M. E. Wolff, J. F. Kerwin, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, and V. Georgian, *J. Am. Chem. Soc.*, **82**, 4117 (1960); (b) Present address, School of Pharmacy, University of California; (c) Present address, Department of Chemistry, Tufts University.

(2) See K. Schaffner, D. Arigoni, and O. Jeger, *Experientia*, **16**, 169 (1960) for leading references and a review of this area.

(3) E. J. Corey and N. R. Hertler, *J. Am. Chem. Soc.*, **80**, 2903 (1958); **81**, 5209 (1959).

(4) P. Buchschacher, J. Kalvoda, D. Arigoni, and O. Jeger, *ibid.*, **80**, 2905 (1958).

(5) F. Greuter, J. Kalvoda, and O. Jeger, *Proc. Chem. Soc.*, 349 (1958).

(6) P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959); N. C. Yang and D. H. Yang, *Tetrahedron Letters*, (4), 10 (1960).

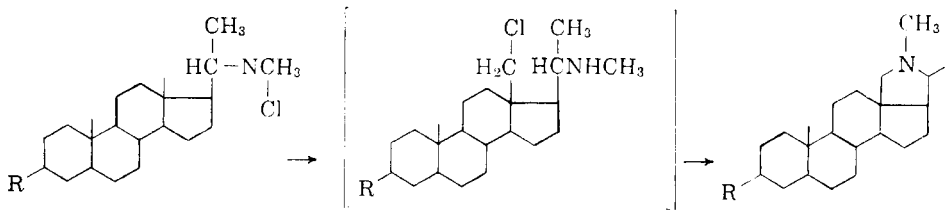
(7) G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(8) Ch. Meystre, K. Heusler, J. Kolvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961).

(9) (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); (b) D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960); (c) A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian, and D. H. R. Barton, *ibid.*, **82**, 2973 (1960); (d) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *ibid.*, **82**, 4076 (1961); (e) D. H. R. Barton and J. M. Beaton, *ibid.*, **83**, 4083 (1961).

photolysis of 20-hypochlorites to 18-chloro-20-hydroxy compounds,[10a] and irradiation of a 20-azido steroid to form conessine.[10b]

The synthesis of 18,20-imino steroids (conanines) from *N*-chloro-20-amino steroids by the Hofmann–Loeffler–Freytag reaction has not been exploited to any extent beyond the initial examples. Corey and Hertler[3] converted 3β-dimethylamino-*N*-chloro-20α-methylamino-5α-pregnane (Ia) into dihydroconessine (IIIa) and Buchschacher and coworkers[4] prepared conanine (IIIb) from *N*-chloro-20α-methylamino-5α-pregnane (Ib). The successful application of this reaction to the synthesis of of 3-acetoxyconanine (IIIc) from Ic as well as the preparation, in low yield, of the 3-keto derivative (IIId) from Id has also been reported.[2]



I II III

a. R = $(CH_3)_2N$
b. R = H
c. R = CH_3COO
d. R = O=

Conanines derived from natural sources have served as starting materials for hormone analogs having a substituent or functional group at the 18-position.[11] A facile synthesis of conanines already containing desirable functional groups would offer an obvious advantage in this direction and therefore the preparative utility of the Hofmann–Loeffler–Freytag reaction was investigated as part of a program to study the physiological effects of 18-substituted steroids. Modification of the usual Hofmann–Loeffler–Freytag reaction conditions made possible the synthesis of 3-oxygenated and 3,11-dioxygenated conanines as well as 3-keto-4-conanenes in good yield. During the development of optimum conditions for the over-all conversion of *N*-chloro-20-methylamino steroids into conanines it was found that the 18-chloro-20-methylamino compounds could be isolated, often in excellent yield, as the acid addition salts. Isolation of these intermediates enhances the versatility of the Hofmann–Loeffler–Freytag reaction as a preparative tool since transformations other than pyrrolidine ring closure can now be visualized for the 18-chloro-20-amino compounds.

A survey of methods previously used to prepare the required intermediate 20α-methylaminosteroids showed that such compounds have been prepared by Decker–Becker methylation of the corresponding primary amines[12] or by lithium aluminum hydride reduction of the *N*-formyl derivatives.[3,4,13] The primary amines were in turn prepared by catalytic hydrogenation of 20-oximes,[4,14] a method which forms both 20α- and 20β-amines,[14] or by Curtius degradation of bisnorcholenic acids,[15] a stereospecific reaction which yields exclusively the 20α-amines.

We have found that 20-methylamino steroids can be prepared directly from 20-keto steroids by reductive amination with methylamine and platinum oxide catalyst. Both the 20α- and 20β-methylamines were formed by this procedure but the 20α-methylamine predominated and, in most of the cases studied, the pure isomer could be obtained by a few recrystallizations of the total amine fraction. Some of the 20-hydroxy steroid was also formed during reductive amination. However, the amount of neutral product could be minimized by allowing the keto steroid and methylamine to interact before reduction. In one instance when a solution of the two reactants was hydrogenated immediately with prereduced platinum, practically no amino steroid was formed.

Hydrogenation of 3β-hydroxy-5α-pregnane-20-one (IVa) and excess methylamine in alcohol solution with Adams catalyst at three atmospheres pressure gave the known 20α-methylamino-5α-pregnane-3β-ol (Va)[4,13] in 53% yield. When 3β-hydroxy-5-pregnene-20-one (VI) was subjected to the same conditions, only one mole of hydrogen was absorbed and the basic product was the unsaturated amine, 20α-methylamino-5-pregnene-3β-ol (VII). Its structure was established by direct comparison with material prepared by methylation of the 20α-primary amine,[12] obtained from 3β-acetoxybisnorcholenic acid azide.[15] Further hy-

(10) (a) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 2213 (1961); (b) D. H. R. Barton and L. R. Morgan, *Proc. Chem. Soc.*, 206 (1961).

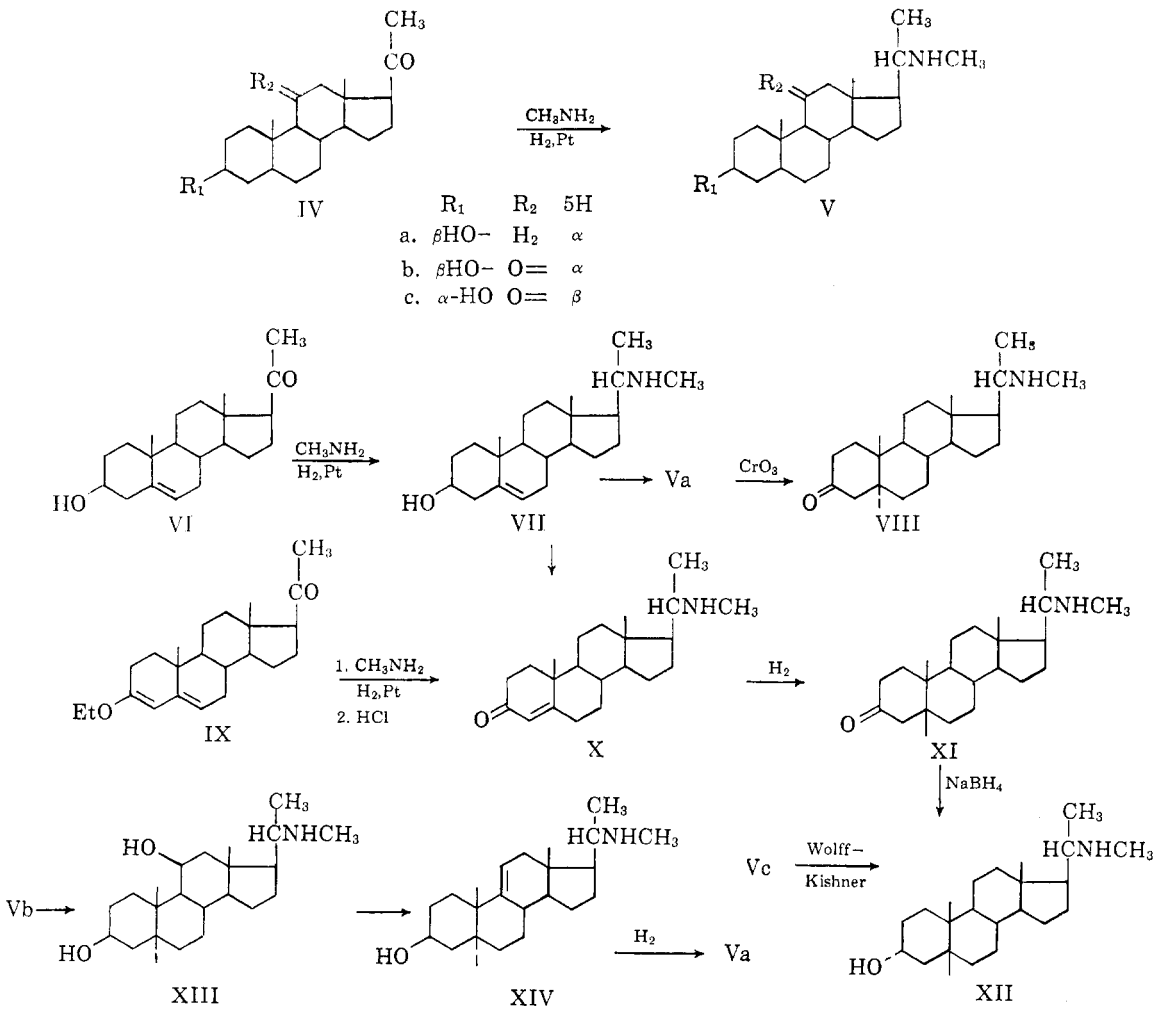
(11) (a) L. Labler and F. Sorm, *Chem. Ind.* (London), 1661 (1958); (b) L. Labler and F. Sorm, *ibid.*, 598 (1959); (c) R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959); (d) F. Buzzetti, W. Wicki, J. Kalvoda, and O. Jeger, *Helv. Chim. Acta*, **42**, 388 (1959); (e) L. Labler and F. Sorm, *Chem. Ind.* (London), 935 (1960).

(12) P. L. Julian, E. W. Meyer, and R. Schroeder, U. S. Patent 2,582,258 (1952).

(13) M. Janot, Q. Khuong-Huu, and R. Goutarel, *Compt. rend.*, **250**, 2445 (1960).

(14) V. Cerny, L. Labler, and F. Sorm, *Collection Czech. Chem. Commun.*, **22**, 76 (1957).

(15) P. L. Julian, E. W. Meyer, and H. C. Printy *J. Am. Chem. Soc.*, **70**, 887 (1948).



drogenation of VII over palladium–carbon in acetic acid gave Va, thus confirming the configuration of the 20-methylamino group in the saturated compound. Chromic acid oxidation of Va gave the known 3-keto compound VIII.[4,13,16]

Selective reduction at the 20-position was also possible in the presence of the conjugated system in 3-ethoxy-3,5-pregnadiene-20-one (IX). Under the reductive amination conditions, one mole of hydrogen was taken up rapidly and then the rate of reduction slowed markedly. The reaction was interrupted at this point and the product treated with acid to generate the α,β-unsaturated ketone. 20α-Methylamino-4-pregnene-3-one (X) was readily obtained in 61% yield by recrystallization of the liberated amine. The lower melting 20β-isomer was isolated from the filtrate in about 18% yield. The identity of the major product was confirmed by comparison with a sample prepared by Oppenauer oxidation of 20α-methylamino-5-pregnene-3β-ol (VII).[12] Hydrogenation of X with palladium–carbon in the presence of potassium hydroxide afforded 20α-methylamino-5β-pregnane-3-one (XI).

(16) It is interesting to note that compounds Va and VIII have been isolated from the plant species *Funtumia africana*: R. Goutarel, *Tetrahedron*, **14**, 126 (1961).

The 5β-configuration of the reduction product was evident from the non-identity of compounds VIII and XI. Further reduction of XI with sodium borohydride gave 20α-methylamino-5β-pregnane-3α-ol (XII).

Reductive amination of 3β-hydroxy-5α-pregnane-11,20-dione (IVb) resulted in a 59% yield of 3β-hydroxy-20α-methylamino-5α-pregnane-11-one (Vb), obtained by recrystallization of the reduction product. A low yield of the 20β-isomer could be isolated by chromatography of the recrystallization residue. The configuration of the 20α-isomer was established by its conversion into the 11-desoxy compound in the following manner: reduction with lithium aluminum hydride to the 3β,11β-diol (XIII), dehydration to the 9,11-pregnene (XIV), followed by hydrogenation to 20α-methylamino-5α-pregnane-3β-ol (Va), identical with material prepared by methods described above.

The product from the reductive amination of 3α-hydroxy-5β-pregnane-11,20-dione (IVc) was a syrup which was difficult to crystallize. However, the mixture formed a crystalline *N*-chloro derivative which could be separated into two components. Reduction of each component back to the secondary amine afforded the isomeric

TABLE I

N-CHLORO-20-METHYLAMINO STEROIDS

Compound	M.p.,[a] °C.	[α]D	Yield, %	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XVa	166	+ 46	82	71.80	71.77	10.41	10.52
XVb	184	+ 79	94	69.17	69.42	9.50	9.23
20β-XVb	140	+ 3	84	69.17	68.78	9.50	9.43
XVc	168	+ 67	77	69.17	68.98	9.50	9.79
20β-XVc	167	+ 7	81	69.17	68.92	9.50	9.17
XVd	135	+106	92	72.60	72.40	9.42	9.38
20β-XVd	124	+140	84	72.60	72.54	9.42	9.61
XVe	137	+214	91	69.91	69.66	8.53	8.32

[a] Temperature at which decomposition begins.

3α-hydroxy-20-methylamino-5β-pregnane-11-ones, m.p. 130–132° and m.p. 174.5–176.5°. Wolff–Kishner reduction of the lower melting isomer produced 20α-methylamino-5β-pregnane-3α-ol (X-II), previously prepared from compound X as described above.

Oxidation of 3α-hydroxy-20α-methylamino-5β-pregnane-11-one (Vc) produced the 3,11-dione. Attempts to introduce a 4,5-double bond into this compound by bromination and dehydrobromination failed to yield a crystalline product. However, when the amino group was trifluoroacetylated to form *N*-trifluoroacetyl-20α-methylamino-5β-pregnane-3,11-dione, the bromination – dehydrobromination sequence proceeded smoothly with the formation of *N*-trifluoroacetyl-20α-methylamino-4-pregnene-3,11-dione. Basic hydrolysis of the amide group led to 20α-methylamino-4-pregnene-3,11-dione. This compound was also prepared by reductive amination of the crude, noncrystalline ethyl enol ether of 11-ketoprogesterone. Acid hydrolysis of the resulting mixture gave 20α-methylamino-4-pregnene-3,11-dione in low yield.

The secondary amines were readily converted into *N*-chloroamines (XV) with aqueous sodium hypochlorite. The highly crystalline character of the *N*-chloro derivatives was used to advantage in separating mixtures of the 20α- and 20β-isomers. The secondary amines were easily regenerated by sodium bisulfite reduction of the *N*-chloro derivatives.

The free radical nature of the Hofmann–Loeffler–Freytag reaction and the necessity for a strong acid in order to protonate the *N*-chloroamine seem well established.[17] The reaction is customarily run in strong sulfuric acid or sulfuric acid–acetic acid mixtures with heat or ultraviolet light used to initiate the free radical reaction.[17,18] This results in formation of a δ-haloamine[19] which normally is treated directly with base to form a pyrrolidine. The low solubility and apparent decomposition of our *N*-chloroamines is 85% sulfuric acid and precluded the use of this acid as a solvent. Dilution of the sulfuric acid with glacial acetic acid resulted in reasonably stable solutions of *N*-chloroamines. However, when these solutions were irradiated, none or, at best, traces of the desired tertiary amines were isolated after neutralization of the quenched acid solution and base treatment of the crude product.

In contrast, trifluoroacetic acid proved to be an ideal medium for the radical reaction. The steroidal *N*-chloroamines were extremely soluble in the acid and solutions prepared with thorough cooling were stable for several hours in the dark. Irradiation caused a rapid disappearance of positive halogen with only slight darkening of the solution. Evaporation of excess acid under reduced pressure circumvented the need for neutralization of large volumes of acid as is required in the classical Hofmann–Loeffler–Freytag procedure. The volatility of the acid also facilitated the isolation of the 18-chloro-20-methylamino steroids as their trifluoroacetate salts. After this work was begun, Wawzonek[18b] also reported the use of trifluoroacetic acid as a solvent for the Hofmann–Loeffler–Freytag reaction.

The 18-chloro compounds containing a 3-keto-Δ^4 system (XVId and XVIe) were easily isolated as their trifluoroacetate salts by crystallization of the syrup remaining after removal of excess trifluoroacetic acid. Isolation of 3-hydroxy intermediates was complicated by partial esterification of the alcohol function and at first only low yields of crystalline 3-trifluoroacetoxy derivatives XVIf and XVIg were obtained. However, addition of one equivalent of trifluoroacetic anhydride to the irradiated solution followed by removal of the volatile material resulted in excellent yields of XVIf and XVIg. The 18-chloro compound derived from the 5β-*N*-chloroamine (XVc) failed to crystallize when similiarly treated and the clear sirup was used in subsequent reactions.

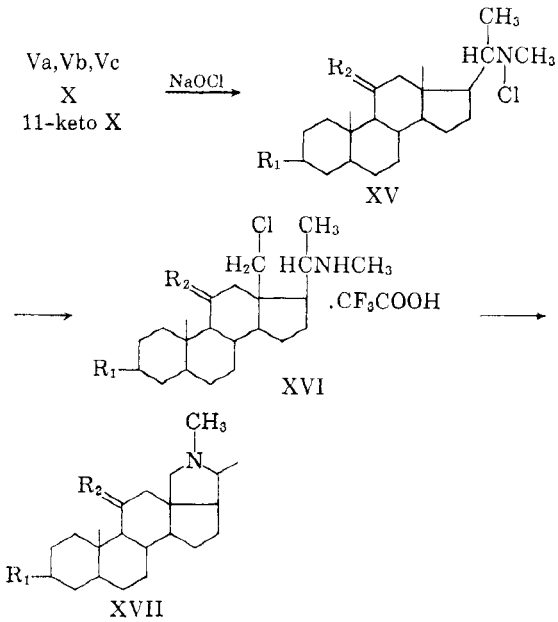
N-Chloro derivatives of 20β-methylamines could also be isomerized to the 18-chloro-20β-methylamino structures. Thus, 3β-hydroxy-*N*-chloro-20β-methylamino-5α-pregnane-11-one (20β-XVb) gave crystalline 20β-XVIg upon irradiation and subsequent trifluoroacetic anhydride treatment

(17) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **82**, 1657 (1960).

(18) For leading references, see (a) R. Lukes and M. Ferles, *Collection Czech. Chem. Commun.*, **20**, (1955); (b) S. Wawzonek and T. P. Culbertson, *J. Am. Chem. Soc.*, **81**, 3367 (1959).

(19) See, however, S. Wawzonek, and P. J. Thelen, *ibid.*, **72**, 2118 (1950), and S. Wawzonek, M. F. Nelson, and P. J. Thelen, *ibid.*, **73**, 2806 (1951).

although the yield was lower than with the 20α-isomer. Lower yields with 20β- *vs.* 20α-isomers have also been observed in the formation of 18,20-epoxides from 20-hydroxy steroids[20] and of 18-oximes from 20-nitrite esters.[9c] *N*-Chloro-20β-methylamino-4-pregnene-3-one also underwent the Hofmann–Loeffler–Freytag reaction but the resulting 18-chloro derivative (20β-XVId) could not be obtained in crystalline form.



	R_1	R_2	5H
a.	βHO	H_2	α
b.	βHO	O=	α
c.	αHO	O=	β
d.	O=	H_2	Δ_4
e.	O=	O=	Δ_4
f.	β-CF_3COO	H_2	α
g.	β-CF_3COO	O=	α

Treatment of 3β-trifluoroacetoxy-18-chloro-20α-methylamino-5α-pregnane trifluoroacetate (XVIf) with either potassium carbonate or potassium hydroxide in methanol afforded 3β-hydroxyconanine (XVIIa) in good yield. Comparable yields of XVIIa were obtained without isolation of the 18-chloro intermediate. Thus, when irradiated solutions of XVa were freed of trifluoroacetic acid and the residual sirup, presumably a mixture of 3β-hydroxy compound (XVIa) and trifluoroacetoxy derivative (XVIf), was warmed with base, yields of 3β-hydroxyconanine approached 85%. The 3β-hydroxyconanine synthesized by this procedure was identical with material prepared from conessine by the method of Cerny and Sorm.[21]

Similarly, 18-chloro-20α-methylamino-4-pregnene-3-one trifluoroacetate (XVId) was transformed in basic solution into the known 4-conanene-3-one (XVIId).[22] Treatment of the noncrystalline 20β-isomer (20β-XVId) in the same manner afforded 20-iso-4-conanene-3-one (20-iso-XVIId).

Reaction of the 11-keto-18-chloro compound (XVIg) with potassium carbonate gave 3β-hydroxyconanine-11-one (XVIIb) as the sole product. However, when potassium hydroxide was used to effect ring closure, the conanine was accompanied by a secondary amine by-product which could be removed readily by acetylation of the total reaction mixture. It was then noted that the amount of by-product varied with the size of the experiment; it was appreciable in small scale experiments when a solution of XVIg in methanolic potassium hydroxide attained reflux temperature in a few minutes and minimal when a large volume of solution was slowly brought to the boiling point. By adding a solution of XVIg dropwise to refluxing methanolic potassium hydroxide, the yield of by-product was increased to about 50%.

The by-product was isomeric with the 11-keto-conanine XVIIb, formed an *O,N*-diacetyl derivative with acetic anhydride and had a carbonyl absorption at 5.98 μ in the infrared spectrum as compared to a carbonyl absorption at 5.88 μ for XVIIb. The position of the carbonyl absorption and the lack of high intensity absorption in the 240-mμ region of the ultraviolet spectrum pointed to an 11-keto-12,18-cyclo structure (XVIII) for the by-product. Structure XVIII was further supported by location of sharp, weak bands[23] at 3.27 and 3.31 μ due to C—H stretching of the cyclopropyl methylene.[24] The n.m.r. spectrum of compound XVIII was uninformative regarding the presence of a cyclopropyl ring. Stork and Finici[25] have recently reported that the n.m.r. absorption of the cyclopropyl methylene in bicyclo[0.1.4]heptanone-2 is lowered to τ *ca.* 8.9 by conjugation with the carbonyl. With our compound, C-19 methyl absorption and unresolved background absorption in this region prevented identification of peaks due to cyclopropyl protons.

Definite evidence for the 12,18-cyclo structure was obtained, however, when the 11-keto group of XVIII was removed by Wolff-Kishner reduction. The n.m.r. spectrum of the 11-desoxy derivative XXVI contained two complex signals, each equivalent to one proton, centered at τ 9.67 and 10.08[26] (chloroform as the reference standard).

Precedent for the transformation XVIg → XVIII is found in the recently reported cyclization

(20) L. Velluz, G. Muller, R. Bardoneschi, and A. Poittevin, *Compt. rend.*, **250**, 725 (1960).

(21) V. Cerny and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 4015 (1959).

(22) W. S. Johnson, V. J. Bauer, and R. W. Franck, *Tetrahedron Letters*, (2), 72 (1961).

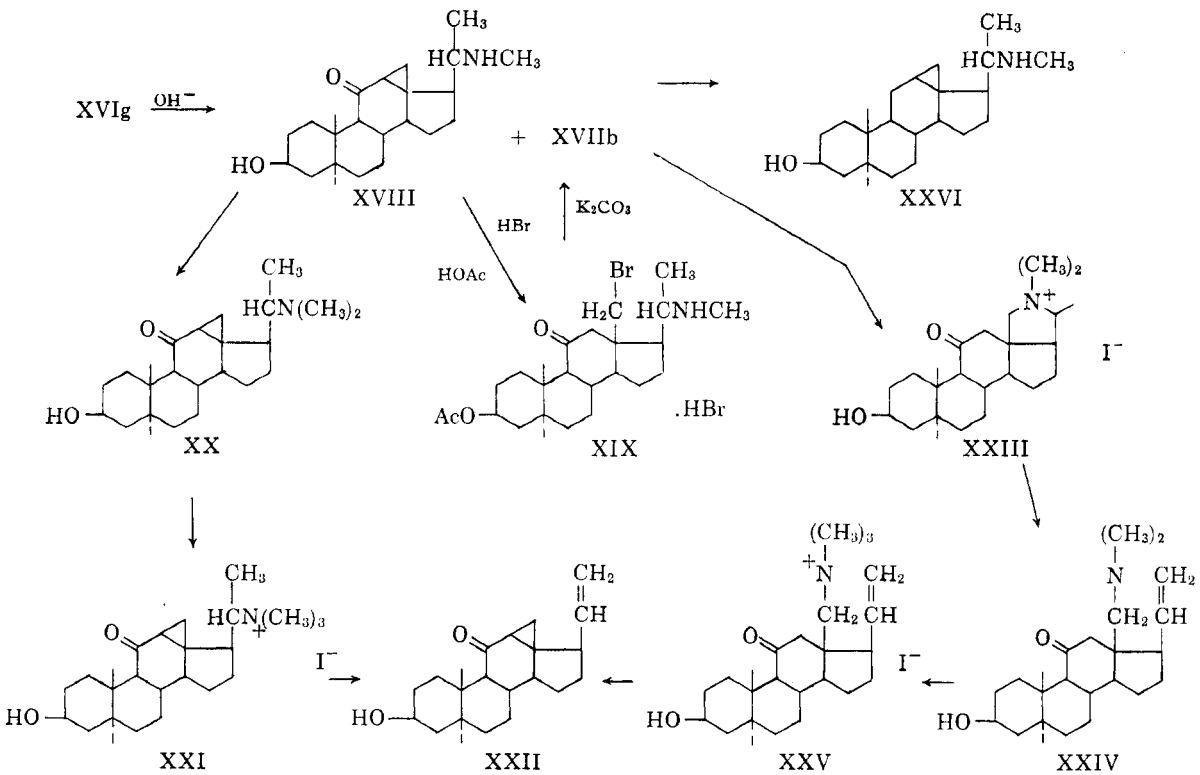
(23) Spectrum determined with a Perkin-Elmer Model 137-G grating spectrophotometer.

(24) S. A. Liebman and B. J. Gudzinowicz, *Anal. Chem.*, **33**, 931 (1961).

(25) G. Stork and J. Finici, *J. Am. Chem. Soc.*, **83**, 4678 (1961).

(26) K. Kocsis, P. G. Ferrini, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **43**, 2178 (1960) report a complex signal at τ *ca.* 10.0 for 4α,5-methylene cholestane and R. McCrindle and C. Djerassi, *Chem. Ind.* (London), 1311 (1961), report doublets at 20 and 35 c.p.s. for cyclopropyl hydrogens of the cycloartane nucleus.

of a 19-tosyloxy-11-ketopregnane to a 9,19-cyclo-11-keto structure[27] as well as in many other examples of similar cyclizations of γ-halo, γ-tosyloxy-, or γ-quaternary ammonium ketones with base.[28] In the present instance, cyclopropyl ring formation actually competes, in media favoring enolization, with a very facile pyrrolidine ring closure. Cyclization of compound XVIg could be directed entirely to the 12-position when the secondary amine group was temporarily blocked. Thus, the *N*-trifluoroacetyl derivative of XVIg on refluxing with alcoholic sodium hydroxide for several hours gave XVIII in practically quantitative yield.



Additional evidence for the 12,18-cyclo structure was obtained from further transformations. Whereas compound XVIII was stable to dilute aqueous acids, anhydrous hydrogen bromide in acetic acid at room temperature opened the cyclopropyl ring as evidenced by a shift of the carbonyl absorption from 5.98 to 5.88 μ. The 3β-hydroxy group was simultaneously esterified to the 3-acetate. Formulation of the product as the 18-bromo compound XIX follows from its elemental analysis and the fact that treatment of an aqueous solution with potassium carbonate caused an immediate precipitation of 3β-acetoxy-5α-conanine-11-one. Hydrolysis of the acetoxy group with a stronger base gave 3β-hydroxy-5α-conanine-11-one (XVIIb).

Cyclopropyl ring closure could also be effected by operating on the 11-ketoconanine. Thus, compound XVIIb was methylated to form XXIII and the corresponding quaternary hydroxide heated to open the pyrrolidine ring to the 18-dimethylamino-20-pregnene (XXIV). Quaternization of XXIV with methyl iodide gave the 18-trimethylammonium salt XXV which on heating with sodium methoxide in dimethylformamide eliminated trimethylamine and produced 3β-hydroxy-12,18-cyclo-5α-pregn-20-ene-11-one (XXII). The normal carbonyl absorption for an 11-keto function was present in the infrared spectra of XXIII, XXIV, and XXV but was shifted to 6.0 μ with compound XXII. The same compound (XXII) was also formed from the 12,18-cyclo secondary amine XVIII. Methylation with formaldehyde and formic acid formed the tertiary amine XX which with methyl iodide then gave the quaternary iodide XXI. The 20,21 double bond was generated by elimination of trimethylamine from XXI in the presence of sodium methoxide.

Reaction of 18-chloro-20α-methylamino-4-pregnene-3,11-dione trifluoroacetate (XVIe) with potassium carbonate gave 4-conanene-3,11-dione (XVIIe) with two well separated carbonyl peaks in the infrared spectrum. Treatment of XVIe with alcoholic potassium hydroxide, analogous to the XVIg → XVIII reaction, yielded 20α-methylamino-12,18-cyclo-4-pregnene-3,11-dione which had a single, broad band at 5.96–6.0 μ in the carbonyl region.

Since one of the objectives of this study was to provide a convenient synthesis of 11-ketoconanines

(27) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(28) For recent examples, see R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959); G. H. R. Summers, *Proc. Chem. Soc.*, 24 (1960); ref. 25.

which were desired as starting materials for further transformations, the overall process from 20-keto steroids IX to conanines XVII was conducted without isolation of intermediates. For example, 3β-hydroxy-5α-pregnane-11,20-dione (XVb) was reductively aminated and the total amine fraction, without separation of the 20α- and 20β-isomers, was converted to the *N*-chloro derivative. This material was irradiated, the acid stripped and the residue treated with alkali. Acetylation of the crude product removed secondary amine and afforded 3β-acetoxy-5α-conanine-11-one in approximately 36% yield. The fact that the 20β-*N*-chloroamine gave a poor yield of 18-chloro intermediate was an advantage here in helping to eliminate the unwanted 20β-isomer. Although some of the 20-isoconanine was probably formed, one recrystallization of the final product brought the melting point up to that of material prepared from pure 20α-methylamine.

Substantially the same results were obtained when 3α-hydroxy-5β-pregnane-11,20-dione IVc was carried through to 3α-hydroxy-5β-conanine-11-one (XVIIc) without isolation of intermediates. On the other hand, this procedure was not very satisfactory when applied to compounds containing the 3-keto-Δ^4 system. In these instances, separation of the 20α-methylamines from the reductive amination mixtures was necessary in order to obtain good yields in the Hofmann–Loeffler–Freytag reaction.

Experimental

Melting points were taken in a Thomas–Hoover apparatus and are uncorrected. Rotations were determined in chloroform at 25° unless noted otherwise. We want to thank the following members of the Analytical and Physical Chemistry Section of Smith Kline and French Laboratories: Mrs. Doris Rolston and staff for elemental analyses, Dr. Walter Thompson and staff for infrared and ultraviolet absorption spectra and X-ray diffraction patterns, and Dr. Walter Hamill and staff for rotations. We also thank Dr. Gerald Dudek of Harvard University for the n.m.r. spectra.

Reductive Amination Procedure.—A general procedure was employed to prepare 20-methylamino steroids from 20-keto steroids. Dry methylamine was passed into alcohol with cooling until a 10% solution (w./v.) was attained. Solutions or, in the case of IVa and VI, suspensions of 20-keto steroid were prepared in the proportion of 0.025 mole of steroid per 100 ml. of alcoholic methylamine. The mixtures were allowed to stand for 1 hr. and then hydrogenated at 3 atm. pressure with approximately 0.25 g. of platinum oxide catalyst per 0.025 mole of steroid. Uptake of one equivalent of hydrogen usually occurred in less than 2 hr. The filtered solutions were treated as described in the individual examples.

20α-Methylamino-5-pregnene-3β-ol (VII).—The mixture resulting from reductive amination of VI was diluted with chloroform to dissolve the product, filtered to remove catalyst, and evaporated under reduced pressure. The residue was dissolved in chloroform and extracted with 5% acetic acid until all the basic material was removed from the organic solution. The solid precipitated on neutralization of the acid extracts was recrystallized from aqueous methanol to give a 48% yield of VII, m.p. 222–224°; $[\alpha]_D$ −44° (*c* 1.0); lit.,[12] m.p. 225–226°. Direct comparison (mixed m.p. and X-ray diffraction patterns) of our material with a sample prepared by the method of ref. 12 established identity.

20α-Methylamino-5α-pregnane-3β-ol. (Va). Method A.—The solution obtained on reductive amination of IVa was evaporated to dryness, the product dissolved in 40 ml. of acetic acid and then diluted to 700 ml. with water. The cloudy solution was extracted with ether and the aqueous portion neutralized with sodium hydroxide solution. Recrystallization of the solid from alcohol afforded a 53% yield of Va, m.p. 209–212°; $[\alpha]_D$ +23° (*c* 0.9); lit., m.p. 211°[4] and 215°.[13]

Method B.—Eight grams of 20α-methylamino-5-pregnene-3β-ol (VII) in acetic acid was hydrogenated over palladium–carbon catalyst at 3 atm. The filtered solution was diluted with water and made basic with 40% sodium hydroxide solution. Recrystallization of the filtered solid from acetone–methanol gave 6.6 g. (82%) of Va, m.p. 207.5–211.5°, not depressed by material prepared by method A.

Method C.—A solution of 1.5 g. of XIV in 25 ml. of acetic acid was hydrogenated with 0.5 g. of platinum oxide at 3 atm. and 60°. The filtered solution was evaporated; the residue was dissolved in 20 ml. of methanol and made alkaline with sodium methoxide. The solution was refluxed for 30 min., poured into water, and the product isolated with chloroform. Evaporation of the solvent and recrystallization of the residue afforded Va, m.p. 207–209°, undepressed on admixture with material prepared as above.

20α-Methylamino-5α-pregnane-3-one (VIII).—One gram of Va in 60 ml. of acetic acid and 35 ml. of acetone was treated with 1.4 ml. of 8 *M* chromium trioxide solution and heated on a steam bath to reflux. The cooled and diluted solution was neutralized with 40% sodium hydroxide solution and extracted with chloroform. Evaporation of the dried chloroform solution and recrystallization of the solid from ethyl acetate afforded 0.52 g. of VIII, m.p. 158–159°; lit.,[13] m.p. 160°.

Anal. Calcd. for $C_{22}H_{37}NO$: C, 79.70; H, 11.25. Found: C, 79.79; H, 11.45.

3β-Hydroxy-20α-methylamino-5α-pregnane-11-one (Vb).—Compound IVb (100 g.) was reduced by the general procedure, the solvent evaporated and the crude product dissolved in 10% acetic acid. The solution was filtered through Super-cel to remove a small amount of neutral material and the amine precipitated by addition of sodium hydroxide solution to the filtrate. The dried solid was recrystallized from toluene to yield 61.7 g. (59%) of Vb, m.p. 183–186°. The analytical sample was recrystallized from acetonitrile, m.p. 187–189°; $[\alpha]_D$ +56°; λ_{max}^{KBr} 2.93, 3.0, 5.86 μ.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 76.27; H, 10.85.

In another experiment, the basic fraction from 250 g. of starting material was recrystallized several times from acetone to give 107 g. of Vb and 150 g. of residue. Twenty-grams of the residue was chromatographed on a silica gel column. Solid eluted with 5% diethylamine in ethyl acetate was **3β-hydroxy-20β-methylamino-5α-pregnane-11-one**, m.p. 187–191°, wt. 7.0 g. This represents a 20% yield from IVb. Recrystallization of the 20β-isomer raised its m.p. 191–193°, $[\alpha]_D$ +37° (*c* 0.8). A mixture with the 20α-isomer melted at 164–177°.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 75.83; H, 10.85.

Further elution of the column wih 1:1 ethyl acetate–methanol followed by recrystallization of the solid from acetone afforded an additional 5.0 g. of 20α-methylamine Vb bringing the total yield to 55%.

20α-Methylamino-5α-pregnene-3β,11β-diol (XIII).—To a stirred solution of 1.0 g. of lithium aluminum hydride in 40 ml. of tetrahydrofuran was added a solution of 5.0 g. of 3β-hydroxy-20α-methylamino-5α-pregnane-11-one (Vb) in

the same solvent. The stirred mixture was refluxed for 1 hr., cooled, and excess reducing agent decomposed with water. The granular precipitate was removed by filtration and the filtrate was evaporated *in vacuo* to leave a crystalline residue. Recrystallization of the solid from acetone gave 4.5 g. of crystals, m.p. 192–193.5°; $[\alpha]_D$ +36° (*c* 0.5).

Anal. Calcd. for $C_{22}H_{39}NO_2$: C, 75.59; H, 11.25. Found: C, 75.65; H, 11.31.

20α-Methylamino-5α-pregn-9(11)-ene-3β-ol (XIV).—A solution of 2.85 g. of XIII in 45 ml. of acetic acid–concentrated hydrochloric acid (4:1) was heated at 95° for 30 min. and then poured into water. The resulting solution was made alkaline and the precipitated product collected. Infrared examination of the product showed it to be the 3-acetate (5.8 and 8.0 μ). Therefore the compound was heated with methanolic potassium hydroxide for 20 min., the solution diluted with water, and the product extracted into chloroform. Evaporation of the solvent and recrystallization of the residue from methanol gave XIV, m.p. 194–198°; $[\alpha]_D$ +33° (*c* 0.4).

Anal. Calcd. for $C_{22}H_{37}NO$: C, 79.70; H, 11.25. Found: C, 79.76; H, 11.27.

3α-Hydroxy-20α-methylamino-5β-pregnane-11-one (Vc).—The solution from reductive amination of 25 g. of IVc was evaporated and the reduction product partitioned between 300 ml. of 1 *N* hydrochloric acid and 100 ml. of methylene chloride. The aqueous layer was made alkaline with sodium hydroxide solution and extracted again with methylene chloride. The organic layer was separated and stirred with 300 ml. of sodium hypochlorite solution ("Clorox") for 1 hr. to convert the crude amine fraction into the *N*-chloro derivative. Evaporation of the washed and dried methylene chloride solution left an oil which crystallized readily on trituration with alcohol. Recrystallization from alcohol gave, in two crops, the *N*-chloro derivative of Vc as prisms, m.p. 167° dec. The combined crops were suspended in 200 ml. of methanol, 50 ml. of 10% sodium metabisulfite solution was added in portions, and the mixture was stirred for 10 min. Dilution with water and then addition of sodium hydroxide solution precipitated a solid which was recrystallized from acetone to give Vc in 51% yield from IVc, m.p. 126–129°. Another recrystallization from acetone raised the m.p. to 130–132°; $[\alpha]_D$ +49° (*c* 0.8).

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 76.28; H, 11.02.

The alcohol filtrate from recrystallization of 20α-*N*-chloro derivative was evaporated to a small volume whereupon an isomeric *N*-chloro compound separated as needles. This material was also converted back to secondary amine with sodium bisulfite to give a 23% yield of **3α-hydroxy-20β-methylamino-5β-pregnane-11-one**, m.p. 174.5–176.5°; $[\alpha]_D$ +45° (*c* 1.1), after recrystallization from acetone.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 76.22; H, 10.89.

20α-Methylamino-4-pregnene-3-one (X). Method A.—Compound VII was oxidized by the Oppenauer method[12] to afford a 62% yield of X, m.p. 166–168°; $[\alpha]_D$ +93° (*c* 0.8); λ_{max}^{EtOH} 241 mμ (ε 17,200).

Method B.—The solution from the reductive amination of 154 g. of 3-ethoxy-3,5-pregnadiene-20-one (IX) was evaporated, the reaction product treated with 2 l. of 0.5 *N* hydrochloric acid and allowed to stand overnight. Slow addition of aqueous sodium hydroxide to the filtered solution precipitated a solid amine fraction. The dried solid was triturated with a large volume of ether and then recrystallized from acetone to yield 90.5 g. (61%) of X, m.p. 165–168°, which did not depress the melting point of material prepared as described in method A.

Evaporation of the ether solution from above left a lower melting residue which was dissolved in methylene chloride and stirred with sodium hypochlorite solution ("Clorox") for 1 hr. The organic layer was dried, evaporated, and the solid recrystallized from ether to afford 26.5 g. of *N*-chloro-20β-methylamino-4-pregnene-3-one.

A methanolic solution of 1 g. of the *N*-chloro derivative was stirred with aqueous sodium bisulfite solution for a few minutes, diluted with water, and made basic with sodium hydroxide solution. Recrystallization of the secondary amine from aqueous acetone gave 0.6 g. of **20β-methylamino-4-pregnene-3-one**, m.p. 142.5–143.5°; $[\alpha]_D$ +133° (*c* 0.25); λ_{max}^{EtOH} 240 mμ (ε 18,000).

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.71. Found: C, 80.16; H, 10.64.

20α-Methylamino-5β-pregnane-3-one (XI).—Palladium–carbon catalyst (0.25 g.) was slurried with 1.0 ml. of water, 5 ml. of methanol, and 0.25 g. of potassium hydroxide. A solution of 9.1 g. of X in 20 ml. of benzene and 40 ml. of methanol was added and hydrogenated for 30 min. when one mole equivalent of hydrogen had been absorbed. The filtered solution was taken to dryness and the residue recrystallized from aqueous acetone and from ethyl acetate to give 3.1 g. of product, m.p. 135–138°. The material was chromatographed on silica gel and the fractions eluted with petroleum ether and ether were combined and recrystallized from ethyl acetate to yield XI, m.p. 142.5–144.5°, $[\alpha]_D$ +39° (*c* 0.3). Admixture with VIII depressed the m.p. of XI to 115–139°.

Anal. Calcd. for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.88; H, 11.36; N, 4.23.

20α-Methylamino-5β-pregnane-3α-ol (XII). Method A.—A solution of 0.5 g. of XI in 10 ml. of methanol was treated with 0.15 g. of sodium borohydride in 0.5 ml. of water. After 1 hr. at room temperature, the solution was diluted with water. Recrystallization of the resulting solid from aqueous acetone and then from ethyl acetate gave XII, m.p. 155–156°; $[\alpha]_D$ +37° (*c* 0.6).

Anal. Calcd. for $C_{22}H_{39}NO$: C, 79.22; H, 11.79; N, 4.20. Found: C, 79.07; H, 11.95; N, 4.29.

Method B.—Sodium (0.4 g.) was dissolved in 15 ml. of redistilled diethylene glycol, followed by the addition of 1.5 g. of 3α-hydroxy-20α-methylamino-5β-pregnane-11-one (Vc). Two milliliters of anhydrous hydrazine, dried by refluxing over sodium hydroxide, was distilled into the reaction flask and the mixture was refluxed at 180° overnight. Hydrazine was then distilled out of the reaction mixture until the temperature reached 210° and heating was continued for 16 hr. at the higher temperature. The cooled mixture was diluted with water and the solid was recrystallized from aqueous acetone and then from acetone, m.p. 156–157°. Identity with XII prepared by method A was shown by mixed melting point and comparison of X-ray diffraction patterns.

20α-Methylamino-5β-pregnane-3,11-dione—3α-Hydroxy-20α-methylamino-5β-pregnane-11-one (Vc) was oxidized in the manner described for the preparation of VIII. Recrystallization of the product from ethyl acetate afforded the dione in 35% yield, m.p. 170–171.5°; $[\alpha]_D$ +71° (*c* 0.7).

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.23; H, 10.15.

***N*-Trifluoroacetyl-20α-methylamino-5β-pregnane-3,11-dione.**—A solution of 0.5 g. of 20α-methylamino-5β-pregnane-3,11-dione and 0.4 ml. of trifluoroacetic anhydride in 10 ml. of dry benzene was refluxed for 1 hr. and then evaporated to dryness. Recrystallization of the residue from aqueous alcohol and then ethyl acetate gave 0.3 g. of amide, m.p. 193–194.5°; $[\alpha]_D$ +23° (*c* 0.7).

Anal. Calcd. for $C_{24}H_{34}F_3NO$: C, 65.29; H, 7.76. Found: C, 65.56; H, 7.77.

***N*-Trifluoroacetyl-20α-methylamino-4-pregnene-3,11-dione.**—Bromine (1.1 g.) in 10 ml. of dimethylformamide was added dropwise over a 3-hr. period to a stirred solution of 3.1 g. of *N*-trifluoroacetyl-20α-methylamino-5β-pregnane-3,11-dione and 75 mg. of *p*-toluenesulfonic acid in 25 ml. of dimethylformamide. The colorless solution was diluted with water and extracted with methylene chloride. The washed and dried solution was evaporated, finally under

high vacuum to remove last traces of dimethylformamide. The noncrystalline bromo compound was redissolved in 40 ml. of methylene chloride and added to a suspension of 1.0 g. of semicarbazide in 70 ml. of *t*-butyl alcohol under nitrogen. After the mixture was stirred for 1 hr., 3 ml. of pyruvic acid, 5 ml. of water, and 25 ml. of acetic acid were added and the resulting solution was allowed to stand overnight. The solution was concentrated, diluted with water, and extracted with methylene chloride which was washed with sodium carbonate solution and water. Evaporation of the dried solution left a residue which crystallized from alcohol. Recrystallization from methanol afforded 1.4 g. of product, m.p. 204–206°; $[\alpha]D$ +113° (*c* 1) λ_{max}^{KBr} 5.88 5.98, 6.2 μ; λ_{max}^{EtOH} 238 mμ (ϵ 15,500).

Anal. Calcd. for $C_{24}H_{32}F_3NO_3$: C, 65.58; H, 7.34. Found: C, 65.34; H, 7.05.

20α-Methylamino-4-pregnene-3,11-dione. Method A.—To a solution of 126 g. of 11-ketoprogesterone and 66 ml. of triethyl orthoformate in 2 l. of benzene was added 0.4 g. of *p*-toluenesulfonic acid dissolved in 60 ml. of absolute alcohol. The solution was refluxed for 3 hr., cooled, washed with sodium bicarbonate solution and water, dried, and evaporated.

The crude, noncrystalline 3-ethoxy-3,5-pregnadiene-11,20-dione was reductively aminated by the general procedure. The reduced solution was evaporated, the residue was dissolved in 1500 ml. of 1 *N* hydrochloride acid and allowed to stand for 48 hr. A few grams of nonbasic material was filtered off and the filtrate made basic with sodium hydroxide. The resulting gum was extracted into methylene chloride, and the solution was washed with water, dried, and evaporated. Crystallization of the residue from ether–petroleum ether gave 59 g. of crude product in two crops. This material was redissolved in methylene chloride, the solution was stirred with excess "Clorox" for 0.5 hr. and then separated, washed, and evaporated. Recrystallization of the residue gave 23 g. of *N*-chloro-20α-methylamino-4-pregnene-3,11-dione. Reduction of this derivative with sodium metabisulfite as described in the preparation of Vc and recrystallization of the secondary amine from acetone afforded 16.4 g. (12%) of 20α-methylamino-4-pregnene-3,11-dione, m.p. 163–167°. Further recrystallization from acetone raised the melting point to 165–167.5°; λ_{max}^{EtOH} 239 (ϵ 16,000); $[\alpha]D$ +200°; λ_{max}^{Nujol} 5.85, 6.0, 6.2 μ.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 77.08; H, 9.67.

Method B.—A solution of 0.4 g. of *N*-trifluoroacetyl-20α-methylamino-4-pregnene-3,11-dione and 0.2 g. of potassium hydroxide in alcohol was refluxed under nitrogen for 3 hr. The solution was concentrated, poured into water, and extracted with methylene chloride. The product obtained by evaporation of the organic solution was recrystallized from acetone to give 0.2 g. of 20α-methylamino-4-pregnene-3,11-dione, m.p. 164–167°. It was identical to product from method A by comparison of melting points and infrared spectra.

Preparation of *N*-Chloroamines (XV).—The N-chloroamines listed in Table I were prepared according to a general procedure. A methylene chloride solution of the secondary amine was stirred for 0.5 hr. with excess aqueous sodium hypochlorite ("Clorox"), the aqueous layer was siphoned off, fresh hypochlorite solution was added, and stirring was continued another 0.5 hr. The organic layer was separated, washed with water, dried, and evaporated. The products were recrystallized from methanol or ethanol and dried in a vacuum desiccator to remove traces of solvent. The purity of the *N*-chloroamines was checked by titration of samples with potassium iodide–sodium thiosulfate. Unrecrystallized materials gave satisfactory results in the subsequent Hofmann-Loeffler–Freytag reaction providing they assayed at least 95% *N*-chloroamine by titration.

Irradiation Procedure.—A 10% solution of the requisite *N*-chloroamine in redistilled trifluoroacetic acid was prepared by slowly adding the finely powdered chloroamine to the stirred acid at 0°. The resulting clear, colorless or nearly colorless solution was transferred to a Vycor #7910 Florence flask equipped with Teflon covered magnetic stirring bar. After the solution had been purged with dry nitrogen for 15 min., a 5-drop sample was removed and added to 5 ml. of 5% potassium iodide in 50% aqueous acetone to obtain a dark red color standard.

The stirred reaction mixture, kept at 20–25°, was then exposed to the light of three General Electric 15 W Germicidal lamps. Five drops of the reaction mixture were removed at intervals and treated with the potassium iodide reagent to follow the course of the reaction. A negative chloroamine test was usually obtained in 15–60 min.

3β-Trifluoroacetoxy-18-chloro-20α-methylamino-5α-pregnane-11-one Trifluoroacetate (XVIg).—Eighty-seven grams of 3β-hydroxy-*N*-chloro-20α-methylamino-5α-pregnane-11-one (XVb) was irradiated in four portions in trifluoroacetic acid and then the solutions were combined. Trifluoroacetic anhydride (25 ml.) was added and the solution allowed to stand at room temperature for 1 hr. Excess acid and anhydride were removed under reduced pressure (Dry Ice trap) and the residual oil was dissolved in acetone. Addition of ether and petroleum ether caused crystallization of product in nearly quantitative yield. Recrystallization from acetone yielded three crops of crystals, totaling 109.8 g. (81%). The analytical sample was recrystallized from acetone, m.p. 156–160°; $[\alpha]D$ +6° (*c* 1.2); λ_{max}^{KBr} 4.6, 5.88–5.98 μ.

Anal. Calcd. for $C_{26}H_{36}ClF_6NO_5$: C, 52.75; H, 6.13. Found: C, 52.62; H, 6.35.

When the trifluoroacetic anhydride treatment was omitted, the product was isolated in but 15–26% yield; the remainder of the reaction mixture persisted as an oil.

3β-Trifluoroacetoxy-18-chloro-*N*-(trifluoroacetyl)-20α-methylamino-5α-pregnane-11-one.—Eight milliliters of trifluoroacetic anhydride was added dropwise to a stirred and cooled suspension of 25.0 g. of 3β-trifluoroacetoxy-18-chloro-20α-methylamino-5α-pregnane-11-one trifluoroacetate (XVIg) in 625 ml. of dry benzene. The resulting solution was refluxed for 1 hr. and then evaporated to a sirup which crystallized upon addition of 70 ml. of methanol. The yield of amide was 20.3 g. (84%), m.p. 175–177°. A sample recrystallized from methanol melted at 177–178.5°; $[\alpha]D$ +14° (*c* 1.0); λ_{max}^{KBr} 5.61, 5.85, 5.92 μ.

Anal. Calcd. for $C_{26}H_{34}ClF_6NO_4$: C, 54.40; H, 5.97. Found: C, 54.28; H, 6.10.

3β-Trifluoroacetoxy-18-chloro-20β-methylamino-5α-pregnane-11-one Trifluoroacetate.—This compound was prepared from 7.8 g. of 3β-hydroxy-*N*-chloro-20β-methylamino-5α-pregnane-11-one as described for the corresponding 20α-isomer. The crude product was crystallized from ether–petroleum ether, wt. 3.7 g. (31%), m.p. 154–155° dec., $[\alpha]D$ +8°.

Anal. Calcd. for $C_{26}H_{36}ClF_6NO_5$: C, 52.75; H, 6.13; Cl, 5.99. Found: C, 52.89; H, 6.63; Cl, 5.83.

3β-Trifluoroacetoxy-18-chloro-20α-methylamino-5α-pregnane Trifluoroacetate (XVIf).—The *N*-chloro derivative XVa (4.6 g.) was irradiated in trifluoroacetic acid, 1.2 ml. of trifluoroacetic anhydride was added, and the solution was permitted to stand for 1 hr. at room temperature. After removal of the solvent under reduced pressure, the residue was crystallized from acetone–ether–petroleum ether. Recrystallization of the solid from acetone gave 5.1 g. (68%) of first crop material, m.p. 156–159°; $[\alpha]D$ −10° (*c* 1.1) and 0.7 g. of second crop material, m.p. 150–153°.

Anal. Calcd. for $C_{26}H_{38}ClF_6NO_4$: C, 54.02; H, 6.63. Found: C, 54.23; H, 6.85.

18-Chloro-20α-methylamino-4-pregnene-3-one Trifluoroacetate (XVId).—Irradiation of 23.7 g. of *N*-chloro-20-α-methylamino-4-pregnene-3-one (XVd) and removal of the trifluoroacetic acid produced an oil which crystallized upon addition of methanol. Several crops obtained from the methanol solution were combined and recrystallized from acetone–methanol to give 26.9 g. (87%) of crystals, m.p.

164–167° (varied considerably with rate of heating); $[\alpha]_D$ +138° (*c* 0.28); λ_{max}^{EtOH} 240 mμ (ε 16,900); λ_{max}^{KB} 5.97 (broad), 6.18 μ.

Anal. Calcd. for $C_{24}H_{35}ClF_3NO_3$: C, 60.31; H, 7.38; Cl, 7.42. Found: C, 60.26; H, 7.82; Cl, 7.17.

18-Chloro-20α-methylamino-4-pregnene-3,11-dione Trifluoroacetate (XVIe).—*N*-Chloro-20α-methylamino-4-pregnene-3,11-dione (4.4 g.) was irradiated in the usual manner. After removal of the trifluoroacetic acid, the residue was crystallized from acetone–ether–petroleum ether. Recrystallization from acetone gave 3.7 g. of product, m.p. 165–170° dec.; $[\alpha]_D$ +111°; λ_{max}^{EtOH} 239 mμ (ε 16,500).

Anal. Calcd. for $C_{24}H_{33}ClF_3NO_4$: C, 58.59; H, 6.76. Found: C, 58.86; H, 6.90.

5α-Conanine-3β-ol (XVIIa). Method A.—A solution of 2 g. of 3β-trifluoroacetoxy-18-chloro-20α-methylamino-5α-pregnane trifluoroacetate (XVIf), 1.2 g. of potassium hydroxide, and 25 ml. of methanol was refluxed for 1 hr. and the cooled mixture poured into water. Recrystallization of the solid from acetone gave 0.9 g. (78%) of first crop material, m.p. 168–170°, and 0.2 g. of second crop material, m.p. 160–164°.

Method B.—After irradiation of 21 g. of XVa and evaporation of the trifluoroacetic acid, the residual oil was refluxed for 1 hr. with 25 g. of potassium hydroxide in 300 ml. of methanol. The reaction mixture was concentrated, diluted with water, and extracted with chloroform. Evaporation of the dried chloroform solution and recrystallization of the solid from acetone afforded an 84% yield of XVIIa.

Method C.—5α-Conanine-3β-ol (XVIIa) was also prepared from conessine *via* dihydroisoconessimine by essentially the method described by Cerny and Sorm,[21] m.p. 169–171°; $[\alpha]_D$ +60° (*c* 2.5); lit.,[21] m.p. 169–170°; $[\alpha]_D$ +61°. Samples prepared by the three methods were identical by mixed melting point and infrared comparisons.

3β-Acetoxy-5α-conanine-11-one.—Thirteen grams of 3β-hydroxy-*N*-chloro-20α-methylamino-5α-pregnane-11-one (XVb) was irradiated and most of the trifluoroacetic acid was removed under reduced pressure. The residual oil was dissolved in methanol and 25% methanolic potassium hydroxide was added until the solution remained distinctly basic. The solution was brought to reflux temperature, then concentrated and poured into water. Extraction with chloroform and evaporation of the dried organic solution left a gummy material which was refluxed for 1 hr. with 25 ml. of acetic anhydride. The cooled solution was poured into water and nonbasic material was removed by filtration. The filtrate was made basic and extracted with chloroform. Evaporation of the washed and dried organic solution gave 9.4 g. (71%) of 3β-acetoxy-5α-conanine-11-one, m.p. 180–185°. Recrystallization from alcohol raised the melting point to 186–190°; $[\alpha]_D$ +83; λ_{max}^{KBr} 5.79, 5.90, 8.10 μ.

Anal. Calcd. for $C_{24}H_{37}NO_3$: C, 74.38; H, 9.62. Found: C, 74.12; H, 9.76.

Hydrolysis with alcoholic sodium hydroxide on the steam bath gave XVIIb in 80% yield.

3β-Hydroxy-5α-conanine-11-one (XVIIb).—Two grams of 3β-trifluoroacetoxy-18-chloro-20α-methylamino-5α-pregnane-11-one trifluoroacetate (XVIg) in 50 ml. of methanol was refluxed with 0.65 g. of potassium carbonate for 2 hr. The reaction mixture was concentrated, diluted with water, and extracted with methylene chloride. Evaporation of the solvent and recrystallization of the solid from ethyl acetate afforded 1.0 g. (85%) of product, m.p. 170–173°. Further recrystallization raised the melting point to 174.5–177°; $[\alpha]_D$ +110; λ_{max}^{KBr} 2.87, 5.88 μ.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.51; H, 10.44.

3α-Hydroxy-5β-conanine-11-one (XVIIc).—Five grams of 3α-hydroxy-*N*-chloro-20α-methylamino-5β-pregnane-11-one (XVc) was subjected to the procedure described for the conversion of XVb into 3β-acetoxy-5α-conanine-11-one. The final acetylation step produced 3α-acetoxy-5β-conanine-11-one as an oil which could not be induced to crystallize. The noncrystalline material was heated in alcohol with 10% sodium hydroxide for an hour to hydrolyze the ester. The basic solution was diluted with water, extracted with methylene chloride and the organic solution washed, dried, and evaporated. Recrystallization from aqueous acetone gave 2.9 g. of XVIIc, m.p. 173–175°; $[\alpha]_D$ +104°.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.62; H, 10.21.

4-Conanene-3-one (XVIId).—A suspension of 26.4 g. of 18-chloro-20α-methylamino-4-pregnene-3-one trifluoroacetate (XVId) in 100 ml. of methanol was stirred under nitrogen as 100 ml. of 10% methanolic potassium hydroxide was added. After the starting material dissolved, the mixture was refluxed for 1 hr., concentrated, and poured into water. The solid was collected and recrystallized from aqueous acetone, wt. 13.8 g. (76% yield), m.p. 108–110°; $[\alpha]_D$ +158° (*c* 0.77); λ_{max}^{EtOH} 241 mμ (ε 17,100); reported[22] m.p. 108.5–110°.

20-Iso-4-conanene-3-one.—*N*-Chloro-20β-methylamino-4-pregnene-3-one was irradiated in the usual manner (1 hr.) and the trifluoroacetic acid removed under reduced pressure. The residual oil, which could not be induced to crystallize, was heated under nitrogen with excess methanolic potassium hydroxide for 1 hr. The mixture was diluted with water and extracted with methylene chloride. Evaporation of the dried solution left a brown oil which was heated on the steam bath for 45 min. with 60 ml. of acetic anhydride. The solution was poured into water and acid-insoluble material was filtered with the aid of Super-cel. Sodium hydroxide solution was added to the clear filtrate and the solid so obtained was dried and recrystallized from ether to give 13.6 g. (57% yield) of prisms, m.p. 148–152°. A sample recrystallized from acetone and then from alcohol melted at 149–154°; $[\alpha]_D$ +120° (*c* 1.0) λ_{max}^{EtOH} 242 mμ (ε 17,000).

Anal. Calcd. for $C_{22}H_{33}NO$: C, 80.68; H, 10.16. Found: C, 80.76; H, 10.27.

3β-Hydroxy-20α-methylamino-12,18-cyclo-5α-pregnane-11-one (XVIII). Method A.—A solution of 5 g. of XVIg in 25 ml. of methanol was added dropwise with stirring to a hot solution of 10 g. of potassium hydroxide in 50 ml. of methanol. The mixture was refluxed for 5 min. and quenched with 10 volumes of water. The solid that separated was collected and recrystallized from methanol to give 1.5 g. (52% yield) of 12,18-cyclo compound, m.p. 229–231°; $[\alpha]_D$ +37° (*c* 0.9); λ_{max}^{MeOH} 202 mμ (ε 5600) and 294 (ε 34); λ_{max}^{KBr} 3.0, 3.13, 3.27, 3.31, 5.98 μ.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.51; H, 10.02.

The methanol filtrate was diluted with water, added to the original aqueous filtrate, and the whole was extracted with methylene chloride. After evaporation of the solvent the residue was heated with acetic anhydride for 2 hr., the anhydride was decomposed with water and the mixture was filtered to remove acid-insoluble material. Neutralization of the clear filtrate, extraction with methylene chloride, and evaporation of the solvent left 0.7 g. (22%) of 3β-acetoxy-5α-conanine-11-one, m.p. 185–190°.

In other experiments conducted in essentially the same manner, the yield of 12,18-cyclo compound varied from 40 to 60% and the yield of conanine from 20 to 40%.

Method B.—A solution of 28 g. of 3β-trifluoroacetoxy-18-chloro-N-(trifluoroacetyl)-20α-methylamino-5α-pregnane-11-one and 40 g. of potassium hydroxide in 500 ml. of ethanol was refluxed under nitrogen for 3 hr. The solution was evaporated and diluted with water to yield 16.5 g. (98%) of XVIII, m.p. 229–231.5°. After recrystallization from methanol the yield was 92%. The melting point was not depressed by material from method A.

3β-Acetoxy-*N*-acetyl-20α-methylamino-12,18-cyclo-5α-pregnane-11-one.—3β-Hydroxy-20α-methylamino-12,18-cyclo-5α-pregnane-11-one (0.5 g.) was refluxed with acetic anhydride for 2 hr., the solution poured into water and extracted with methylene chloride. Evaporation of the washed and dried solution and recrystallization of the solid

from 95% alcohol afforded 0.3 g. of derivative, m.p. 200–202°; λ_{max}^{Nujol} 5.76, 5.98, 6.10, 8.0 μ.

Anal. Calcd for $C_{26}H_{39}NO_4$: C, 72.69; H, 9.15. Found: C, 72.70; H, 9.42.

3β-Hydroxy-20α-methylamino-12,18-cyclo-5α-pregnane (XXVI).—3β - Hydroxy - 20α - methylamino - 12,18 - cyclo-5α-pregnene-11-one (XVIII) (2.1 g.) was subjected to the Wolff-Kishner conditions described for the reduction of Vc to XII. Recrystallization of the product from ethyl acetate gave 1.43 g. of 11-desoxy compound, m.p. 191–193.5°; $[\alpha]_D$ +60; λ_{max}^{KBr} 3.0, 3.15, 3.25, 3.29 μ.

Anal. Calcd for $C_{22}H_{35}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.59; H, 11.43; N, 4.44.

3β-Acetoxy-18-bromo-20α-methylamino-5α-pregnane-11-one Hydrobromide (XIX).—Compound XVIII (800 mg.) was dissolved in 15 ml. of a 10% solution of hydrogen bromide in glacial acetic acid. The solution was allowed to stand at room temperature for 2 hr. and then evaporated under reduced pressure. Trituration of the residual oil with ether caused crystallization. Two recrystallizations from methanol–ether afforded 0.8 g. of salt, m.p. 218–220° dec.; λ_{max}^{Nujol} 5.80, 5.89, 8.10 μ; $[\alpha]_D$ +7° (*c* 0.9).

Anal. Calcd. for $C_{24}H_{39}Br_2NO_3$: C, 52.47; H, 7.16; Br, 29.09. Found: C, 52.16; H, 7.37; Br, 28.95.

3β-Hydroxy-20α-dimethylamino-12,18-cyclo-5α-pregnane-11-one (XX).—Five grams of 20α-methylamine XVIII, 10 ml. of 85% formic acid, and 5 ml. of formaldehyde solution were refluxed for 4 hr.; the cooled solution was diluted with water and made alkaline with aqueous sodium hydroxide. The precipitated solid was warmed a few minutes in ethanol containing a few drops of 10% sodium hydroxide solution. Dilution of this solution with water and recrystallization of the product from ethanol gave 3.2 g. of XX, m.p. 181–184°; $[\alpha]_D$ +8° (*c* 1); λ_{max}^{KBr} 2.95, 6.0 μ.

Anal. Calcd. for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37. Found: C, 76.55; H, 10.71.

3β-Hydroxy-20α-dimethylamino-12,18-cyclo-5α-pregnane-11-one Methiodide (XXI).—Four grams of XX, 100 ml. of benzene, and 10 ml. of methyl iodide were refluxed for 5 hr. Ether was added to the cooled mixture and the solid collected. Recrystallization of the quaternary salt from methanol gave 3.1 g. of product which analyzed as the hydrate, m.p. 265–270° dec.; $[\alpha]_D$ −19° (*c* 1); λ_{max}^{KBr} 2.97, 5.98 μ.

Anal. Calcd. for $C_{24}H_{40}NO_2I$: C, 57.48; H, 8.04; Calcd. for $C_{24}H_{40}NO_2I \cdot H_2O$: C, 55.44; H, 8.14. Found: C, 55.22; H, 7.81.

3β-Hydroxy-5α-conanine-11-one Methiodide (XXIII).—A solution of 0.5 g. of XVIIb, 10 ml. of benzene, and 0.7 ml. of methyl iodide was refluxed for 2 hr. The cooled reaction mixture was diluted with ether, and the precipitated solid was recrystallized from alcohol to give 0.5 g. of salt, m.p. above 285°; $[\alpha]_D$ +49° (*c* 2.5 in methanol); λ_{max}^{KBr} 2.75, 2.98, 5.90 μ.

Anal. Calcd. for $C_{23}H_{38}NO_2I$: C, 56.67; H, 7.86; calcd. for $C_{23}H_{38}NO_2I \cdot {}^1/_2H_2O$: C, 55.64; H, 7.92. Found: C, 55.68; H, 7.96.

3β-Hydroxy-18-dimethylamino-5α-pregn-20-ene-11-one (XXIV).—A column was prepared of 70 g. of Amberlite IRA-400 in the hydroxide form. A solution of 25.5 g. of XXIII in 200 ml. of methanol was passed through the column and elution with methanol was continued until the eluate was neutral. The combined methanol eluates were evaporated and the resulting sirup was heated slowly to 160° *in vacuo* and held at that temperature for 20 min. Crystallization of the residue from hexane gave 15.8 g. (82%) of needles, m.p. 132–133.5°; $[\alpha]_D$ +34° (*c* 2.5); λ_{max}^{KBr} 3.0, 5.89 μ.

Anal. Calcd. for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37. Found: C, 76.76; H, 10.47.

3β-Hydroxy-18-dimethylamino-5α-pregn-20-ene-11-one Methiodide (XXV).—One-half gram of tertiary amine XXIV, 10 ml. of acetonitrile, and 2.6 ml. of methyl iodide were refluxed for 18 hr. The solvent was evaporated and the residue triturated with acetone to induce crystallization. Recrystallization of the solid from acetone–methanol gave XXV, m.p. 228–229° dec.; $[\alpha]_D$ +42° (*c* 2.4 in methanol); λ_{max}^{KBr} 2.95, 5.88 μ.

Anal. Calcd. for $C_{24}H_{40}INO_2$: C, 57.48; H, 8.04; calcd. for $C_{24}H_{40}INO_2 \cdot {}^1/_2H_2O$: C, 56.46; H, 8.10. Found: C, 56.56; H, 8.19.

3β-Hydroxy-12,18-cyclo-5α-pregn-20-ene-11-one (XXII). Method A.—A mixture of 1.0 g. of compound XXI, 0.5 g. of sodium methoxide, and 10 ml. of dimethylformamide was refluxed for 10 min. and then heated on a steam bath for 30 min. The cooled mixture was diluted with several volumes of water and extracted with ether. Evaporation of the dried solution left an oil which crystallized upon addition of a few drops of acetone. Recrystallization of the solid from aqueous acetone gave 0.3 g. of product which melted at 126–128°, solidified and remelted at 135–136°; $[\alpha]_D$ −3° (*c* 2.6); λ_{max}^{KBr} 2.87, 6.0 μ.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.13; H, 9.83.

Method B.—Four grams of XXV was treated with sodium methoxide in dimethylformamide as described under method A. Recrystallization of the product from aqueous acetone gave 1.5 g. of XXII. Identity of the material prepared by the two methods was shown by mixed melting point and X-ray diffraction.

4-Conanene-3,11-dione (XVIIe).—To a solution of 1.5 g. of 18-chloro-20α-methylamino-4-pregnene-3,11-dione trifluoroacetate (XVIe) in 50 ml. of methanol was added 0.57 g. of potassium carbonate. The mixture was stirred and heated under nitrogen for 2 hr. and then poured into 500 ml. of water. During concentration of the aqueous methanol solution, 0.5 g. of crystals separated, m.p. 147–153°. Recrystallization from ethyl acetate raised the melting point to 155–157°; $[\alpha]_D$ +268°; λ_{max}^{EtOH} 239 mμ (ϵ 18,000]; λ_{max}^{KBr} 5.87, 5.98, 6.2 μ.

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15. Found: C, 77.06; H, 8.84.

20α-Methylamino-12,18-cyclo-4-pregnene-3,11-dione.—A solution of 5.88 g. of XVIe in 35 ml. of methanol was added dropwise with stirring to a hot solution of 15 g. of potassium hydroxide in 75 ml. of methanol under nitrogen. After the addition, the mixture was refluxed for 5 min., poured into water, and extracted with methylene chloride. The dried organic solution was evaporated and the residue was recrystallized from ethyl acetate to afford 1.4 g. of solid, m.p. 123–130°. Several additional recrystallizations gave material with a melting range of 124.5–132.5° although thin layer chromatography indicated the material was substantially pure; λ_{max}^{EtOH} 239 mμ (ϵ 17,800); λ_{max}^{KBr} 3.0, 3.26, 3.30, 5.96–6.0, 6.2 μ.

Anal. Calcd. for $C_{22}H_{30}NO_2$: C, 77.61; H, 8.88; N, 4.11. Found: C, 77.40; H, 9.10; N, 4.32.

Preparation of 3β-Acetoxy-5α-conanine-11-one without Isolation of Intermediates.—A solution of 250 g. of 3β-hydroxy-5α-pregnane-11,20-dione (IVb) in 2500 ml. of alcoholic methylamine was hydrogenated over 5 g. of platinum oxide at atmospheric pressure. The filtered solution was evaporated, and the residual solid was dissolved in 400 ml. of acetic acid with warming. The acid solution was then diluted to 4 l. with water and extracted several times with methylene chloride. Addition of 40% sodium hydroxide solution to the aqueous acid portion precipitated the amine which was extracted into a total of 10 l. of the methylene chloride. The organic solution was washed and then stirred vigorously for 0.5 hr. with 4 l. of sodium hypochlorite ("Clorox"). The aqueous solution was siphoned off and the process repeated with fresh "Clorox." Finally, the organic layer was washed with water, dried, and evaporated. The resulting crystalline mass was crushed and residual solvent removed in a vacuum desiccator, wt. 241 g. A sample assayed 97% *N*-chloroamine by titration.

Twenty-five-gram batches of the crude *N*-chloroamine were irradiated by the general procedure described above.

After evaporation of the trifluoroacetic acid, the oily residue was dissolved in 100 ml. of methanol, neutralized with alcoholic potassium hydroxide, and then treated with 4 molar equivalents of alkali in 100 ml. of methanol. The mixture was refluxed for 1 hr., concentrated under reduced pressure, poured into water, and extracted with methylene chloride. All organic extracts were combined, washed with water, dried, and evaporated. Acetic anhydride (525 ml.) was added to the residue and refluxed for 2 hr. Hydrolysis of the anhydride in 5 l. of water left a gummy material which was filtered off with the aid of Super-cel. The clear filtrate was made basic with sodium hydroxide and extracted with methylene chloride. Evaporation of the dried solution and recrystallization of the residue (128 g.) from alcohol gave 104 g. (36% over-all) of 3β-acetoxy-5α-conanine-11-one, m.p. 185.5–189°.

Derivatives of Fluorene. XVII. Alkyl Phosphates, Phosphites, and Phosphonates with Lithium Halides or Alkyl Halides in the N-Alkylation of Fluorenamines

HSI-LUNG PAN AND T. LLOYD FLETCHER[1,2]

Chemistry Research Laboratory of the Department of Surgery, University of Washington School of Medicine, Seattle 5, Washington

Received May 22, 1962

Lithium halides, especially lithium bromide, together with trialkyl phosphates, trialkyl phosphites, or dialkyl alkylphosphonates, have conveniently given good yields of a variety of alkylaminofluorenes. The alkylating agent was either the phosphorus acid ester itself or alkyl halide, generated by the dealkylating action of lithium halides on the acid esters, or both. Also, triethyl phosphate was found to be an excellent medium for the alkylation of aromatic amines with alkyl and aralkyl bromides and iodides. A number of new N-mono- and N,N-dialkyl(and aralkyl)aminofluorenes and 9-oxofluorenes were prepared.

After finding that lithium bromide promoted good yields of 2-N-ethylaminofluorenone from 2-aminofluorenone with triethyl phosphate,[3] we have used lithium halide and phosphorus acid ester combinations, extensively in the alkylation of aromatic amines, especially fluorenamines. This is part of a general study of certain metabolites and modifications of the carcinogen, 2-acetamidofluorene. Certain esters of phosphorous and phosphoric acids containing sufficiently electrophilic α-CH_2 groups, were reported to undergo anionic cleavage of the α-carbon from the CH_2—OP linkage in the presence of an anion such as the chloride ion of lithium chloride.[4,5] In the alkylation of weak amines with trialkyl phosphates, this reaction takes place readily when certain halides, such as lithium bromide, are present, as shown in this investigation, whereas in the absence of this salt the reaction requires a higher temperature to give a much poorer yield, or does not take place at all.[6] Therefore the presence of such halides produces a more reactive alkylating system, *i.e.*, an alkyl halide in the presence of a phosphate ester, than the alkyl phosphate alone. This, in turn, produces hydrogen halide from the alkylation of the amine, and the hydrogen halide itself is capable of dealkylating the phosphorus acid esters,[7] thus providing a still higher concentration of alkyl halide in the reaction. The outline of the alkylating system of trialkyl phosphate–lithium halide is as follows

$$(Li^+)X^- + R\overset{\delta+}{-}CH_2-O-P(O)(OCH_2R)_2 \longrightarrow R-CH_2X + {}^-O-P(O)(OCH_2R)_2 \quad \text{(a)}$$

X = Cl, Br, I[8]

$$R-CH_2X + Ar-NH_2 \longrightarrow Ar-NH-CH_2-R + HX \quad \text{(b)}$$

$$H^+X^- + R\overset{\delta+}{-}CH_2-O-P(O)(OCH_2R)_2 \longrightarrow R-CH_2X \longrightarrow HOP(O)(OCH_2R)_2 \quad \text{(c)}$$

This outline would appear to be true also of the trialkyl phosphite–lithium halide system except

(1) This work was supported, in part, by a grant (CY-1744) from the National Cancer Institute, National Institutes of Health and, in part, by Research Career Development Award, GM-K3-14,991 to T.L.F.

(2) For the previous paper in this series, see *J. Org. Chem.*, **26**, 2244 (1961).

(3) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *ibid.*, **20**, 1021 (1955).

(4) V. M. Clark and A. R. Todd, *J. Chem. Soc.*, 2031 (1950).

(5) J. Lecocq and A. R. Todd, *ibid.*, 2381 (1954).

(6) D. G. Thomas, J. H. Billman, and C. E. Davis, *J. Am. Chem. Soc.*, **68**, 895 (1946), reported that *p*-nitroaniline did not undergo alkylation with triethyl phosphate. With the use of lithium bromide in this reaction we were able to obtain about 35% yields of mono-N-ethylated *p*-nitroaniline with evidence of a small amount of the di-N,N-ethylamine.

(7) W. Gerrard, *J. Chem. Soc.*, 1464 (1940); W. Gerrard, *ibid.*, 85 (1944); W. Gerrard, *ibid.*, 848 (1945); W. Gerrard, W. J. Green, and R. A. Nutkins, *ibid.*, 4076 (1952).

(8) Our experiments show that, refluxed in triethyl or tripropyl phosphate, lithium chloride, bromide, and iodide produce the corresponding halide in decreasing yields, with decreasing speeds, in the above order. The ethyl halides, in trialkyl phosphates, however, in the presence of amines, were increasingly effective alkylating agents in the above order. Both phenomena, taking place in the system trialkyl phosphate–lithium halide–amine, gave results indicating that lithium bromide was the best of the three in the promotion of alkylation.