The Synthesis of 17-Disubstituted Steroids by the Claisen Rearrangement

DUANE F. MORROW, TOWNLEY P. CULBERTSON, AND RUTHANN M. HOFER

Research Laboratories, Parke, Davis, and Co., Ann Arbor, Michigan

Received August 4, 1966

A new, convenient preparation of pregna-5,17(20)-diene-3β,21-diol (**2f**) from dehydroisoandrosterone was developed, proceeding *via* 17α-vinylandrost-5-ene-3β,17β-diol (**1b**) through 21-chloropregna-5,17(20)-dien-3β-ol acetate (**2b**) to pregna-5,17(20)-diene-3β,21-diol diacetate (**2d**). When the diol **2f** was heated with 1,1-diethoxy-1-dimethylaminoethane, a Claisen rearrangement occurred, affording N,N-dimethyl-3β-hydroxypregna-5,20-dien-17α-acetamide (**5b**). The stereochemistry at C-17 of the rearrangement product was determined by degradation to products of known configuration. The Favorskii rearrangement of 3β-acetoxy-17α-bromopregn-5-en-20-one (**16**) in dimethoxyethane was shown to proceed stereospecifically to give methyl 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylate. The presence of an N,N-dimethylcarboxamide group at C-17α of a Δ^5 steroid caused catalytic hydrogenation to proceed preferentially from the β face of the molecule to give a 5β-dihydro steroid.

It is well known that the substituents at the 17 position of the steroid nucleus have a more profound effect upon the pharmacological activity of the compound than similar substituents at other positions about this ring system. Whereas substitution at the lower-numbered positions (*e.g.*, 2, 4, 6, 7, etc.) usually modifies only the *intensity* of the pharmacological activity of the parent compound, substitution at C-17 seems to determine the primary *type* of activity displayed by the compound (*e.g.*, anabolic, progestational, aldosterone inhibiting, glucocorticoid, etc.) as well as its effectiveness upon oral administration.[1]

Many attempts have been made in the past few years to prepare steroids with new types of substituents at C-17, such as the recently reported syntheses of 17α-fluoro-[2] and 17-amino-20-keto steroids.[3] Although the preparation of 17α-alkyl-20-keto steroids has been well developed,[4] the addition of a carbon-linked substituent bearing a functional group to the 17 position of a steroid molecule already possessing one such group is rare, and only a few examples of this type of disubstituted steroid have been reported in the literature.[5-8] This relative scarcity of steroids containing two functional substituents attached to C-17 prompted us to investigate synthetic routes leading to this type of compound. One of the most promising appeared to be a Claisen rearrangement of an appropriate allyl vinyl ether.[9] Several groups of investigators have used this reaction to introduce substituents onto the A ring of steroids.[10] A new, much more convenient method for running the Claisen rearrangement, which obviates the separate preparation and isolation of the intermediate allyl vinyl ether, was recently discovered by Meerwein[11] and developed by Eschenmoser.[12] This method, which consists of heating the allylic alcohol with a 1,1-dialkoxy-1-dimethylaminoethane, affords the rearranged N,N-dimethylallylacetamide directly in good yield. The steroidal allylic alcohol required to introduce a new 17 substituent by this method was the known pregna-5,17(20)-diene-3β,21-diol (**2f**),[13a,b] and a convenient synthetic route to this diol was therefore investigated.

Although there are several published procedures for the preparation of this compound,[13] we were unable to obtain consistently reasonable yields of product from any of them. For example, in our hands the direct acid-catalyzed conversion of 17α-vinylandrost-5-ene-3β,17β-diol (**1b**) (Chart I) to **2f**[13a] proceeded erratically (with generally an 8–15% yield) when run on a moderately large scale.[14] A by-product isolated from this reaction was 17β-methyl-17α-vinyl-18-norandrosta-5,13-dien-3β-ol (**3b**). The structure of this compound was deduced from its nuclear magnetic resonance (nmr) spectrum and confirmed by selective catalytic reduction to the known 17α-ethyl-17β-methyl-18-norandrosta-5,13-dien-3β-ol (**3d**).[15] Miescher and Scholz[13a]

(1) N. Applezweig, "Steroid Drugs," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(2) H. L. Herzog, M. J. Gentles, H. M. Marshall, and E. B. Hershberg, *J. Am. Chem. Soc.*, **82**, 3691 (1960); R. Deghenghi and R. Gaudry, *Can. J. Chem.*, **39**, 1553 (1961).

(3) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962); D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965); F. Winternitz and C. R. Engel, *Steroids*, **6**, 805 (1965); G. Nathansohn, G. Winters, and A. Vigevani, *Gazz. Chim. Ital.*, **95**, 1338 (1965); G. Drefahl, K. Ponsold, and B. Schönecker, *Chem. Ber.*, **98**, 186 (1965).

(4) (a) P. A. Plattner, H. Heusser, and P. T. Herzig, *Helv. Chim. Acta*, **32**, 270 (1949); (b) H. Heusser, C. R. Engel, P. T. Herzig, and P. A. Plattner, *ibid.*, **33**, 2229 (1950); (c) H. Heusser, C. R. Engel, and P. A. Plattner, *ibid.*, **33**, 2237 (1950); (d) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. J. Coscia, *Chem. Ind.* (London), 118 (1963); (e) R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand, and R. Gaudry, *Tetrahedron*, **19**, 289 (1963); (f) R. Deghenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963); (g) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); (h) D. Burn, J. W. Ducker, B. Ellis, A. K. Hiscock, A. P. Leftwick, C. M. Peach, V. Petrow, and D. M. Williamson, *J. Chem. Soc.*, 4242 (1963).

(5) W. Fritsch, G. Seidl, and H. Ruschig, *Ann.*, **677**, 139 (1964); U. Stache, W. Fritsch, and H. Ruschig, *ibid.*, **685**, 228 (1965); T. P. Culbertson, G. W. Moersch, and W. A. Neuklis, *J. Heterocyclic Chem.*, **1**, 280 (1964). See also G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **30**, 1272 (1965); G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *ibid.*, in press.

(6) A. A. Patchett, U. S. Patent 3,257,390 (1966).

(7) D. Bertin, H. Fintel, and L. Nedelee, *Bull. Soc. Chim. France*, 1068 (1962).

(8) A. J. Solo, H. S. Sachdev, and S. S. H. Gilani, *J. Org. Chem.*, **30**, 769 (1965); A. J. Solo and B. Singh, *J. Med. Chem.*, **9**, 179 (1966); P. Sunder-Plassman, J. Zderic, and J. H. Fried, *Tetrahedron Letters*, 3451 (1966).

(9) D. S. Tarbell, *Org. Reactions*, **2**, 1 (1944).

(10) A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961); M. Torigoe and J. Fishman, *Tetrahedron Letters*, 1251 (1963); T. L. Patton, *Chem. Ind.* (London), 1567 (1960); P. G. Holton, *J. Org. Chem.*, **27**, 357 (1962); T. L. Patton, *ibid.*, **27**, 910 (1962); R. Gardi and P. P. Castelli, *Gazz. Chim. Ital.*, **93**, 1681 (1963); A. Jefferson and F. Scheinmann, *Chem. Comm.*, 239 (1966).

(11) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961).

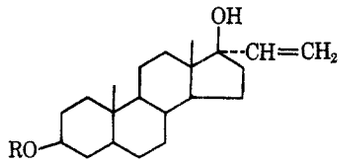
(12) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964).

(13) (a) K. Miescher and C. Scholz, *ibid.*, **22**, 120 (1939); (b) L. Ruzicka and P. Müller, *ibid.*, **22**, 416 (1939); (c) A. Serini, W. Logemann, and W. Hildebrand, *Ber.*, **72**, 391 (1939); (d) R. E. Marker, H. M. Crooks, Jr., R. B. Wagner, and E. L. Wittbecker, *J. Am. Chem. Soc.*, **64**, 2089 (1942); (e) H. Heusser, K. Eichenberger, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 370 (1950); (f) D. Mograth, D. S. Morris, V. Petrow, and R. Royer, *J. Chem. Soc.*, 2393 (1950).

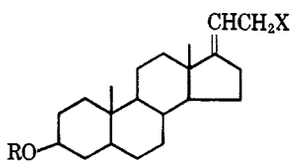
(14) It was found that changing the conditions of Miescher and Scholz[13a] from 1.5 hr at 60° to 24 hr at room temperature gave slightly higher and more consistent yields.

(15) H. Dannenberg and H. G. Neumann, *Chem. Ber.*, **94**, 3094 (1961).

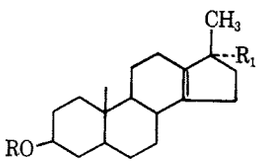
CHART I



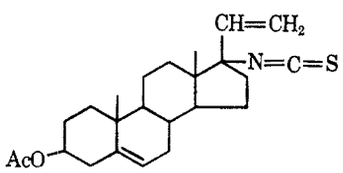
1a, 5α-H, R = H
b, Δ⁵, R = H
c, 5α-H, R = Ac
d, Δ⁵, R = Ac



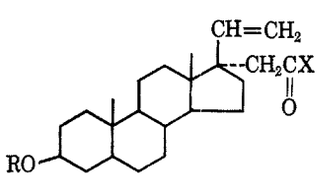
2a, 5α-H, R = Ac; X = Cl
b, Δ⁵, R = Ac; X = Cl
c, 5α-H, R = Ac; X = OAc
d, Δ⁵, R = Ac; X = OAc
e, 5α-H, R = H; X = OH
f, Δ⁵, R = H; X = OH
g, Δ⁵, R = Ac; X = SCN



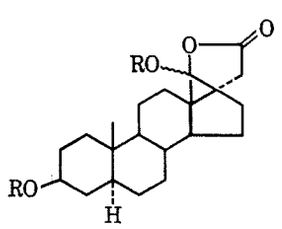
3a, 5α-H, R = H; R_1 = CH=CH₂
b, Δ⁵, R = H; R_1 = CH=CH₂
c, Δ⁵, R = Ac; R_1 = CH=CH₂
d, Δ⁵, R = H; R_1 = CH₂CH₃



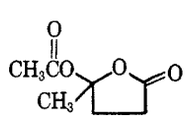
4



5a, 5α-H, R = H; X = NMe₂
b, Δ⁵, R = H; X = NMe₂
c, 5α-H, R = H; X = OH
d, Δ⁵, R = H; X = OH
e, Δ⁵, R = Ac; X = OH



6a, R = H
b, R = Ac



7

also obtained a by-product from this reaction, which had physical constants very similar to those of **3b**, which they claimed to be pregna-5,16,20-trien-3β-ol.

A fairly rapid and convenient five-step synthesis was finally devised for the preparation of the diol **2f** from commercially available dehydroisoandrosterone, which afforded the product in approximately 50% overall yield (on a 50–100-g scale). Addition of vinyllithium to dehydroisoandrosterone gave 17α-vinylandrost-5-ene-3β,17β-diol (**1b**),[16] which was selectively acetylated at the 3 position (**1d**)[17] and treated at 0° with thionyl chloride in ether containing 1 equiv of pyridine.[18] The resulting 21-chloropregna-5,17(20)-dien-3β-ol acetate (**2b**) was treated with potassium acetate, affording pregna-5,17(20)-diene-3β,21-diol diacetate (**2d**)[13a,b] which was saponified to give the diol **2f** in 49% over-all yield. A similar series of reactions in the 5α series, starting with isoandrosterone, afforded 5α-androst-17(20)-ene-3β,21-diol (**2e**)[13c] in 41% over-all yield. These two diols, **2e** and **f**, were thus readily obtainable intermediates for our studies of the Claisen rearrangement at C-17.

The chlorine atom of **2b** was easily displaced by potassium thiocyanate, giving 21-thiocyanopregna-5,17(20)-dien-3β-ol acetate (**2g**). In the hope of obtaining a useful intermediate in the synthesis of 17α-amino-20-keto steroids, several attempts were made to rearrange this allylic thiocyanate to the isomeric 17-isothiocyanopregna-5,20-dien-3β-ol acetate (**4**). Although this reaction has been reported to proceed well in simpler systems,[19] we were able to isolate only starting material and decomposition products from the reactions.

In contrast with the failure of this "pseudo-Claisen" rearrangement to take place, the Claisen rearrangement of the diols **2e** and **f** proceeded very readily. When **2f** was heated with 1,1-diethoxy-1-dimethylaminoethane[11] at 120° for 5 hr, a 91% yield of N,N-dimethyl-3β-hydroxypregna-5,20-dien-17α-acetamide (**5b**) was obtained, which could be saponified to the corresponding acetic acid derivative (**5d**). The gross structures of these compounds were assigned on the basis of their infrared and nmr spectra, but the stereochemistry at C-17 could not be determined as readily and required degradation to a simpler compound of known configuration. The most logical choice for this comparison compound was an appropriate derivative of one of the known epimeric 3β-hydroxy-17-methylandrost-5-ene-17-carboxylic acids (**12c** and **15c**).[20] A degradation to this derivative would leave intact both of the exocyclic carbon–carbon bonds at C-17, thus avoiding any possibility of epimerization at that position during the degradation, and would provide a definite *positive* comparison for either of the two possible configurations.

The first step of this degradative procedure consisted of shortening the vinyl side chain of the Claisen rearrangement products **5** by one carbon and converting the remaining carbon to a methyl group. It was hoped that the vinyl group could be selectively ozonized, but both the amide **5b** and the acid **5d** were attacked by ozone rather slowly and selectively at the Δ⁵ double bond. Therefore, the 5α-diol **2e** was also heated with 1,1-diethoxy-1-dimethylaminoethane and converted to the corresponding amide **5a** and then to the acid **5c**. Ozonization of this vinyl acid afforded an aldehydo acid, isolated in its cyclized form (**6a**). This structure was confirmed by the infrared spectrum of the diacetate **6b**, which exhibited peaks at 1795, 1760, and 1725 cm^{-1} for the three different ester groups [*e.g.*, the spectrum of acetyllevulinic acid (**7**) exhibits the carbonyl peaks of the lactone group at *ca.* 1790 cm^{-1},[21] and the spectrum of acetal diacetate has the carbonyl

(16) (a) H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Chem. Ber.*, **71**, 1024 (1938); (b) L. Ruzicka, K. Hofmann, and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 597 (1938); (c) P. Karrer and F. Kehrer, *ibid.*, **25**, 29 (1942).

(17) (a) L. Ruzicka, K. Hofmann, and H. F. Meldahl, *ibid.*, **21**, 371 (1938); (b) H. Reich, C. Montigel, and T. Reichstein, *ibid.*, **24**, 977 (1941).

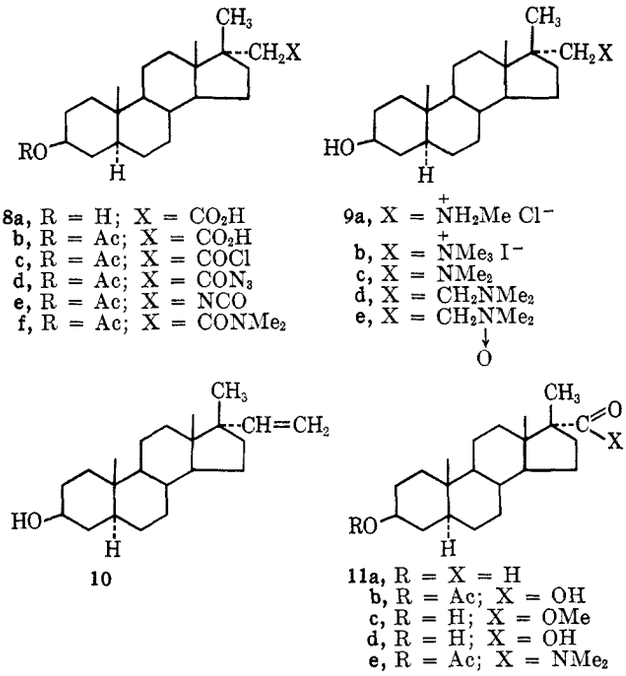
(18) It is interesting to note that the tertiary alcohol **1d** was recovered unchanged when treated at room temperature with thionyl chloride in ether in the absence of any added base.

(19) O. Mumm and H. Richter, *Ber.*, **73**, 483 (1940); P. A. S. Smith and D. W. Emerson, *J. Am. Chem. Soc.*, **82**, 3076 (1960); A. Iliceto, A. Fava, and V. Mazzucato, *Tetrahedron Letters*, No. 11, 27 (1960).

(20) (a) P. A. Plattner, H. Heusser, and S. F. Boyce, *Helv. Chim. Acta*, **31**, 603 (1948); (b) C. R. Engel and G. Just, *J. Am. Chem. Soc.*, **76**, 4909 (1954); (c) A. S. Kende, *Chem. Ind.* (London), 1346 (1959).

(21) S. Olsen and H. Russwarm, *Ann.*, **639**, 1 (1961).

CHART II



peak at 1761 cm^{-1} [22], and by the nmr spectrum of **6b**, which exhibited a sharp one-proton peak at δ 6.63 for the C-20 proton. Wolff–Kishner reduction of **6a** afforded 3β-hydroxy-17β-methyl-5α,17α-pregnan-21-oic acid (**8a**) (Chart II). This acid was subjected to a Curtius degradation, affording 3β-acetoxy-17β-methyl-21-nor-5α,17α-pregnan-20-yl)isocyanate (**8e**), which was reduced to the monomethylamine derivative **9a**. This secondary amine was quaternized with methyl iodide (**9b**) and then reduced with lithium aluminum hydride to N,N-dimethyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylamine (**9c**). Comparison of this amine with the amines prepared by reduction of the dimethylamides of the epimeric 3β-acetoxy-17-methyl-5α-androstane-17-carboxylic acids (**11e** and **14b**) readily revealed the identity of the degradation product **9c** with the amine prepared from **11e**. The 17β-vinyl-17α-acetic acid configuration for the Claisen rearrangement products **5a** and **b** was thus firmly established.

This stereochemical assignment at C-17 was confirmed by an alternate degradative procedure. The 3β-hydroxy-17β-methyl-5α,17α-pregnan-21-oic acid (**8a**) obtained above was converted to its dimethylamide (**8f**) and reduced to N,N-dimethyl-3β-hydroxy-17β-methyl-5α,17α-pregnan-21-ylamine (**9d**). This amine was oxidized to the N-oxide **9e** and pyrolyzed to give 17β-methyl-5α,17α-pregn-20-en-3β-ol (**10**). Ozonolysis of this olefin afforded 3β-hydroxy-17β-methyl-5α-androstane-17α-carboxaldehyde (**11a**), which was acetylated and oxidized to 3β-acetoxy-17β-methyl-5α-androstane-17α-carboxylic acid (**11b**). This compound was identical with the acid prepared by catalytic reduction of the known 3β-acetoxy-17β-methylandrost-5-ene-17α-carboxylic acid,[20] again establishing the 17β-vinyl-17α-acetic acid stereochemistry for **5c**.

The 17α, pseudo-axial orientation of the acetic acid moiety introduced by the Claisen rearrangement was considered by us to be the more likely of the two possible epimeric configurations. Inspection of molecular models indicated that approach of the 1-dimethylaminovinyl ether group[11,12] to the β face of the $\Delta^{17(20)}$ double bond was considerably hindered by the 18-methyl group. (The hindrance between the dimethylamino group and the 15 and 16 protons was judged to be about the same whether α- or β-face attack occurred.) In a comparable situation in a terpene synthesis involving a Claisen rearrangement of a substituted *trans*-Δ^1-octalin-2-methyl vinyl ether, Ireland and coworkers[23] showed that the rearrangement proceeded stereospecifically to introduce the acetaldehyde group into the *1-axial* position of the resulting 2-methylene decalin ring system. The stereoselective introduction of axial substituents by the Claisen rearrangement has been confirmed by Ireland[24] by observations in simpler monocyclic systems where no other substituent effects could interfere.

During the elucidation of the stereochemistry of the steroidal Claisen rearrangement products **5**, some problems of synthetic interest were encountered. The synthesis of methyl 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylate (**12a**)[20] (Chart III) had previously been achieved only in low yield as a minor product of the Favorskii reaction of 21-chloro-3β-hydroxypregn-5-en-20-one, the major product being the epimeric methyl 3β-hydroxy-17α-methylandrost-5-ene-17β-carboxylate (**15a**).[20] The Favorskii reaction of 3β-acetoxy-17α-bromopregn-5-en-20-one (**16**), when run with sodium bicarbonate in methanol, also afforded **15a** as the major product.[25] The Favorskii reaction of the latter α-halo ketone apparently proceeds more selectively, for the 17β ester **15b** could be isolated in 64% yield with just one recrystallization, whereas chromatography was necessary to separate the two epimers from the former reaction. Presumably the 17α ester **12a** was also formed as a by-product from the reaction of **16**, although it has not yet been identified in the mother liquors. The Favorskii reaction of 3α-acetoxy-17α-bromopregnane-11,20-dione demonstrated that the proportion of the 17α ester could be increased to 40% by the introduction of an 11-keto group.[26]

The 17α ester is the epimer which should be formed if the Favorskii reaction proceeded stereospecifically through the intermediate cyclopropanone derivative **17** formed by SN2 displacement of the halide by the enolate carbanion at C-21. The fact that this epimer was formed in low yield, if at all, indicated that the reaction proceeded instead *via* the nonstereospecific zwitterion mechanism.[27] It has been shown[27b,c,e]

(22) J. P. Freeman, *J. Am. Chem. Soc.*, **80**, 5954 (1958).

(23) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **27**, 1118 (1962).

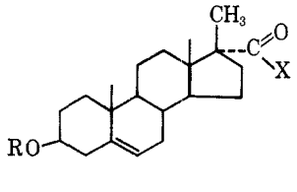
(24) R. E. Ireland, personal communication.

(25) R. E. Marker and R. B. Wagner, *J. Am. Chem. Soc.*, **64**, 216 (1942).

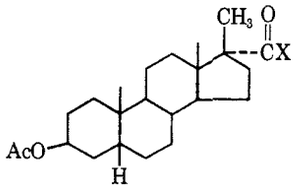
(26) N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(27) The mechanism of the Favorskii reaction is still being debated. Several articles have appeared in the past few years discussing various aspects of this problem: (a) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972, 3980 (1961); (c) A. Gaudemer, J. Parello, A. Skrobek, and B. Tchoubar, *Bull. Soc. Chim. France*, 2405 (1963); (d) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 164 (1963); (e) H. O. House and G. A. Frank, *ibid.*, **30**, 2948 (1965); (f) H. Ginsburg, *Bull. Soc. Chim. France*, 3645 (1965); (g) N. J. Turro and W. B. Hammond, *J. Am. Chem. Soc.*, **87**, 3258 (1965); (h) E. E. Smissman, T. L. Lemke, and O. Kristiansen, *ibid.*, **88**, 334 (1966); (i) R. Deghenghi, G. Schilling, and G. Papineau-Couture, *Can. J. Chem.*, **44**, 789 (1966).

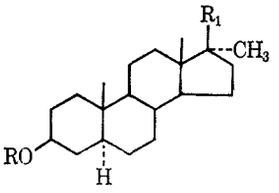
CHART III



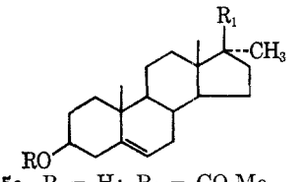
12a, R = H; X = OMe
b, R = Ac; X = OMe
c, R = H; X = OH
d, R = Ac; X = OH
e, R = Ac; X = NMe_2



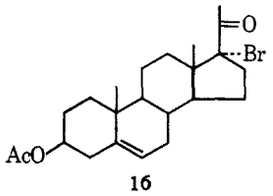
13a, X = NMe_2
b, X = OH



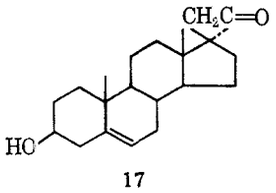
14a, R = H; R_1 = CO_2H
b, R = Ac; R_1 = $CONMe_2$
c, R = H; R_1 = CH_2NMe_2



15a, R = H; R_1 = CO_2Me
b, R = Ac; R_1 = CO_2Me
c, R = H; R_1 = CO_2H
d, R = Ac; R_1 = CO_2H
e, R = Ac; R_1 = $CONMe_2$
f, R = H; R_1 = CH_2OH



16



17

that the use of nonpolar, aprotic solvents favors the stereospecific cyclopropanone pathway, whereas the use of polar, hydroxylic solvents favors an alternate nonstereospecific route. Moderate quantities of the 17α ester **12a** were needed to prepare derivatives for comparison with the degradation products (*e.g.*, **9c**) of the Claisen rearrangement products **5**. Therefore, the Favorskii reaction of the 17α-bromo ketone **16** was rerun, using sodium methoxide in 1,2-dimethoxyethane in an effort to improve the proportion of the 17β-methyl-17α-carboxylate epimer. As expected, methyl 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylate (**12a**) was isolated from this reaction in high yield, and investigation of the crude product by vapor phase chromatography (vpc) indicated that under these conditions less than 2% of the epimeric ester **15a** was formed. This route, therefore, constitutes a new useful synthesis for this previously difficultly accessible compound. It is interesting to note that the infrared absorption band of the carbonyl group of the pseudo-axial ester **12a** was at the unusually low frequency of 1715 cm^{-1}, whereas that of the pseudo-equatorial ester **15a** was in the normal ester range of 1733 cm^{-1}.

Although the lithium aluminum hydride reduction of N,N-dimethyl-3β-acetoxy-17β-methyl-5α,17α-pregnan-21-amide (**8f**) proceeded normally to give the amine **9d**, a similar reduction of the more hindered N,N-dimethyl-3β-acetoxy-17α-methylandrost-5-ene-17β-carboxamide (**15e**) afforded only a trace of basic material. The major product obtained from this reduction was found to be 17α-methyl-21-norpregn-5-ene-3β,20-diol (**15f**), identified by comparison with an authentic sample prepared by reduction of the corresponding acid **15d**.[28] However, when the 5α-dihydro derivative of this amide (**14b**) was reduced instead with aluminum hydride, N,N-dimethyl-3β-hydroxy-17α-methyl-21-nor-5α-pregnan-20-ylamine (**14c**) was obtained in a very pure state in nearly quantitative yield. Similarly a high yield of very clean amine **9c** was obtained from the aluminum hydride reduction of the epimeric N,N-dimethyl-3β-acetoxy-17β-methyl-5α-androstane-17α-carboxamide (**11e**). Both the high yields and the purity of the product obtained with aluminum hydride indicate that this reagent is superior to lithium aluminum hydride for the reduction of tertiary amides.[29]

Another unusual reduction was encountered in the catalytic reduction of N,N-dimethyl-3β-acetoxy-17β-methylandrost-5-ene-17α-carboxamide (**12e**). The major product (72%) was not the expected 5α-dihydro derivative **11e** but instead the 5β epimer **13a**. The 5α-amide **11e** was synthesized from 3β-acetoxy-17β-methyl-5α-androstane-17α-carboxylic acid (**11b**) and was shown to be different from the amide obtained by reduction. The 5β configuration of **13a** was established by means of its nmr spectrum. The equatorial nature of the 3-proton was shown by its downfield position (5.1 ppm) in the spectrum and its small coupling constants with the neighboring protons ($W_{h/2}$ = 6 cps).[30] The possibility that epimerization had occurred at C-3 during the catalytic reduction rather than a top-side hydrogenation at the 5β position was discounted by the position of the 19-methyl peak (0.97 ppm), which was in the range reported for 3β-acetoxy 5β steroids (0.96–0.99) and far removed from that reported for 3α-acetoxy 5α compounds (0.82–0.83).[31] Apparently the large steric bulk of the N,N-dimethylcarboxamide group at C-17α is close enough to the Δ^5 double bond to impede somewhat the approach of the catalyst surface to the α side of the steroid molecule. Hydrogenation therefore occurred from the relatively less hindered β side of the molecule. An investigation (by nmr) of the mother liquors from a similar catalytic reduction of 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylic acid (**12c**) indicated that 30–35% of the 5β epimer **13b** was still formed, even with this less bulky 17α substituent.

The formation of these Claisen rearrangement products (**5**) makes possible the synthesis of a great number of new steroids having *two* substituents bearing a

(28) The reduction of other highly hindered amides to alcohols has been previously observed. See V. M. Micović and M. L. Mikailović, *J. Org. Chem.*, **18**, 1190 (1963), and references therein.

(29) We are indebted to Dr. Donald E. Butler of our laboratories for suggesting the use of this reagent to us. Dr. Butler also has found aluminum hydride to be very useful in the reduction of hindered secondary and tertiary amides to the corresponding amines. After this work was complete, Brown reported that neither aldehydes nor ketones were found upon reduction of amides with aluminum hydride: H. C. Brown and N. Min Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966).

(30) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy to Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 78–80.

(31) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

variety of functional groups at the 17 position. The synthesis of some examples of this novel type of steroids will be described in a following paper.

Experimental Section[32]

17α-Vinyl-5α-androstane-3β,17β-diol (1a).—To a cooled solution of 80.0 g of 3β-hydroxy-5α-androstan-17-one in 1.5 l. of tetrahydrofuran was added 400 ml of 2.0 *M* vinyllithium in tetrahydrofuran. The solution was stirred at 0° for 0.5 hr, allowed to warm to room temperature, and stirred an additional hour. Concentrated ammonium chloride solution was added, and the mixture was concentrated under reduced pressure until a precipitate began to form. The slurry was poured into water, and the precipitate was filtered and recrystallized twice from methanol, affording 52.2 g (60%) of product, mp 205–207.5° (lit.[13c,33] mp 207°).

17α-Vinylandrost-5-ene-3β,17β-diol (1b).—Similarly 100.0 g of 3β-hydroxyandrost-5-en-17-one was treated with 400 ml of 2.5 *M* vinyllithium in tetrahydrofuran, affording 75.2 g (68%) of product, mp 183–186° (lit. mp 184–187[16a,b] and 192.5–193.5°[16c]). Concentration of the mother liquors yielded an additional 21.3 g (19%), mp 176–179°.

17α-Vinyl-5α-androstane-3β,17β-diol 3-Acetate (1c).—A solution of 60.0 g of 17α-vinyl-5α-androstane-3β,17β-diol (**1a**) in 1200 ml of pyridine was treated with 127 ml of acetic anhydride and left at room temperature for 24 hr. The solution was then poured into dilute hydrochloric acid, and the precipitate was filtered, air dried, and recrystallized from methanol, affording 47.4 g (70%) of product, mp 152–153.5°. Concentration of the mother liquors yielded an additional 10.6 g (16%), mp 152–154°. A sample was recrystallized from methanol for analysis, mp 153–155° (lit.[13c] mp 152–154°).

17α-Vinylandrost-5-ene-3β,17β-diol 3-Acetate (1d).—Similarly 25.0 g of 17α-vinylandrost-5-ene-3β,17β-diol (**1b**) was converted to 23.7 g (84%) of product, mp 158–160° (lit. mp 160–161[17a] and 163–165°[17b]).

21-Chloro-5α-pregn-17(20)-en-3β-ol Acetate (2a).—A solution of 47.4 g of 17α-vinyl-5α-androstane-3β,17β-diol 3-acetate (**1c**) in 1160 ml of ether and 13.3 ml of pyridine was cooled to 0° and treated with 30.0 ml of thionyl chloride. The mixture was stirred at 0° for 10 min and then concentrated to dryness under reduced pressure. The solid was suspended in benzene and concentrated to dryness three times. The residue was dissolved in ether and water, and the ether layer was washed with sodium bicarbonate solution and with water. The dried ether solution was concentrated to a small volume and cooled, affording 29.4 g (59%) of product, mp 154–156°. Further concentration of the mother liquors afforded an additional 5.7 g (11%), mp 154–157°. A sample was recrystallized from ether for analysis, mp 155–156.5°, $[\alpha]^{24}D$ +26°.

Anal. Calcd for $C_{23}H_{35}ClO_2$: C, 72.89; H, 9.31; Cl, 9.36. Found: C, 73.02; H, 9.25; Cl, 9.47.

21-Chloropregna-5,17(20)-dien-3β-ol Acetate (2b).—Similar treatment of 6.3 g of 17α-vinylandrost-5-ene-3β,17β-diol 3-acetate (**1d**) afforded 4.0 g (60%) of product, mp 152–154°. Concentration of the mother liquors afforded crops of 0.55 g (8%), mp 150–152° and 0.56 g (8%), mp 145–147°. A sample was recrystallized from ether for analysis, mp 153–154°, $[\alpha]^{27}D$ −55°.

Anal. Calcd for $C_{23}H_{33}ClO_2$: C, 73.28; H, 8.82; Cl, 9.41. Found: C, 73.01; H, 8.96; Cl, 9.47.

5α-Pregn-17(20)-ene-3β,21-diol Diacetate (2c).—A solution of 8.66 g of 21-chloro-5α-pregn-17(20)-en-3β-ol acetate (**2a**) in 350 ml of dimethylformamide was treated with a solution of 34.6 g of potassium acetate in 35 ml of water and refluxed for 1.5 hr. The cooled solution was poured into water and the precipitate was collected. This crude diacetate was usually used directly for the preparation of the diol. However, on this run the crude material was recrystallized from hexane, affording 7.13 g (77%) of product, mp 145–148°. Another recrystallization raised the melting point to 150–152° (lit.[13c] mp 156°).

Pregna-5,17(20)-diene-3β,21-diol Diacetate (2d).—In a similar manner, 21-chloropregna-5,17(20)-dien-3β-ol acetate (**2b**) was converted to the diacetate **2d**, which was not purified but used directly for the preparation of the diol. However, this intermediate was characterized from one run. The crude diacetate obtained from 0.50 g of **2b** was recrystallized from hexane to give 0.40 g (75%) of product, mp 131–133° (lit.[13a,b] mp 136–137°).

5α-Pregn-17(20)-ene-3β,21-diol (2e). A. From 5α-Pregn-17(20)-ene-3β,21-diol Diacetate.—A solution of 4.52 g of **2c** in 244 ml of methanol was treated with a solution of 1.5 g of potassium hydroxide in 10 ml of water and refluxed for 1 hr under an atmosphere of nitrogen. The cooled solution was concentrated to a small volume and poured into water, and the precipitate was collected and dried. Recrystallization from methanol afforded 2.79 g (78%) of diol, mp 207–209.5° (lit.[13c] mp 202–205°). Concentration of the mother liquors yielded an additional 0.39 g (11%), mp 205–210°. The over-all yield of **2e** from **1a** was 41%.

B. From 17α-Vinyl-5α-androstane-3β,17β-diol.—Following generally the procedure of Miescher and Scholz,[13a,14] a solution of 52.0 g of **1a** in 620 ml of acetic anhydride was heated on the steam bath for 1 hr. The cooled solution was treated with a solution of 212 g of trichloroacetic acid in 426 ml of acetic acid and left at room temperature for 24 hr. The solution was then poured into ice water and extracted with ether. The ether layer was washed several times with water, then with dilute sodium hydroxide solution, and with water again. The dried ether solution was concentrated to an oil, which was dissolved in 520 ml of methanol and treated with 50 ml of a 50% solution of sodium hydroxide. After 1 hr at room temperature, the base was neutralized with acetic acid and the solution was concentrated under reduced pressure to a small volume and poured into water. The precipitate was collected and recrystallized twice from acetone, affording 3.17 g (6%) of 5α-pregn-17(20)-ene-3β,21-diol, mp 205–207°.

The material obtained by concentration of the mother liquors was recrystallized from acetone, affording 7.79 g (16%) of **17β-methyl-17α-vinyl-18-nor-5α-androst-13-en-3β-ol (3a)**, mp 132–133°, $[\alpha]^{25}D$ +22°. The nmr spectrum exhibited two three-proton singlets at 0.78 (19-Me) and 1.07 (17β-Me), a broad one-proton hump centered at 3.6 (3α-H), and a three-proton multiplet at 4.7–6.1 ppm characteristic of a vinyl group.

Anal. Calcd for $C_{21}H_{32}O$: C, 84.01; H, 10.73. Found: C, 83.72; H, 10.78.

Pregna-5,17(20)-diene-3β,21-diol (2f). A. From Pregna-5,17(20)-diene-3β,21-diol Diacetate.—Saponification of 15.98 g of crude **2d** (prepared from 16.00 g of **2b**), in the same manner as in the preparation of **2e**, afforded 11.52 g (86%, based on **2b**) of product, mp 197–201° (MeOH) (lit.[13a,b] mp 198–199°). The over-all yield from **1b** was 49%.

B. From 17α-Vinylandrost-5-ene-3β,17β-diol.—Following generally the procedure of Miescher and Scholz,[13a,14] as described above, **1b** was converted to pregna-5,17(20)-diene-3β,21-diol (**2f**) in yields varying from 2 to 30%, although the majority of the runs were in the 8–15% range.

The material obtained by concentration of the combined mother liquors was recrystallized from acetone, affording **17β-methyl-17α-vinyl-18-norandrosta-5,13-dien-3β-ol (3b)** in 10% yield, mp 119–122°. Another recrystallization raised the melting point to 123–125°. (The reported melting point for Miescher's pregna-5,16,20-trien-3β-ol was 125.5–126°.)[13a] The ultraviolet spectrum exhibited only end absorption. The nmr spectrum exhibited two three-proton singlets at 1.00 (19-Me) and 1.10 (17β-Me), a broad one-proton hump at 3.55 (3α-H), a narrow one-proton hump at 5.4 (6-H) in the middle of a characteristic three-proton multiplet of a vinyl group at 4.7–6.1 ppm.

The **acetate 3c**, prepared with pyridine–acetic anhydride, was recrystallized from methanol, mp 93–94.5°. (The reported melting point for the acetate of Miescher's product was 86.5–87°.)[13a]

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.87; H, 9.39.

17α-Ethyl-17β-methyl-18-norandrosta-5,13-dien-3β-ol (3d).—A solution of 0.55 g of 17β-methyl-17α-vinyl-18-norandrosta-5,13-dien-3β-ol (**3b**) in 75 ml of methanol was treated with 0.1 g of 6% palladium on carbon and hydrogenated at 50 psi until 1 equiv of hydrogen was absorbed (3 min). The solution was fil-

(32) Melting points were determined on a Fisher-Johns block and are corrected. The ultraviolet spectra were run in methanol. Optical rotations were determined on an approximately 1% solution in chloroform unless otherwise noted. The nmr spectra were obtained on a Varian A-60 instrument; the spectra were determined in deuteriochloroform solution, and the shifts are expressed as parts per million downfield from tetramethylsilane, used as an internal standard. All compounds had infrared spectra which agreed with the assigned structures.

(33) A. Serini and W. Logemann, *Ber.*, **71**, 1362 (1938).

tered and concentrated to dryness under reduced pressure. The residue was recrystallized from petroleum ether (bp 35–60°), affording 0.14 g (25%) of product, mp 130–132°. Another recrystallization from petroleum ether raised the melting point to 133–135°, $[\alpha]^{25}D$ −184° (*c* 0.6, EtOH). The reported constants for this compound are mp 135–136°, $[\alpha]^{23}D$ −197° (EtOH).[15]

21-Thiocyanopregna-5,17(20)-dien-3β-ol Acetate (2g).—A suspension of 2.49 g of 21-chloropregna-5,17(20)-dien-3β-ol acetate (**2b**) in 100 ml of dimethyl sulfoxide was treated with a solution of 10.0 g of potassium thiocyanate in 10 ml of water and stirred at room temperature for 4 hr. The mixture was poured into water, filtered, and dried, affording 2.45 g (93%) of product, mp 155–159°. A sample was recrystallized for analysis from ether, mp 162–164°, $[\alpha]^{26}D$ −61°. The nmr spectrum exhibited a two-proton doublet (J = 7 cps) centered at 3.61 (21-CH_2) and a two-proton hump centered at 5.3 (6-H and 20-H), indicating that no rearrangement had occurred.

Anal. Calcd for $C_{24}H_{33}NO_2S$: C, 72.14; H, 8.32; N, 3.51; S, 8.02. Found: C, 72.29; H, 8.32; N, 3.50; S, 7.80.

N,N-Dimethyl-3β-hydroxy-5α-pregn-20-en-17α-acetamide (5a).—A solution of 15.0 g of 5α-pregn-17(20)-ene-3β,21-diol (**2e**) in 125 ml of 1,1-diethoxy-1-dimethylaminoethane[11] was slowly distilled under an atmosphere of nitrogen until the vapor temperature reached 120°. The residual solution was refluxed under nitrogen an additional 5 hr. The cooled solution was concentrated under reduced pressure to an oil, which was dissolved in 100 ml of methanol and chilled. The precipitate which formed was filtered, affording 4.44 g (24%) of product, mp 173–175°. The filtrate was poured into water, and the precipitate was collected, dried, and recrystallized from acetonitrile, affording an additional 10.32 g (57%) of product, mp 172–173.5°. A sample was recrystallized for analysis from aqueous methanol, mp 175–177°, $[\alpha]^{25}D$ −40° (*c* 1.0, MeOH). The nmr spectrum exhibited two three-proton singlets at 0.67 (18-Me) and 0.83 (19-Me), two one-proton singlets at 2.32 and 2.50 ($CH_2C{=}O$), an unsymmetrical six-proton doublet at 2.88 and 2.97 (NMe_2), a broad hump at 3.7 (3α-H), and a vinyl multiplet at 4.7–6.1 ppm.

Anal. Calcd for $C_{25}H_{41}NO_2$: C, 77.47; H, 10.67; N, 3.61. Found: C, 77.32; H, 10.48; N, 3.46.

N,N-Dimethyl-3β-hydroxypregna-5,20-dien-17α-acetamide (5b).—Similarly, a solution of 10.41 g of pregna-5,17(20)-diene-3β,21-diol (**2f**) in 86 ml of 1,1-diethoxy-1-dimethylaminoethane[11] was distilled until the vapor temperature reached 120° and then refluxed under an atmosphere of nitrogen for 5 hr. The solution was concentrated under reduced pressure to an oil, which was triturated with cold methanol until it crystallized. The precipitate was filtered and dried, affording 11.73 g (89%) of product containing 0.5 mole of methanol of crystallization, mp 183–185.5°. Concentration of the mother liquors yielded an additional 0.23 g (2%) of material, mp 180–183°. A sample was recrystallized for analysis from methanol, mp 186–188°, $[\alpha]^{24}D$ −60°. The nmr spectrum was very similar to that of **5a**, but with the 19-Me peak at 1.04, a peak at 5.3 (6-H), and a small (*ca.* one proton) sharp peak at 3.45 ppm (MeOH).

Anal. Calcd for $C_{25}H_{39}NO_2 \cdot 0.5CH_3OH$: C, 76.26; H, 10.29; N, 3.49. Found: C, 76.38; H, 10.36; N, 3.64.

3β-Hydroxy-5α-pregn-20-en-17α-acetic Acid (5c).—A solution of 15.41 g of N,N-dimethyl-3β-hydroxy-5α-pregn-20-en-17α-acetamide (**5a**) in 570 ml of ethylene glycol was treated with 110 g of potassium hydroxide and refluxed overnight under an atmosphere of nitrogen. At this time, the condenser was removed and the solvent was distilled until the temperature of the solution reached 195°. The reaction was refluxed an additional 2 hr, cooled, and poured into dilute hydrochloric acid. The precipitate was filtered, dried, and recrystallized from dichloromethane–petroleum ether, affording 13.63 g (95%) of product, mp 208–210°. Concentration of the mother liquors yielded an additional 0.49 g (3%) of product, mp 203–205°. A sample was recrystallized for analysis from the same solvent mixture, mp 208–210°, $[\alpha]^{25}D$ −22° (*c* 1.0, MeOH).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.01. Found: C, 76.53; H, 10.14.

3β-Hydroxypregna-5,20-dien-17α-acetic Acid (5d).—In a similar manner, 5.73 g of N,N-dimethyl-3β-hydroxypregna-5,20-dien-17α-acetamide (**5b**) was saponified to give 5.06 g (95%) of product, mp 212–214°. Concentration of the mother liquors and dilution with additional petroleum ether yielded 0.24 g (4%), mp 210–213°. A sample was recrystallized for analysis from dichloromethane–petroleum ether, mp 212–214°, $[\alpha]^{26}D$ −97°.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.06; H, 9.56. Found: C, 76.86; H, 9.66.

3β-Acetoxypregna-5,20-dien-17α-acetic Acid (5e).—A solution of 10.78 g of 3β-hydroxypregna-5,20-dien-17α-acetic acid (**5d**) in 110 ml of pyridine was treated with 30 ml of acetic anhydride and left overnight at room temperature. The solution was poured into dilute hydrochloric acid and stirred for 1 hr. The precipitate was collected, dried, and recrystallized from aqueous ethanol, affording 10.96 g (91%) of product, mp 222–224°. A sample was recrystallized for analysis from aqueous ethanol, mp 222–224°, $[\alpha]^{26}D$ −96°.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.97; H, 9.16.

3β,20,20-Trihydroxy-21-nor-5α-pregnan-17α-acetic Acid Lactone (6a).—A stream of ozone-containing oxygen (535 mg of ozone/ft³) was passed through (0.06 ft³/min) an ice-cold solution of 1.50 g of 3β-hydroxy-5α-pregn-20-en-17α-acetic acid (**5c**) for 40 min. The solution was allowed to stand at 0° for an additional 45 min, and was then treated with a solution of 3.0 g of potassium iodide in 12 ml of water and 30 ml of acetic acid. After an additional 45 min the solution was decolorized by the addition of sodium bisulfite solution, and the mixture was poured into 2 l. of water. The product was extracted with ether, and the ether layer was washed well with water, dried, concentrated to a small, volume, and chilled. The precipitate was filtered and dried, affording 0.95 g (63%) of product, mp 228–232°, $[\alpha]^{26}D$ −22° (*c* 1.0, MeOH). The infrared spectrum exhibited a peak at 1773 cm^{-1}.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.62; H, 9.27.

3β,20-Diacetoxy-20-hydroxy-21-nor-5α-pregnan-17α-acetic Acid Lactone (6b).—A solution of 90 mg of 3β,20,20-trihydroxy-21-nor-5α-pregnan-17α-acetic acid lactone (**6a**) in 5 ml of acetic anhydride was refluxed for 1 hr. The cooled solution was treated with 5 ml of methanol, refluxed briefly, and concentrated to dryness under reduced pressure. The residue was recrystallized from methanol, affording 49 mg (44%) of product, mp 249–251°. The infrared spectrum exhibited peaks at 1795 (20-OAc), 1760 (lactone), and 1725 cm^{-1} (3-OAc). The nmr spectrum exhibited a sharp peak at 6.63 for the C-20 proton, as well as peaks at 0.83 (19-Me), 0.92 (18-Me), 2.00 and 2.10 (OAc groups), 2.50 and 2.57 (CH_2CO_2), and 4.7 ppm (3α-H).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.80; H, 8.58.

3β-Hydroxy-17β-methyl-5α,17α-pregnan-21-oic Acid (8a).—A solution of 2.75 g of 3β,20,20-trihydroxy-21-nor-5α-pregnan-17α-acetic acid lactone (**6a**) in 400 ml of diethylene glycol was treated with 40 g of potassium hydroxide and 48 ml of anhydrous hydrazine. After the solution was refluxed for 2 hr, the condenser was removed and the water was distilled until the temperature of the mixture reached 215°. The solution was refluxed under an atmosphere of nitrogen for an additional 1.5 hr, cooled, and poured into dilute hydrochloric acid. The product was extracted with ether, and the ether solution was washed with water and dried. Concentrating the ether solution to a small volume and chilling afforded 1.95 g (74%) of product, mp 218–222°. A sample was recrystallized from methanol–acetonitrile for analysis, mp 226–227.5°, $[\alpha]^{25}D$ −18° (*c* 0.8, MeOH).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.84; H, 10.49.

3β-Acetoxy-17β-methyl-5α,17α-pregnan-21-oic Acid (8b).—A solution of 1.55 g of 3β-hydroxy-17β-methyl-5α,17α-pregnan-21-oic acid (**8a**) in 75 ml of pyridine and 75 ml of acetic anhydride was left overnight at room temperature. In the morning 75 ml of water was added, and the solution was warmed on the steam bath for 0.75 hr and then poured into dilute hydrochloric acid. The precipitate was filtered, dried, and recrystallized from acetonitrile, affording 1.53 g (88%) of product, mp 184–188°. An additional recrystallization from acetonitrile yielded 1.32 g (76%) of analytically pure material, mp 193–195°, $[\alpha]^{25}D$ −30°.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.91; H, 9.82.

N-Methyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylamine Hydrochloride (9a).—A solution of 0.71 g of 3β-acetoxy-17β-methyl-5α,17α-pregnan-21-oic acid (**8b**) in 7 ml of ice-cold thionyl chloride was kept overnight at 0°. The solution was then allowed to warm to room temperature, and after 1 hr the solution was diluted with benzene and concentrated to dryness under reduced pressure. The residue was dissolved in benzene

and reconcentrated to dryness four times. The residue, **3β-acetoxy-17β-methyl-5α,17α-pregnan-21-oyl chloride (8c)**, was dissolved in 38 ml of acetone, cooled to 0°, treated with a solution of 1.05 g of sodium azide in 3 ml of water, and stirred at 0° for 30 min. Benzene and water were then added, and the benzene layer was washed well with water and dried. The benzene solution of **3β-acetoxy-17β-methyl-5α,17α-pregnan-21-oyl azide (8d)** was refluxed for 4 hr, and then concentrated to dryness under reduced pressure. The residual **3β-acetoxy-17β-methyl-21-nor-5α,17α-pregnan-20-yl isocyanate (8e)**, which exhibited a strong infrared absorption at 2280 cm^{-1}, was dissolved in 150 ml of tetrahydrofuran and treated with 700 mg of lithium aluminum hydride. The mixture was stirred at room temperature for 4 hr, then refluxed for 1 hr and cooled. The excess reagent was decomposed by the addition of 0.70 ml of water, 0.70 ml of 16% sodium hydroxide solution, and 2.1 ml of water. The solution was filtered and concentrated to dryness under reduced pressure. The residue was dissolved in 200 ml of ether and treated with anhydrous hydrogen chloride. The precipitated salt was filtered and dried, yielding 0.42 g (63%) of product. One recrystallization from ethanol afforded 0.29 g (43%) of analytically pure N-methyl-3β-hydroxy-17β-methyl-21-nor-5α,-17α-pregnan-20-ylamine hydrochloride, mp >300°, $[\alpha]^{24}D$ −7° (*c* 1.0, MeOH).

Anal. Calcd for $C_{22}H_{40}ClNO$: C, 71.41; H, 10.90; Cl, 9.58; N, 3.79. Found: C, 71.28; H, 10.89; Cl, 9.29; N, 3.82.

N,N,N-Trimethyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylammonium Iodide (9b).—A suspension of 0.50 g of N-methyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylamine hydrochloride (**9a**) in 40 ml of acetonitrile was treated with 0.70 g of potassium carbonate and 5 ml of methyl iodide, and the mixture was stirred and refluxed overnight. The cooled mixture was concentrated to dryness under reduced pressure, and the residue was triturated with water. The precipitate was filtered and the crude salt, 0.52 g (79%), was recrystallized from methanol–ether for analysis, mp 262–265°, $[\alpha]^{25}D$ ±0° (*c* 0.9, MeOH).

Anal. Calcd for $C_{24}H_{44}INO$: C, 58.88; H, 9.06; I, 25.92; N, 2.86. Found: C, 58.77; H, 9.06; I, 25.61; N, 2.65.

N,N-Dimethyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylamine (9c).—A solution of 0.31 g of crude N,N,N-trimethyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylammonium iodide (**9b**) in 60 ml of tetrahydrofuran was treated with 0.30 g of lithium aluminum hydride, and the mixture was stirred and refluxed overnight. The excess reagent was decomposed by the addition of 0.30 ml of water, 0.30 ml of 16% sodium hydroxide solution, and 0.90 ml of water. The solution was filtered and concentrated to dryness. The residue was recrystallized from acetonitrile, affording 0.17 g (77%) of product, mp 134–135°. Another recrystallization from acetonitrile gave 0.11 g (50%) of analytically pure material, double mp 139–140 and 159–160°, $[\alpha]^{25}D$ +11°. A mixture melting point with an authentic sample (see below) showed no depression, mp 158.5–159°.

Anal. Calcd for $C_{23}H_{41}NO$: C, 79.47; H, 11.89; N, 4.03. Found: C, 79.44; H, 11.82; N, 3.89.

N,N-Dimethyl-3β-acetoxy-17β-methyl-5α,17α-pregnan-21-amide (8f).—The 3β-acetoxy-17β-methyl-5α,17α-pregnan-21-oyl chloride (**8c**) prepared from 1.95 g of 3β-acetoxy-17β-methyl-5α,17α-pregnan-21-oic acid (**8b**) as described above was dissolved in 300 ml of ether and treated with a solution of 5 ml of dimethylamine in 175 ml of ether. The mixture was stirred at room temperature for 30 min and then washed successively with water, sodium carbonate solution, dilute hydrochloric acid, and water. The dried ether solution was concentrated to dryness and the residue (1.87 g) was recrystallized twice from ethyl acetate–hexane, affording 1.10 g (53%) of product, mp 133.5–135°, $[\alpha]^{24}D$ −21°.

Anal. Calcd for $C_{26}H_{43}NO_3$: C, 74.77; H, 10.38; N, 3.35. Found: C, 74.76; H, 10.33; N, 3.32.

N,N-Dimethyl-3β-hydroxy-17β-methyl-5α,17α-pregnan-21-ylamine (9d).—The procedure used for the reduction of 1.14 g of N,N-dimethyl-3β-acetoxy-17β-methyl-5α,17α-pregnan-21-amide (**8f**) was the same as that used for the preparation of **9c** from **9b**. The crude product was recrystallized from methanol, affording 0.77 g (78%) of product, mp 153–155°, $[\alpha]^{25}D$ −8°.

Anal. Calcd for $C_{24}H_{43}NO$: C, 79.71; H, 11.99; N, 3.87. Found: C, 79.54; H, 12.04; N, 3.78.

17β-Methyl-5α,17α-pregn-20-en-3β-ol (10).—A solution of 1.25 g of N,N-dimethyl-3β-hydroxy-17β-methyl-5α,17α-pregnan-21-ylamine (**9d**) in 60 ml of methanol was treated with 60 ml of 30% hydrogen peroxide and stirred at room temperature overnight. The solution was diluted with water and chilled to 0°. The precipitate was collected and dried under reduced pressure, affording 1.29 g (99%) of a hydrate of **N,N-dimethyl-3β-hydroxy-17β-methyl-5α,17α-pregnan-21-ylamine oxide (9e)**, mp 161–163° dec. The infrared spectrum of **9e** was transparent at 2785 cm^{-1} where the starting material had shown absorption ($\overset{+}{N}Me_2$).

This amine oxide was heated at 180–190° at 15 mm until the product of decomposition had all sublimed. The sublimate was recrystallized from aqueous methanol, affording 0.44 g (40%, based on the amine) of product, mp 165–167°, $[\alpha]^{25}D$ −6°.

Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.47; H, 11.47.

3β-Acetoxy-17β-methyl-5α-androstane-17α-carboxylic Acid (11b).—The procedure used for the ozonization of 0.27 g of 17β-methyl-5α,17α-pregn-20-en-3β-ol (**10**) was the same as that used for the ozonization of **5c**. The crude oily **3β-hydroxy-17β-methyl-5α-androstane-17α-carboxaldehyde (11a)** was dissolved in 20 ml of acetic anhydride, and the solution was refluxed for 1.5 hr. After 20 ml of methanol was added, the solution was refluxed briefly and concentrated under reduced pressure. The oily residue was dissolved in 10 ml of acetic acid, treated with 1.0 ml of 4 *N* chromic acid solution, and stirred at room temperature for 1 hr. The solution was poured into water and the precipitate was filtered and dried, yielding 0.16 g of crude acid. Two recrystallizations from acetonitrile afforded 0.06 g (21%) of product, mp 211.5–213°, $[\alpha]^{25}D$ +13° (*c* 0.8, MeOH). The mixture melting point with an authentic sample of 3β-acetoxy-17β-methyl-5α-androstane-17α-carboxylic acid was undepressed, mp 212–213.5°.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.12; H, 9.63.

Methyl 3β-Acetoxy-17β-methylandrost-5-ene-17α-carboxylate (12b).—A solution of 10.0 g of 3β-acetoxy-17α-bromopregn-5-en-20-one (**16**) in 780 ml of 1,2-dimethoxyethane was treated with 12.5 g of sodium methoxide. The mixture, which became warm, was stirred overnight and then refluxed for 3 hr. The cooled mixture was poured into dilute hydrochloric acid, sodium chloride was added, and the precipitate was filtered, washed, and dried. Vapor phase chromatography of the trifluoroacetate of this crude product and comparison with the trifluoroacetates of purified samples of both **12a** and **15a** indicated that these two esters were formed in a 52:1 ratio. The crude hydroxy ester **12a** was dissolved in 200 ml of acetic anhydride and refluxed for 1 hr. The excess reagent was decomposed by adding 200 ml of methanol and refluxing briefly, and the solution was then concentrated to dryness under reduced pressure. The residue was recrystallized from acetonitrile, affording 5.1 g (58%) of product, mp 143–145° (lit.[4c] mp 152°). The infrared spectrum exhibited carbonyl peaks at 1730 (3-OAc) and 1718 cm^{-1} (CO_2Me).

In one run, the intermediate **methyl 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylate (12a)** was isolated and recrystallized from acetonitrile, mp 174–176° (lit.[4c] mp 177°). The infrared spectrum exhibited a carbonyl peak at 1715 cm^{-1}, and the nmr spectrum had peaks at 0.78 (18-Me), 1.02 (19-Me), 1.17 (17β-Me), and 3.62 ppm (CO_2Me).

Methyl 3β-Hydroxy-17β-methyl-5α-androstane-17α-carboxylate (11c).—A solution of 0.27 g of methyl 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylate (**12a**) in 50 ml of acetic acid was treated with 0.1 g of 20% platinum on carbon and hydrogenated at 50 psi until 1 equiv of hydrogen was absorbed (*ca.* 6 min). The solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from aqueous methanol, affording 0.15 g (55%) of product, mp 163–165°. A sample was recrystallized for analysis from aqueous methanol, mp 165–167°, $[\alpha]^{24}D$ −41°.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 76.12; H, 10.14.

3β-Hydroxy-17β-methyl-5α-androstane-17α-carboxylic Acid (11d).—A similar hydrogenation of 0.70 g of 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylic acid (**12c**)[4c] was carried out. Hydrogen uptake was complete in *ca.* 1 hr. The crude material was recrystallized twice from aqueous methanol, affording 0.42 g (60%) of product, mp 284–285.5°, $[\alpha]^{25}D$ +4° (*c* 0.8, dioxane).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.18; H, 10.09.

3β-Acetoxy-17β-methyl-5α-androstane-17α-carboxylic Acid (11b).—The procedure used for the acetylation of 0.35 g of 3β-hydroxy-17β-methyl-5α-androstane-17α-carboxylic acid (**11d**)

was the same as that used for the preparation of **8b**. The crude material was recrystallized from acetonitrile, affording 0.23 g (58%) of product, mp 213–214.5°. A mixture melting point with the degradation product of N,N-dimethyl-3β-hydroxy-5α-pregn-20-en-17α-acetamide (**5a**) was not depressed, mp 212–213.5°.

N,N-Dimethyl-3β-acetoxy-17β-methylandrost-5-ene-17α-carboxamide (12e).—This amide was prepared from 2.0 g of 3β-acetoxy-17β-methylandrost-5-ene-17α-carboxylic acid (**12d**)[4c] by the same procedure as that used for the synthesis of **8f**. The initial product, which contained some 3β-hydroxy compound (by infrared), was recrystallized from aqueous methanol, affording 1.02 g (48%) of crude product, mp 148–153°. A sample was recrystallized for analysis from methanol, mp 159–161°.

Anal. Calcd for $C_{25}H_{39}NO_3$: C, 74.77; H, 9.79; N, 3.48. Found: C, 74.65; H, 9.86; N, 3.37.

N,N-Dimethyl-3β-acetoxy-17β-methyl-5α-androstane-17α-carboxamide (11e).—Similarly, 0.47 g of 3β-acetoxy-17β-methyl-5α-androstane-17α-carboxylic acid (**11b**) was converted into 0.31 g (62%) of purified product, mp 162–164° (MeOH–H_2O), $[\alpha]^{24}D$ +32° (MD 129°). The nmr spectrum exhibited peaks at 0.83 (18- and 19-Me groups), 1.36 (17β-Me), 2.00 (3β-OAc), and 4.7 ppm (3α-H).

Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.39; H, 10.20; N, 3.53.

N,N-Dimethyl-3β-hydroxy-17β-methyl-21-nor-5α,17α-pregnan-20-ylamine (9c).—A suspension of 0.32 g of lithium aluminum hydride in 36 ml of tetrahydrofuran was treated with a slurry of 0.35 g of aluminum chloride in 12 ml of toluene and stirred at room temperature for 30 min. A solution of 0.30 g of N,N-dimethyl-3β-acetoxy-17β-methyl-5α-androstane-17α-carboxamide (**11e**) in 12 ml of tetrahydrofuran was added and the mixture was stirred overnight at room temperature. The excess reagent was decomposed by the addition of 0.31 ml of water, 1.2 ml of 16% sodium hydroxide solution, and 0.72 ml of water. The solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from acetonitrile, affording 0.23 g (89%) of product, mp 139–140°, resolidifying and melting again at 159–160°. A mixture melting point with the degradation product of N,N-dimethyl-3β-hydroxy-5α-pregn-20-en-17α-acetamide (**5a**) was not depressed, mp 158.5–159°.

N,N-Dimethyl-3β-acetoxy-17β-methyl-5β-androstane-17α-carboxamide (13a).—A solution of 0.73 g of N,N-dimethyl-3β-acetoxy-17β-methylandrost-5-ene-17α-carboxamide (**12e**) in 75 ml of acetic acid was added to a prereduced suspension of 0.60 g of platinum oxide in 35 ml of acetic acid and hydrogenated at atmospheric pressure until 1 equiv of hydrogen was absorbed (*ca.* 20 hr). The solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from aqueous methanol and then acetonitrile, affording 0.26 g (36%) of product, mp 161–163°. A sample was recrystallized for analysis from acetonitrile, mp 164.5–166°, $[\alpha]^{25}D$ +44° (MD 178°). The ΔMD between **13a** and **11e** is 49° [calcd for (3β-OAc, 5β) − (3β-OAc, 5α) is 55°].[34] A mixture melting point of this amide and the 5α epimer **11e** was depressed, mp 138–154°.

Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.27; H, 10.28; N, 3.54.

The nmr spectrum exhibited peaks at 0.83 (18-Me), 0.97 (19-Me), 1.36 (17β-Me), 2.02 (3β-OAc), 3.0 (NMe_2), and a narrow ($W_{h/2}$ = 6 cps) hump at 5.1 ppm (3α-H). The mother liquors were evaporated to dryness, and the nmr spectrum of the residue exhibited peaks at 0.83 and 0.97 in a 73:27 ratio, at 1.36 (17β-Me), at 1.99 (5α, 3β-OAc) and 2.02 in 46:54 ratio, at 3.0 (NMe_2), and approximately equal peaks at 4.7 (wide hump, 5α,3α-H) and 5.1 ppm (narrow hump, 5β, 3α-H). Thus, the mother liquors were a 54:46 ratio of the reduced 5β and 5α epimers, and the hydrogenation therefore proceeded 72% 5β and 28% 5α.

3β-Acetoxy-17β-methyl-5β-androstane-17α-carboxylic Acid (13b).—A similar catalytic reduction of 1.2 g of 3β-hydroxy-17β-methylandrost-5-ene-17α-carboxylic acid (**12c**),[4c] followed by acetylation of the crude product with refluxing acetic anhydride, afforded, after recrystallization from acetonitrile, 0.47 g (35%) of **3β-acetoxy-17β-methyl-5α-androstane-17α-carboxylic acid (11b)**, mp 207–210°. The nmr spectrum of the residue obtained by concentration of the mother liquors exhibited approximately equal peaks at 2.03 (5β,3-OAc) and 2.00 (5α,3-OAc), and at 0.99 (5β,19-Me) and 0.84 ppm (5α,19-Me). This corresponds to an over-all 5:3 ratio of compound **11b** to compound **13b** formed by this reaction.

Methyl 3β-Acetoxy-17α-methylandrost-5-ene-17β-carboxylate (15b).—Following the procedure of Plattner, *et al.*,[20a] a solution of 5.0 g of 3β-acetoxy-17α-bromopregn-5-en-20-one (**16**) in 250 ml of methanol was treated with a solution of 11.25 g of potassium bicarbonate in 45 ml of water and refluxed for 3 hr. The cooled solution was concentrated under reduced pressure and poured into water. The precipitate was extracted with ether, and the ether solution was washed with water, dried, and concentrated to dryness. The residue was dissolved in 50 ml of acetic anhydride, and the solution was refluxed for 1 hr. Methanol (50 ml) was added to decompose the excess anhydride, and the solution was concentrated to dryness under reduced pressure. The residue was recrystallized from methanol, affording 2.83 g (64%) of product, mp 155–157° (lit.[20a] mp 163°). Concentration of the mother liquors afforded a second crop, 0.10 g (2%), mp 155–158°.

3β-Hydroxy-17α-methyl-5α-androstane-17β-carboxylic Acid (14a).—The procedure used for the hydrogenation of 0.50 g of 3β-hydroxy-17α-methylandrost-5-ene-17β-carboxylic acid (**15c**)[20a] was the same as that used for the preparation of **11c**. Hydrogen uptake was complete in 6 min. The crude material was recrystallized from methanol, affording 0.31 g (62%) of product, mp 232–234°. A sample was recrystallized for analysis from methanol, mp 234–236°, $[\alpha]^{25}D$ +8° (*c* 0.6, MeOH).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.15; H, 10.40.

N,N-Dimethyl-3β-acetoxy-17α-methylandrost-5-ene-17β-carboxamide (15e).—The amide was prepared from 2.70 g of 3β-acetoxy-17α-methylandrost-5-ene-17β-carboxylic acid (**15d**)[4a] by the same procedure used for the synthesis of **8f**. The crude material was recrystallized from methanol, affording 2.33 g (80%) of product, mp 195–196°, $[\alpha]^{25}D$ −120°.

Anal. Calcd for $C_{25}H_{39}NO_3$: C, 74.77; H, 9.79; N, 3.48. Found: C, 74.59; H, 9.81; N, 3.39.

N,N-Dimethyl-3β-acetoxy-17α-methyl-5α-androstane-17β-carboxamide (14b).—The procedure used for the hydrogenation of 2.33 g of N,N-dimethyl-3β-acetoxy-17α-methylandrost-5-ene-17β-carboxamide (**15e**) was the same as that used for the preparation of **11c**. Hydrogen uptake was complete in *ca.* 1.5 hr. The residue was recrystallized from aqueous methanol, affording 1.31 g (56%) of product, mp 163.5–165°. Concentration of the mother liquors yielded an additional 0.60 g (26%) of material, mp 160–163°. A sample was recrystallized for analysis from ethyl acetate–petroleum ether, mp 165–166°, $[\alpha]^{24}D$ −56°.

Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.21; H, 10.28; N, 3.43.

N,N-Dimethyl-3β-hydroxy-17α-methyl-21-nor-5α-pregnan-20-ylamine (14c).—The procedure for the reduction of 0.25 g of N,N-dimethyl-3β-acetoxy-17α-methyl-5α-androstane-17β-carboxamide (**14b**) was the same as that used for the reduction of **11e** to **9c**. The crude material was recrystallized from acetonitrile, affording 0.17 g (79%) of product, mp 142–144°. A sample was recrystallized for analysis for acetonitrile, mp 143–144°, $[\alpha]^{25}D$ −35°. A mixture melting point with the epimeric degradation product **9c** of N,N-dimethyl-3β-hydroxy-5α-pregn-20-en-17α-acetamide (**5a**) was depressed, mp 118–131°.

Anal. Calcd for $C_{23}H_{41}NO$: C, 79.47; H, 11.89; N, 4.03. Found: C, 79.62; H, 11.88; N, 4.05.

17α-Methyl-21-norpregn-5-ene-3β,20-diol (15f). A. From N,N-Dimethyl-3β-acetoxy-17α-methylandrost-5-ene-17β-carboxamide.—A solution of 0.40 g of **15e** in 100 ml of tetrahydrofuran was treated with 0.40 g of lithium aluminum hydride and stirred and refluxed for 4 hr. The excess reagent was decomposed with ethanol, and the mixture was poured into dilute hydrochloric acid. The product was extracted with ether, and the ether layer was washed with water, dried, and concentrated to dryness. The residue was recrystallized from methanol, affording 0.19 g (60%) of product, mp 186–187°, $[\alpha]^{25}D$ −87°. A second crop, 0.04 g (13%), mp 183.5–185°, was obtained by concentration of the mother liquors.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.96; H, 10.79.

B. From 3β-Acetoxy-17α-methylandrost-5-ene-17β-carboxylic Acid.—Similar treatment of 1.44 g of **15d** afforded 1.05 g (76%) of **15f**, mp 186–187°. A mixture melting point of the two samples was undepressed, mp 185–187°.

(34) C. W. Shoppee, "Chemistry of the Steroids," 2nd ed, Butterworth, Inc., Washington, D. C., 1964, pp 31–32.

Acknowledgment.—The authors wish to express their appreciation to Mr. C. E. Childs and the staff of our Microanalytical Laboratory, Dr. J. M. Vandenbelt and the staff of our Physical Chemistry Laboratory, and Mr. W. M. Pearlman of our High-Pressure Laboratory for their valuable technical assistance. The authors are deeply indebted to Dr. R. E. Ireland for many helpful discussions about this work.

Reduction of Aromatic Compounds with Alkali Metals in Neat Ammonia

LYNN H. SLAUGH AND JOHN H. RALEY

Shell Development Company, Emeryville, California 94608

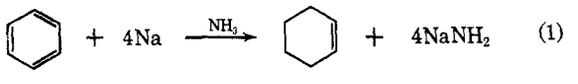
Received August 15, 1966

Benzene is reduced exclusively to cyclohexene by elemental sodium or potassium in neat, liquid ammonia at ~60–130° without the added acids (water, alcohols, etc.) required for the Birch reduction of benzene to cyclohexadiene. Lithium reduces benzene in neat ammonia predominantly to cyclohexadiene. Metal amides are the inorganic products obtained in high yield. Part of the metal reacts directly with the ammonia to form hydrogen and a metal amide. This side reaction is catalyzed by sodium amide and to a lesser degree by hydrogen. Alkyl-substituted benzenes also are reduced to the corresponding cyclohexenes by sodium in neat ammonia. The following orders of ease of reduction are indicated: benzene > toluene > ethylbenzene > *t*-butylbenzene and *p*-xylene > *m*-xylene > *o*-xylene. Biphenyl is reduced mainly to phenylcyclohexane. *p*-Terphenyl is reduced to 1,4-dicyclohexylbenzene and 1-phenyl-4-cyclohexylcyclohexane.

In 1937 Wooster discovered that monocyclic aromatic compounds are reduced mainly to cyclohexadienes by alkali and alkaline earth metals in refluxing ammonia (~−34°) containing a substance more acidic than the solvent.[1] Subsequently, Birch extended the scope of this reaction which now bears his name.[2–4] Birch reductions supposedly do not occur in the absence of the added acid (H_2O, ROH, NH_4Cl etc.). We would like to report the results of our investigation wherein metal reductions of aromatic hydrocarbons have been carried out at elevated temperatures (~60–130°) in neat, liquid ammonia without added acids. During the course of this investigation, a patent appeared which disclosed that benzene and toluene are reduced to cyclohexenes by alkali and alkaline earth metals in liquid ammonia containing less than a stoichiometric amount of or no added protic material.[5] Temperatures >0° were employed.

Results and Discussion

An efficiently stirred, stainless steel, Magnadrive autoclave was employed for all experiments. In contrast to the Birch reaction which produces mainly dienes, sodium in excess neat ammonia reduces benzene at ~60–130° exclusively to cyclohexene (eq 1). Cy-



(1)

clohexane, cyclohexadienes, or dimeric products could not be detected by glpc even when the reaction times were short and the conversions of benzene low. Upon distillation of the liquid products, high yields of white, powdery sodium amide were obtained as residues. The time required for complete consumption of 4 moles of sodium per mole of benzene in 28 moles of ammonia follows: >>24 hr at 60°, 4–8 hr at 100°, 1–3 hr at 125°, and ~0.8 hr at ~130°. Conversions of benzene as high as 43–45% were obtained. The ultimate conversion of benzene for a given quantity of sodium was not affected significantly by increasing the temperature from 100 to 130°.

Part of the metal reacted directly with the ammonia to produce hydrogen (eq 2). The hydrogen producing side reaction was found to be autocatalytic. Most of

$$2Na + 2NH_3 \longrightarrow 2NaNH_2 + H_2 \quad (2)$$

the cyclohexene formation occurs during the early stages of the reaction whereas the sodium–ammonia reaction (eq 2) is dominant thereafter. There are two obvious possibilities which might account for the autocatalytic effect. Sodium amide is known to promote its own formation from sodium and ammonia.[6] Also, the captive hydrogen being produced may unite with unconverted sodium metal to form sodium hydride which, in turn, would react readily with ammonia to form sodium amide and additional hydrogen (eq 3–5). As would be expected, the addition of either

$$2Na + H_2 \longrightarrow 2NaH \quad (3)$$

$$2NaH + 2NH_3 \longrightarrow 2NaNH_2 + 2H_2 \quad (4)$$

$$\text{net reaction: } 2Na + 2NH_3 \longrightarrow 2NaNH_2 + H_2 \quad (5)$$

extraneous sodium amide or hydrogen to the autoclave at the start of the reaction decreased the conversion of benzene to cyclohexene by promoting the side reaction of sodium with ammonia. The catalytic effect of sodium amide was more pronounced than that of hydrogen.

Relative reagent concentrations are important. With a given quantity of sodium, variations in the ammonia–benzene molar ratio from 28:1 to ~1:1 result in marked changes in the yield[7] of cyclohexene (Table I).

At 100°, if stirring is not applied, the time required for complete consumption of sodium varies erratically from 2 to 24 hr and the conversion of benzene varies from 13 to 60%. These observations indicate that the system may not be homogeneous.

(1) C. B. Wooster and K. L. Godfrey, *J. Am. Chem. Soc.*, **59**, 596 (1937); C. B. Wooster, U. S. Patent 2,182,242 (1939).
(2) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).
(3) A. J. Birch, *ibid.*, **12**, 17 (1958).
(4) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, Part 2, Interscience Publishers, Inc., New York, N. Y., 1963.
(5) M. Amagasa and T. Yamaguchi, French Patent 1,363,841 (May 4, 1964).
(6) R. Levin and W. C. Fernelius, *Chem. Rev.*, **54**, 449 (1959).
(7) Based on metal reacted, assuming the stoichiometry of eq 1.