Methyl *p*-Orsellinate (II). *p*-Orsellinic acid (5.05 g, 0.03 mole) was dissolved in 50 ml of ether. To the solution was added 1.68 g (0.04 mole) of diazomethane in ether.[22] The mixture was allowed to stand at room temperature for a period of 2 hr. Dilute acetic acid was added to decompose the excess diazomethane. The ether layer was separated and extracted with two 25-ml portions of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording a white solid. Recrystallization from hot water yielded a solid (3.5 g, 70%) identical in all respects with the ester obtained in 10% yield from the Fisher esterification of *p*-orsellinic acid, mp 96–98° (lit.[15] mp 97°).

Methyl 2-Formyl-*p*-orsellinate (V). Methyl *p*-orsellinate (5.0 g, 0.027 mole) and aluminum chloride (11.0 g, 0.082 mole) were dissolved in 200 ml of ether, with continuous stirring. The solution turned cloudy in 10 min. Zinc cyanide (5.0 g, 0.065 mole) was added, and gaseous hydrochloric acid was introduced into the stirred mixture for a period of 8 hr. Water (100 ml) was added, and the mixture was heated on a steam bath for 1.5 hr. On cooling, a solid (4.7 g, 94%) precipitated and was removed by filtration. Recrystallization from hot water afforded white crystals, mp 146–148° dec.

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.15; H, 4.76. Found: C, 57.47; H, 4.98.

Orcylaldehyde [4,6-dihydroxy-2-methylbenzaldehyde (VI)] was prepared according to the method of Adams and Levine, mp 179–181° (lit.[23] mp 178–180°).

(22) H. A. Blatt, Ed., "Organic Synthesis," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1955, p 165.

***o*-Orsellinic acid (VII)** was prepared from orcylaldehyde (VI) by a reaction sequence developed by Hoesch,[24] mp 194–196° (effervescence) [lit.[25] mp 176° (effervescence)].

Methyl *o*-orsellinate (VIII) was prepared in the same manner as methyl *p*-orsellinate (II), mp 138–140° (lit.[26] mp 140°).

2-Nitroorcinol [3,5-dihydroxy-2-nitrotoluene (IV)] and 4-nitroorcinol [3,5-dihydroxy-4-nitrotoluene (IX)] were prepared by nitration of orcinol according to the method of Henrich and Meyer: for IV, mp 119–121° (lit.[27] mp 122°); for IX, mp 126–127° (lit.[27] mp 127°).

Methyl 3,5-dihydroxy-2-formylbenzoate (XI) was prepared from the methyl ester of 3,5-dihydroxybenzoic acid (X) according to the method of Birkinshaw and Bracken, mp 164–165° (lit.[28] mp 163.5°).

Acknowledgments. We are grateful to Professor Robert Barker for making the nmr spectrometer in the biochemistry department available for our use. We wish to thank the referee for helpful suggestions.

(23) R. Adams and I. Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923).
(24) K. Hoesch, *Ber.*, **46**, 886 (1913).
(25) O. Hesse, *Ann.*, **139**, 22 (1866).
(26) J. Herzig, F. Wenzel, and P. Kurzweil, *Monatsh.*, **24**, 898 (1903).
(27) F. Henrich and W. Meyer, *Ber.*, **36**, 885 (1903).
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An Ionic Aromatization of Steroidal Dienones

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Abstract: Treatment of a 9α,11β-dichloro or 9α,11β-halohydrin steroid in refluxing dimethylformamide or refluxing pyridine afforded a ring AB aromatic compound. It was further shown that the C-19 methyl group was expelled as the appropriate methyl halide. A mechanism, based on these facts, is discussed.

The preparation of a steroidal ring AB aromatic compound from simpler aromatic or nonaromatic systems has been of interest principally to provide "equilenin"-type compounds. Apart from total synthetic methods,[1] most of the published procedures depended upon (a) dehydrogenation of a suitable ring A[2-4] or ring B[3] aromatic precursor, (b) dehydrogenation of a Δ^6-ring A aromatic system,[5] (c) dehydrogenation of a $\Delta^{3,5}$-19-nor system,[6] and (d) acid elimination of an allylic hydroxyl group in a suitably unsaturated system.[7] Ionic processes that provide aromatization with concomitant expulsion of the C-19 methyl group have generally been applied to prepare ring A aromatic compounds only.[8] This paper is concerned with the preparation of ring AB aromatic steroids from nonaromatic intermediates by a new ionic method[9] with elimination of the C-19 methyl group. The method, moreover, may be generalized so that the preparation of ring AB aromatic steroids with a variety of substituents may be devised.

The method may be illustrated by the following experiment. 21-Acetoxy-9α,11β-dichloro-17α-hydroxypregna-1,4-diene-3,20-dione (Ia)[10] was refluxed in DMF for 30 min to produce at least three products as indicated by thin layer chromatography. One of the products was not in sufficient quantity to be isolated. A second product had the ultraviolet[11] and infrared spectra characteristic of a ring AB aromatic system and was assigned the structure 21-acetoxy-3,17α-dihydroxy-19-

(1) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 481.
(2) A. Butenandt, A. Wolff, and P. Karlson, *Chem. Ber.*, **74**, 1308 (1941).
(3) W. E. Bachmann and A. S. Dreiding, *J. Am. Chem. Soc.*, **72**, 1323 (1950).
(4) A. S. Dreiding and W. J. Pummer, *ibid.*, **75**, 3162 (1953).
(5) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *ibid.*, **72**, 4531 (1950).
(6) M. Uskokovic and M. Gut, *J. Org. Chem.*, **22**, 996 (1957).
(7) R. P. A. Sneeden and R. B. Turner, *J. Am. Chem. Soc.*, **77**, 130 (1955); Ch. Tamm, G. Volpp, and G. Baumgartner, *Helv. Chim. Acta*, **40**, 1469 (1957).
(8) J. H. Fried and A. N. Nutile, *J. Org. Chem.*, **27**, 914 (1962); K. Tsuda, E. Ohki, and S. Nozoe, *ibid.*, **28**, 783 (1963); H. L. Dryden, Jr., G. M. Webber, and J. J. Wieczorek, *J. Am. Chem. Soc.*, **86**, 742 (1964).
(9) Some of these results were announced in a preliminary communication by M. Heller, R. H. Lenhard, and S. Bernstein, *ibid.*, **86**, 2309 (1964).
(10) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. Gould, *ibid.*, **81**, 2191 (1959).
(11) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

norpregna-1,3,5(10),6,8-pentaen-20-one (IIa). A proton nuclear magnetic resonance (nmr) spectrum in deuteriochloroform of the 3,21-diacetoxypregnapentaene derivative (IIb) indicated the presence of the C-18 methyl group (0.58 ppm) and the two methyl groupings associated with the acetate functions (2.21 and 2.39 ppm), but no other methyl groups aromatic or otherwise, showing the complete loss of the C-19 methyl group in the reaction.

Complete confirmation of the nature of the ring system was achieved by the following series of transformations. Mild saponification of the 21-acetoxypregnapentaene IIa yielded 3,17α-21-trihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIc) which was degraded to equilenin (III) by heating in methanol with dimethylamine.[12,15] In a similar manner, refluxing of 9α,11β-dichloroandrosta-1,4-diene-3,17-dione (IV)[10] in dimethylformamide afforded equilenin (III). Thus, the proposed ring structure was established unequivocally.

The third product isolated from heating Ia in dimethylformamide, according to its elemental analysis and infrared and ultraviolet absorption spectra [λ_{max}^{MeOH} 241 mμ (ϵ 19,100)], appeared to be an unsaturated derivative of 21-acetoxy-17α-hydroxypregna-1,4-diene-3,20-dione. Mass spectrometry further established that the molecular weight was 382 (actually the largest mass ion was 322, caused by the facile loss of acetic acid).[18] The nmr spectrum disclosed only one additional vinyl hydrogen at 5.72 ppm besides those represented by the $\Delta^{1,4}$ double bonds. These combined data suggested a diunsaturated derivative of the compound mentioned above, one of the new double bonds being ditertiary while the other must be a tertiary–secondary double bond. The most reasonable structure for the new compound would be 21-acetoxy-17α-hydroxypregna-1,4,8-(14),9(11)-tetraene-3,20-dione (V). The intensity and asymmetry of the peak in the ultraviolet absorption spectrum supports such a combined chromophoric system when one considers the low values reported for the $\Delta^{8(14),9(11)}$ conjugated system.[19] Further evidence was obtained for the structure of V[20] by its reaction with maleic anhydride to form the adduct VI. This confirmed the presence of a cisoid diene form in the molecule. For the purposes of the later discussion on mechanism, it should be emphasized here that the tetraene V is a stable product of the reaction and cannot be converted to the aromatic compound by prolonged treatment in dimethylformamide.

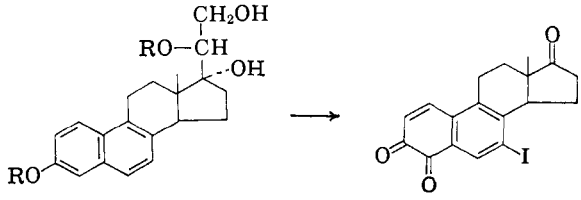
Further investigation of this aromatization reaction revealed that some variation of the substituents[23] at the

(12) This procedure was suggested by the work of Dr. J. J. Brown of these laboratories. It is presumably analogous to previously reported[13,14] alkaline degradations of the cortical side chain.

(13) H. L. Mason, *Proc. Staff Meetings Mayo Clinic*, **13**, 235 (1938).

(14) N. L. Wendler and R. P. Graber, *Chem. Ind.* (London), 1549 (1956).

(15) An attempt was made to degrade the side chain of IIc by the more usual method of treating IIc with sodium borohydride to form the crude tetrol i, further characterized as the triacetate ii, which was in turn treated with periodic acid. Unexpectedly, a compound (iii) was formed whose infrared and ultraviolet absorption spectra were very reminiscent of the simple β-naphthoquinone analog of equilenin.[16] Elemental analysis and an analysis of the nmr spectrum ($CDCl_3$) indicated that the structure was most likely 7-iodoestra-1,5(10),6,8-tetraene-3,4,17-trione. The nmr spectrum showed only three aromatic protons, suggesting that the iodine atom occupied one of the aromatic positions. Two of the aromatic protons were coupled to give two doublets, one centering at 7.29 ppm and another at 7.91 ppm (J = 9 cps). The third aromatic proton was at 8.51 ppm. The latter figure would be quite reasonable for a C-6 aromatic proton *peri* to a carbonyl group at C-4 which is further under the influence of an *ortho* iodo group.[17] No other formulation would be expected to satisfy the nmr spectrum so well. For example, if the iodo group were at C-1 or C-2, the coupled protons would be those at C-6 and C-7. Neither an aromatic proton at C-2 nor at C-1 under these formulations could satisfactorily explain the 8.51-ppm signal.



i, R = H
ii, R = Ac

iii

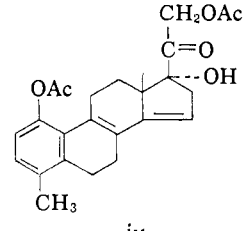
(16) H-J. Teuber, *Chem. Ber.*, 86, 1495 (1953).

(17) Private communications from R. B. Conrow and G. O. Morton of these laboratories.

(18) The mass spectrum was obtained on a CEC 21-103A spectrometer by T. Mead of the Central Research Laboratories, American Cyanamid Co., Stamford, Conn.

(19) (a) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957); (b) N. L. Wendler, R. P. Graber, C. S. Snoddy, Jr., and F. W. Bollinger, *ibid.*, **79**, 4476 (1957).

(20) Treatment of the tetraene V with anhydrous hydrogen chloride in methylene chloride at 0° followed by acetylation (the intermediate free hydroxyl compound was extremely unstable) afforded a new compound assigned the structure 1,21-diacetoxy-17α-hydroxy-4-methyl-19-norpregna-1,3,5(10),8,14-pentaen-20-one (iv). It has already been well established that the $\Delta^{8(14),9(11)}$ chromophore rearranges to a $\Delta^{8,14}$ system in acid,[19b] but it was unexpected that a dienone–phenol rearrangement would occur under these mild conditions.[21] The assignment of the structure of iv was based on the nmr spectrum ($CDCl_3$): a pair of doublets centering at 6.88 and 7.13 ppm (J = 8 cps) for the C-2 and C-3 vinyl hydrogens, 5.76 ppm for the C-15 hydrogen, 2.30 ppm for the aromatic methyl group; and the ultraviolet absorption spectrum with maxima at 222, 238, 246, 292, 304, and 319 mμ. It is of interest to note especially the clear triplet of peaks at 292 mμ (ϵ 21,800), 304 mμ (ϵ 25,700), and 319 mμ (ϵ 18,000) since the previous reports for a $\Delta^{1,3,5(10),8,14}$ system indicate only one peak somewhere between 307 and 313 mμ (the location depending upon the nature of the substituent in ring A) at an intensity value of 28,000–35,000.[22] Possibly the difference of substitution in ring A may be responsible for this effect.

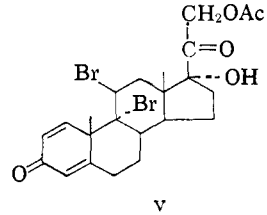


iv

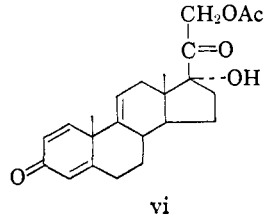
(21) It is interesting to speculate that the relative ease of this rearrangement may be under the influence of the $\Delta^{8(9)}$ double bond which may help in the attack at an electron-deficient center; *e.g.*, H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Am. Chem. Soc.*, **82**, 4099 (1960); W. Herz and G. Caple, *J. Org. Chem.*, **29**, 1691 (1964).

(22) S. N. Ananchenko, V. Ye. Limanov, V. N. Leonov, V. N. Rzheznikov, and I. V. Torgov, *Tetrahedron*, **18**, 1355 (1962); D. J. Crispin and J. S. Whitehurst, *Proc. Chem. Soc.*, 356 (1962); G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).

(23) It had been noted[10] previously that 21-acetoxy-9α,11β-dibromo-17α-hydroxypregna-1,4-diene-3,20-dione (v) was unstable upon standing at room temperature in the solid state and that hydrogen bromide was an elimination product. Consideration of our results with the 9α,11β-dichloro analog Ia provoked our interest to investigate the stability of v. Upon allowing v to stand for 2 months, the solid turned dark brown and a loss of weight amounting to approximately two-thirds of the equivalent weight of bromine occurred, although it could not be verified that hydrogen bromide was given off. The nature of all the products is not known due to difficulties in purification, but the major product was certainly the $\Delta^{1,4,9(11)}$ triene vi.[24] When the dibromo compound v



v

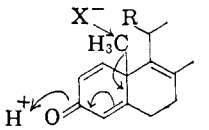


vi

9,11 positions was permissible. For instance, 9α-bromoprednisolone acetate (Ib),[25] when refluxed for 0.5 hr in dimethylformamide, gave after acetylation the previously described 19-norpregnapentaene IIa and the $\Delta^{1,4,8(14),9,(11)}$-tetraene V in the same approximate yields as in the reaction from the dichloro compound Ia. Furthermore, 21-acetoxy-9α-chloro-11β-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione (VIIa)[26] aromatized in refluxing dimethylformamide to afford after acetylation 3,21-diacetoxy-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (VIIIa).[28] This reaction, however, required much more time for completion, approximately 22 hr. Treatment of 21-acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione (VIIb)[29] in refluxing dimethylformamide for 67 hr returned only starting material after the usual work-up. It should be pointed out that the elaborate side chain of the compounds just discussed does not affect the kinetics of the reaction since 9α,11β-dichloro-16α,17α-isopropylidenedioxy-21-methanesulfonyloxypregna-1,4-diene-3,20-dione (IX)[31] and lithium chloride in refluxing dimethylformamide for 0.5 hr, followed by acetylation, afforded 3-acetoxy-21-chloro-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (VIIIb) in approximately 55% yield.

In order to gain some insight into the mechanism involved in the aromatization reaction, the 9α,11β-dichloro compound Ia was refluxed in several appropriate solvents to reflect a difference in polarity, namely, xylene, cyclohexanol, *n*-butyl alcohol, and pyridine. The aromatization reaction occurred only in pyridine, giving essentially the same mixture of products, but the reaction had to be conducted over longer periods of time (approximately 6–20 hr) in order to complete the preparation.

Vapor phase chromatography of the gaseous products evolved in the heating of the dichloro compound Ia or the bromohydrin Ib in dimethylformamide revealed the form of the elimination of the C-19 methyl group. In the former reaction, methyl chloride was evolved, whereas in the latter, methyl bromide was eliminated. These experiments implied a type of reaction mechanism as shown in A whereby the halide ion produced by



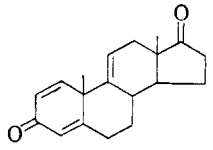
A

elimination at C-9 (*vide infra*) would attack the C-19 methyl grouping, while the "electron shift" to form the aromatic product would be aided by a proton (or equivalent cation) attracting electrons at the C-3 oxygen atom. This scheme, or course, makes understandable why a weakly basic solvent such as dimethylformamide or pyridine is most suitable for the reaction, since, in effect, it must perform a dehydrohalogenation while still permitting halide ion and a cation to work at different parts of the molecule.[33] It is obvious that the resultant Δ^8-C-11 system can provide the unsaturation necessary to produce a ring AB aromatic compound under the reaction conditions.

The above structure A suggested several experiments as a test. For instance, 21-acetoxy-11β,17α-dihydroxy-

was allowed to stand in solution in pyridine (*vide infra*) for 45 hr at room temperature, an excellent yield of vi resulted. The dibromo compound v was also heated at steam-bath temperature in a solution of dimethylformamide for 0.5 hr. Again vi was the main product, albeit in poorer yield. The mechanism of these reactions is not understood at present.

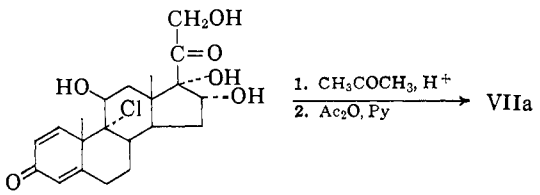
(24) It is of interest to note that a mass spectrum[18] of the 9α,11β-dichloro compound IV gave a molecular ion at *m/e* 282 corresponding to androsta-1,4,9(11)-triene-3,17-dione (vii). There was no indication of a further breakdown to an equilenin structure.



vii

(25) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *J. Am. Chem. Soc.*, 77, 4181 (1955).

(26) Compound VIIa was prepared by acetonide formation of the 9α-chloro analog of triamcinolone (viii)[27] followed by acetylation, mp 255.5–257°; λ_{max} 238–239 mμ (ε 14,500); $[\alpha]^{25}D$ +119° (chloroform); ν_{max} 3425, 1754, 1733, 1667, 1612, 1227, and 856 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}O_7Cl$: C, 63.64; H, 6.75; Cl, 7.19. Found: C, 63.94; H, 7.01; Cl, 7.66.

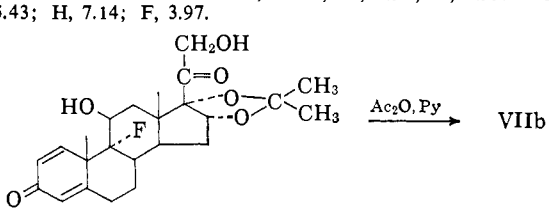


viii

(27) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, 81, 1689 (1959).

(28) It is interesting to note that the compounds with acetonide substituents usually gave somewhat better yields of aromatic products. Part of the explanation may be that very little (or no) $\Delta^{1,4,8(14),9(11)}$ compounds were formed by these derivatives.

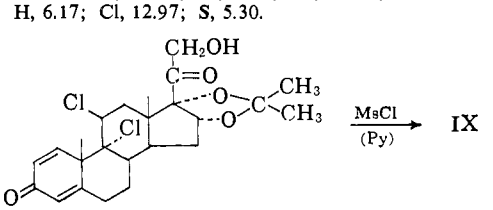
(29) Compound VIIb was prepared by acetylation of the free 11β,21-diol ix,[27,30] mp 257–262.5°; λ_{max} 238 mμ (ε 15,200); $[\alpha]^{25}D$ +98° (chloroform); ν_{max} 3420, 1755, 1732, 1668, 1617, 1232, and 858 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}O_7F$: C, 65.53; H, 6.98; F, 3.99. Found: C, 65.43; H, 7.14; F, 3.97.



ix

(30) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, 80, 2338 (1958).

(31) Compound IX was prepared by treatment of 9α,11β-dichloro-21-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione (x)[32] with methanesulfonyl chloride in pyridine at −5°, mp 234–236° dec; λ_{max} 236 mμ (ε 15,100), 268 mμ (I); $[\alpha]^{25}D$ +159° (chloroform); ν_{max} 1750, 1680, 1644, 1622, 1365, 1180, and 858 cm^{-1}. *Anal.* Calcd for $C_{25}H_{32}O_7Cl_2S$: C, 54.84; H, 5.89; Cl, 12.95; S, 5.86. Found: C, 55.53; H, 6.17; Cl, 12.97; S, 5.30.



x

(32) M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, 1, 331 (1963).

(33) It is important to note[34] that compound Ia when heated in dimethylacetamide in the presence of calcium carbonate gave no reaction.

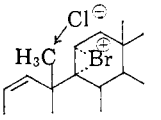
(34) T. R. Carrington, S. Eardley, J. Elks, G. F. H. Green, G. I. Gregory, A. G. Long, and J. C. P. Sly, *J. Chem. Soc.*, 4560 (1961).

pregna-1,4,8-triene-3,20-dione (X),[35] though unaltered by refluxing in dimethylformamide up to 4 hr, aromatized in the usual way to give IIa when refluxed in dimethylformamide containing lithium chloride and a drop of hydrochloric acid for 0.5 hr. Similarly, treatment of 21-chloro-16α,17α-isopropylidenedioxypregna-1,4,6,9(11)-tetraene-3,20-dione (XI)[36] in refluxing dimethylformamide with lithium chloride and hydrochloric acid afforded after acetylation the previously mentioned 21-chloro aromatic compound VIIIb. It should be noted that the latter reaction did not occur without the addition of hydrochloric acid. Both of these aromatization reactions and the conditions investigated support the type of mechanism suggested in A.

Furthermore, on the surface A does not preclude the formation of simple ring A aromatic compounds. In fact, treatment of compounds such as 21-acetoxy-17α-hydroxypregna-1,4,9(11)-triene-3,20-dione (XIIa), 21-acetoxy-17α-hydroxypregna-1,4,6-triene-3,20-dione (XIIb), and triamcinolone diacetate (XIII) in refluxing dimethylformamide with lithium chloride and hydrochloric acid gave no reaction. Obviously, the proper transition state cannot be achieved unless two double bonds or an incipient two double bonds are distributed over rings B and C. Two double bonds in ring C only, as in the $\Delta^{1,4,8(14),9(11)}$-tetraene V, are insufficient to provide an aromatic product.

Although it is quite clear that the halide ion performing the nucleophilic attack on the C-19 angular methyl group according to A would be that originally at C-9 in the halohydrins, the origin of the halide ion performing this function when a 9α,11β-dichloro compound is the substrate is not clear. In order to investigate this problem more definitively, the following experiment was performed.

Treatment of 21-acetoxy-9α-bromo-11β-chloro-17α-hydroxypregna-1,4-diene-3,20-dione (Ic)[10] in refluxing dimethylformamide afforded, by sweeping the reaction mixture out with nitrogen, a mixture of methyl chloride and methyl bromide separated by vapor phase chromatography, which indicated approximately twice the quantity of methyl chloride formed over the quantity of methyl bromide. This, of course, suggests that the halide ion attacking the C-19 methyl group is not only that produced by simple dehalogenation at C-9. Furthermore, the gas evolved by the treatment of 21-acetoxy-11β,17α-dihydroxypregna-1,4,8-triene-3,20-dione (X)[35] with an equimolar mixture of hydrochloric and hydrobromic acid in acetone at room temperature (*vide infra*) proved to be exclusively methyl bromide by vpc (in fact, methyl bromide was the only product even with an overwhelming excess of hydrochloric acid). The same experiment done in dimethylformamide as a solvent gave a mixture of methyl bromide and methyl chloride, with the methyl bromide predominating by a factor of three or four to one. It is evident that in these dipolar aprotic solvents[37] the bromide ion may be considered a better nucleophile than the chloride ion. Therefore, the preferential formation of methyl chloride during the aromatization of Ic is not dependent on the preferential elimination of halide ion from the C-9 position nor on the preferential nucleophilicity of the halide ions in the solution. One rationalization would be for the *trans*-diaxial bromochloro Ic to ionize to the cyclic bromonium ion B (the presumed intermediate in the formation of Ic)[38] which would provide the chloride ion in a preferential manner for attack on the C-19 methyl group.



B

The best procedure found both quantitatively and as to mildness of conditions for aromatization has been alluded to in the preceding paragraph. Treatment of the 1,4,8-triene X[35] in acetone with hydrochloric acid at room temperature provided the aromatic product IIa in approximately 70% yield. Thin layer chromatography revealed that the reaction was essentially complete upon solution (*ca.* 10–20 min). These are unusually mild conditions for cleavage of a carbon–carbon bond of this nature. A small amount (*ca.* 15%) of the tetraene V was also obtained in the reaction.

It was further discovered that, when the above reaction was carried out at 0°, the principal product was 21-acetoxy-17α-hydroxypregna-1,4,7,9(11)-tetraene-3,20-dione (XIV), the structure of which was confirmed by ultraviolet absorption and nmr spectra. An attempt to prepare XIV by treatment of X in pyridine with methanesulfonyl chloride, in analogy to the reaction in the $\Delta^{4,8}$-3-one series,[19b] gave only a mixture of XIV and the $\Delta^{1,4,9(11)}$-trien-3-one XIIa. The origin of the triene XIIa is obscure at present. Unfortunately, the mixture could not be resolved to give pure tetraene XIV, but the ultraviolet absorption and nmr spectra of mother liquors confirmed its presence. Treatment of this impure XIV with hydrochloric acid in acetone at room temperature again gave the aromatic compound IIa.

A few qualitative studies of the aromatization reaction were attempted utilizing the formation of the equilenin ultraviolet absorption spectrum as a guide. Thus, it was demonstrated that the reaction (actually acid treatment of the Δ^{8}-11β-ol X[35]) was much faster in a dipolar aprotic solvent, such as acetonitrile, than in methanol. This might have been inferred from Parker's discussions.[37] It was also noticed that in methanol there seemed to be some indication of a more highly conjugated nonaromatic chromophoric system first formed in solution. There was also a transient yellow formation which may be associated with this chromophore ($\Delta^{1,4,6,8}$-3-one?).[39] It must be emphasized that this system has not been isolated. Also, the reaction seemed to be occurring even with the use of perchloric acid. The reaction time in this case was quite slow (after 0.5 hr a good spectrum of a $\Delta^{1,4,7,9(11)}$ chromophore was obtained), but the proper ultraviolet absorption spectrum was certainly suggested. Unfortunately, it was not

(35) M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, 7, 381 (1966).
(36) M. Heller, R. H. Lenhard, and S. Bernstein, *ibid.*, 5, 615 (1965).
(37) An instructive discussion of the properties of anions in dipolar aprotic solvents may be obtained in A. J. Parker, *Quart. Rev.* (London), 16, 163 (1962).
(38) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, 72, 1066 (1950); C. A. Grob and S. Winstein, *Helv. Chim. Acta*, 35, 782 (1952); G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).
(39) A further discussion of this chromphore is in M. Heller, R. H. Lenhard, and S. Bernstein, *J. Am. Chem. Soc.*, 89, 1919 (1967).

possible to identify the moiety which contained the leaving C-19 methyl group in this case.

Treatment of 21-acetoxy-6β-bromo-7α,17α-dihydroxypregna-1,4-diene-3,20-dione (XV)[40] in refluxing dimethylformamide gave only starting material upon the usual work-up. It might still be interesting to investigate more strenuous methods of dehydrohalogenating this type of compound in order to see if that type of intermediate would lead to aromatization.

It was of interest to consider what might happen to a simple 9α,11β-dichloro-Δ⁴-3-one in refluxing dimethylformamide. Accordingly, 21-acetoxy-9α,11β-dichloro-17α-hydroxypregn-4-ene-3,20-dione (XVI) was prepared in the usual manner[10] and refluxed in dimethylformamide. Preparative thin layer chromatography was employed to isolate two major products which are in too small a quantity to bring to absolute purity. The less polar product was assigned the known structure 21-acetoxy-17α-hydroxypregna-4,8,14-triene-3,20-dione (XVII)[19b] and the more polar product was assigned the structure 21-acetoxy-17α-hydroxypregna-4,6,8-triene-3,20-dione (XVIII).[19a]

The formation of these compounds may be easily rationalized when it is recalled that treatment of a 9α,11β-dichloro-5α-pregnane with dimethylacetamide at 95° in the presence of base is reported to give a mixture of $\Delta^{8(14),9(11)}$-diene and $\Delta^{7,9(11)}$-diene.[34] It need only be remembered that under acidic conditions a $\Delta^{8(14),9(11)}$-diene will rearrange into a $\Delta^{8,14}$-diene as mentioned previously and that a $\Delta^{4,7,9(11)}$-triene will rearrange into a $\Delta^{4,6,8}$-triene.[19a]

Experimental Section[42]

21-Acetoxy-3,17α-dihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIa) and 21-Acetoxy-17α-hydroxypregna-1,4,8(14),-9(11)-tetraene-3,20-dione (V). A. From 9α,11β-Dichloro Ia in Dimethylformamide. A solution of 21-acetoxy-9α,11β-dichloro-17α-hydroxypregna-1,4-diene-3,20-dione (Ia, 1.01 g)[10] and lithium chloride[43] (0.285 g) in dimethylformamide was refluxed 0.5 hr. The yellow solution was evaporated under reduced pressure to near dryness; water was added, and the resultant gum was scratched until it became an amorphous powder (0.82 g), mp 115–175°. Treatment with warm ether followed by filtration gave the crude tetraene V (0.292 g), mp 205–220°. Several crystallizations from acetone–hexane afforded 0.126 g, mp 241–246°; λ_{max} 241 mμ (ε 19,100); nmr, 5.72 (11 H), 6.25 (4 H), 6.38 (2 H, doublet, J = 10 cps), and 7.42 (1 H, doublet, J = 10 cps) ppm (deuteriochloroform).

Anal. Calcd for $C_{23}H_{26}O_5$ (382.44): C, 72.23; H, 6.85. Found: C, 72.05; H, 7.12.

The initial ether filtrate was evaporated to a glass; methanol was added, and the resultant crystalline solid was filtered and washed with methanol to afford IIa (0.207 g), mp 196.5–198.5°. One additional crystallization from acetone–hexane did not appreciably alter the melting point, 197–199°; λ_{max} 230 mμ (ε 66,000), 270 (4780), 280 (5520), 292 (3980), 327 (2280), and 341 (2650); $[\alpha]^{25}D$ +116° (acetone); ν_{max} 3350, 1722 (shoulder), 1710, 1625, 1600, 1573, and 1227 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}O_5$ (368.41): C, 71.72; H, 6.57. Found: C, 71.87; H, 6.60.

B. From 9α,11β-Dichloro Ia in Pyridine. A solution of Ia (1.0 g) in pyridine (50 ml) was heated under reflux for 22.5 hr. The reaction mixture was evaporated *in vacuo* to a glass which was dissolved in a small amount of acetone. The addition of a large volume of water together with scratching with a glass rod precipitated 0.77 g of solid, mp 160–209°. Treatment with warm ether followed by filtration gave V (0.38 g), mp 229–244°; λ_{max} 235–238 mμ (ε 19,100). One crystallization from acetone–hexane and two crystallizations from acetone afforded the analytical sample (0.21 g), mp 249–252°; λ_{max} mμ (ε 18,900); ν_{max} 3320, 1755, 1739, 1664, 1620, and 1230 cm^{-1}; $[\alpha]^{25}D$ + 220° (chloroform).

Anal. Found: C, 71.74; H, 6.95.

The initial ether filtrate was evaporated to a glass; λ_{max} 229 mμ (ε 52,900) (principal peak), indicating a purity of approximately 80%. Crystallization of the residue from methanol gave IIa (0.24 g), mp 193–196° which on recrystallization was raised to 197–199°. The infrared spectrum was identical with that described above.

C. From 1,4,8-Triene X in Dimethylformamide. A solution of 21-acetoxy-11β,17α-dihydroxypregna-1,4,8-triene-3,20-dione (X, 0.30 g) and lithium chloride (0.10 g) in dimethylformamide (15 ml) and concentrated hydrochloric acid (one drop) was heated under reflux for 0.5 hr. The reaction mixture was evaporated under reduced pressure to an oil. Water was added and the resultant viscous oil was worked with a glass rod to afford a pale yellow solid (243 mg); λ_{max} ($E^{1\%}_{1cm}$) 231 mμ (823) (principle peak). The solid was triturated with warm ether (*ca.* 25 ml) and the insoluble portion (113 mg, mp 218–227°) was removed by filtration. Recrystallization from acetone–hexane gave the tetraene V (105 mg, mp 223–231°) as indicated by infrared analysis and thin layer chromatography; λ_{max} 242.5 mμ (ε 17,400).

The initial ether filtrate was evaporated and the residue was crystallized from methanol to afford IIa (46 mg, mp 192.5–195°) as indicated by infrared analysis and thin layer chromatography.

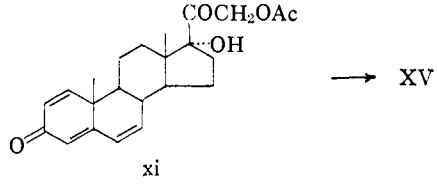
D. From 1,4,8-Triene X in Acetone. A mixture of 21-acetoxy-11β,17α-dihydroxypregna-1,4,8-triene-3,20-dione (X, 1.0 g), concentrated hydrochloric acid (0.25 ml), and acetone (10 ml) was stirred 10 min at room temperature whereupon complete solution occurred. The solution was allowed to stand at room temperature for 1 hr. Thin layer chromatography indicated that the reaction was essentially over at the time of complete solution. Water was added and the solid collected (0.936 g) had mp 167.5–168.5°. One crystallization from methanol gave IIa (0.559 g), mp 197.5–199.5°; λ_{max} 229.5 mμ (ε 62,000) (principal peak).

The mother liquor was evaporated to a solid which was acetylated for 18 hr in pyridine (4 ml) and acetic anhydride (2 ml). Addition of water gave solid plus oil, which were collected and triturated with ether. After filtration, the residue (0.168 g) was crystallized from acetone–hexane to give 21-acetoxy-17α-hydroxypregna-1,4,8(14),-9(11)-tetraene-3,20-dione (V, 0.145 g), mp 238–244°; λ_{max} 241 mμ (ε 18,900). The ether was removed from the filtrate and this residue (0.17 g) was crystallized from acetone–hexane to give 3,21-diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIb, 0.071 g), mp 183.5–186.5°; λ_{max} 231 mμ (ε 76,500) (principal peak).

E. From 1,4,7,9(11)-Tetraene XIV. A crude sample of 21-acetoxy-17α-hydroxypregna-1,4,7,9(11)-tetraene-3,20-dione (XIV, 0.033 g) and concentrated hydrochloric acid (one drop) was allowed to stand in acetone (1.0 ml) at room temperature for 0.5 hr. Addition of water gave a precipitate which was collected, affording a very impure solid (0.024 g). This was placed on a thin-layer preparative plate (silica gel, 20 × 20 cm × 0.5 mm) and developed for 3 hr in the system benzene–acetone–water (2:1:2) (upper phase).

Elution of the least polar zone gave an oil which crystallized upon the addition of a few drops of methanol to give IIa (0.013 g), mp 190–194°. The infrared spectrum of this sample was identical with that of the previously prepared material. A less polar zone upon

(40) Compound XV was prepared by N-bromoacetamide–perchloric acid treatment of 21-acetoxy-17α-hydroxypregna-1,4,6-triene-3,20-dione (xi).[41] The work-up necessitated separation on a preparative thin-layer chromatographic plate, mp 216–218°; λ_{max}^{MeOH} 245 mμ (ε 16,000); $[\alpha]^{25}D$ +20° (pyridine). *Anal.* Calcd for $C_{23}H_{29}O_5Br$: C, 57.38; H, 6.07; Br, 16.60. Found: C, 58.04; H, 6.26; Br, 16.63.

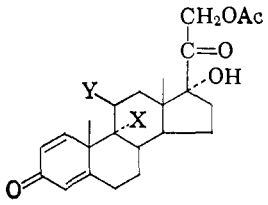


xi

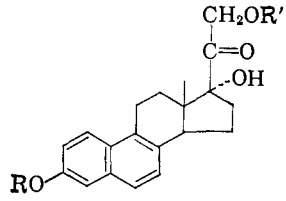
(41) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, 82, 4293 (1960).

(42) All melting points are uncorrected. The infrared spectra, which were determined in a potassium bromide disk, and nmr spectra all corroborated the proposed structures. The ultraviolet absorption spectra were done in methanol. The analyses were carried out by Louis M. Brancone and associates. The infrared, ultraviolet absorption, nmr (Varian A-60 spectrometer, tetramethylsilane internal reference), and optical rotational data were supplied by William Fulmor and associates. The vapor-phase chromatography was done by Charles C. Pidacks and W. Muller.

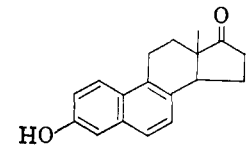
(43) The addition of lithium chloride was, at first, thought to be necessary for the aromatization. Deletion of the lithium chloride gives essentially the same results.



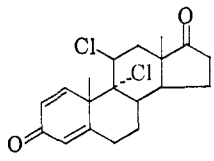
Ia, X = Y = Cl
b, X = Br; Y = OH
c, X = Br; Y = Cl



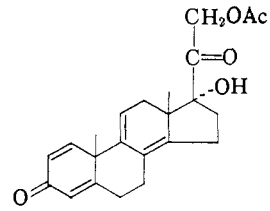
IIa, R = H; R′ = Ac
b, R = R′ = Ac
c, R = R′ = H



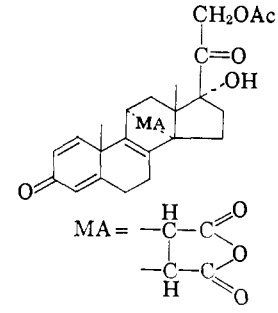
III



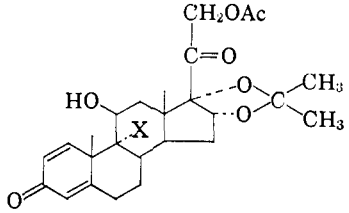
IV



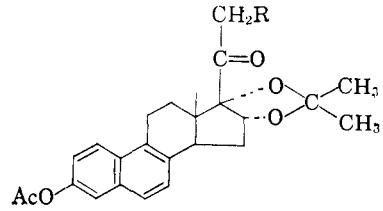
V



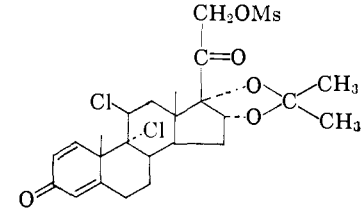
VI



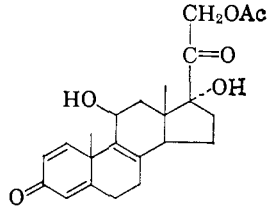
VIIIa, X = Cl
b, X = F



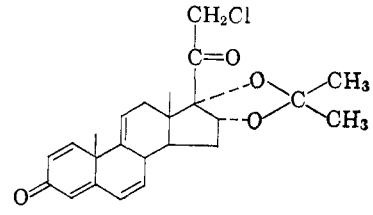
VIIIa, R = OAc
b, R = Cl



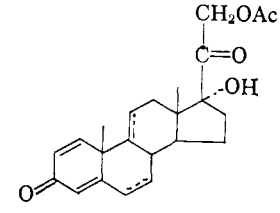
IX



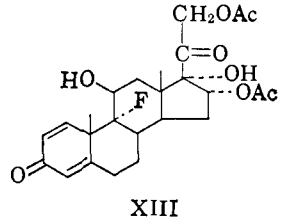
X



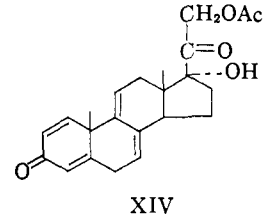
XI



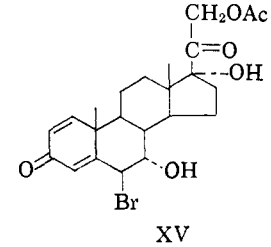
XIIa, $\Delta^{1,4,9(11)}$
b, $\Delta^{1,4,6}$



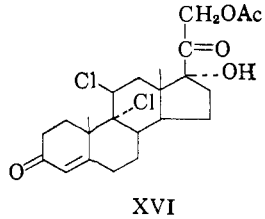
XIII



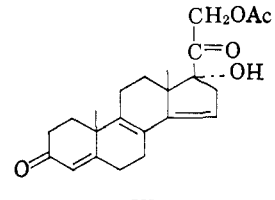
XIV



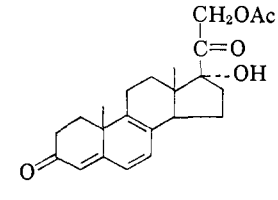
XV



XVI



XVII



XVIII

elution gave the starting material XIV (0.004 g) as revealed by its infrared spectrum.

3,21-Diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIb). A. From 9α,11β-Dichloro Ia in Dimethylformamide. A solution of Ia (2.0 g) and lithium chloride[43] (0.56 g) in dimethylformamide (100 ml) was refluxed and worked up in the usual manner to give 1.50 g of solid, mp 95–155°. A portion (1.3 g) in pyridine (10 ml) and acetic anhydride (5 ml) was allowed to stand at room temperature overnight. After the addition of methanol and benzene the reaction mixture was evaporated *in vacuo* to dryness. The residue (1.35 g) was dissolved in methylene chloride (15 ml) and adsorbed on Florisil[44] (90 g). Elution with 7% acetone–hexane (13 100-ml fractions) afforded IIb (0.34 g), mp 180–183°, after crystallization from acetone–hexane. Three additional crystallizations from the same solvent pair gave the analytical sample (0.27 g), mp 184–186°; λ_{max} 232 mμ (ε 75,300), 270 (4100), 281 (5300), 293 (4100), 312 (1200), and 327 (1300); $[\alpha]^{25}D$ +95° (chloro-

(44) Florisil (Floridin Co.), a synthetic magnesium silicate.

form); ν_{max} 3535, 1744, 1730 (shoulder), 1727, 1607, 1574, and 1208 cm^{-1}.

Anal. Calcd for $C_{24}H_{26}O_6$ (410.45): C, 70.23; H, 6.39. Found: C, 70.09; H, 6.51.

Elution with 12% acetone–hexane (13 100-ml fractions) afforded the tetraene V (0.29 g), mp 218–225°, after crystallization from acetone–hexane. The latter was combined with 32 mg of comparable material (mp 213–223°, obtained from chromatography of a 200-mg acetylation of the original 1.5 g of crude solid) and crystallized from methylene chloride–ether to afford 0.22 g of material, mp 223.5–230°; λ_{max} 246 mμ (ε 27,600). Recrystallization from the same solvent pair gave 0.18 g, mp 227–234°; λ_{max} 244 mμ (ε 24,100). Since the ultraviolet absorption spectrum changed on recrystallization, apparently the material consists of more than one compound or contains a chromophore that is unstable on handling. The material was not further investigated.

B. From 9α-Bromoprednisolone Acetate (Ib). A solution of 9α-bromoprednisolone acetate (Ib, 1.0 g)[25] in dimethylformamide (50 ml) was heated under reflux for 0.5 hr. The yellow solution was evaporated under reduced pressure to a brown oil which was dissolved in pyridine (10 ml), treated with acetic anhydride (5 ml), and allowed to stand at room temperature overnight. After the addition of methanol and benzene, the reaction mixture was evaporated *in vacuo* to dryness. The residue was dissolved in methylene chloride (*ca.* 20 ml) and adsorbed on Florisil (50 g). Elution with 8% acetone–hexane (five 100-ml fractions) afforded IIb (200 mg) which was crystallized from acetone–hexane to give pure IIb (145 mg), 184.5–186°. The infrared spectrum was identical with that of the previously obtained specimen. Elution with 12% acetone–hexane (nine 100-ml fractions) and 14% acetone–hexane (two 100-ml fractions) afforded the by-product V (102 mg) as indicated by thin layer chromatography. Recrystallization from acetone–hexane gave 39 mg, mp *ca.* 175–205°. The infrared spectrum was essentially the same as that of V obtained previously.

3,17α,21-Trihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIc). A solution of 21-acetoxy-3,17α-dihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIa, 0.15 g) in methanol (30 ml) was treated with 10% aqueous potassium carbonate solution (1.5 ml) while under an atmosphere of argon. After 30 min at room temperature, glacial acetic acid (0.12 ml) was added and the reaction mixture was evaporated under reduced pressure to dryness. The residue was heated with acetone and the insoluble potassium acetate removed by filtration. Concentration of the filtrate with simultaneous addition of hexane gave IIc (0.10 g), mp 240–244°. Two further crystallizations from acetone–hexane afforded the analytical sample (0.07 g), mp 245–249°; λ_{max} 229 mμ (ε 66,400), 268 (4300), 279 (5100), 290 (3300), 325 (2100), and 339 (2480); $[\alpha]^{25}D$ +24° (pyridine); ν_{max} 3470, 1710, 1629, 1610 and 1575 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}O_4$ (326.38): C, 73.60; H, 6.79. Found: C, 73.98; H, 7.06.

3-Hydroxyestra-1,3,5(10),6,8-pentaen-17-one (Equilenin) (III).
A. From 1,3,5(10),6,8-Pentaene IIc. A solution of 3,17α,21-trihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIc, 100 mg) in methanol (7.5 ml) and dimethylamine (2.5 ml) was heated under reflux for 2 hr. The reaction mixture was evaporated *in vacuo* to dryness and the residue dissolved in a small amount of aqueous ethanol. After warming briefly on the steam bath, the solution was diluted with water and saturated with salt to precipitate the crude product (85 mg). A thin-layer chromatogram indicated approximately equal amounts of equilenin, starting material, and a highly polar product that remained at the origin. The crude mixture was dissolved in methylene chloride (*ca.* 10 ml) and adsorbed on Florisil (9 g). Elution with 5% acetone–hexane (five 50-ml fractions) afforded 25 mg of III, mp 245–247°, red melt. Recrystallization from aqueous ethanol gave 17 mg, mp 249.5–252°, red melt. The infrared spectrum and mobility on a thin-layer chromatogram were identical with that of a reference sample of equilenin.[45]

B. From 9α,11β-Dichloroandrosta-1,4-diene IV. A solution of 9α,11β-dichloroandrosta-1,4-diene-3,17-dione (IV, 0.2 g) and lithium chloride[43] (0.06 g) in dimethylformamide (10 ml) was heated under reflux for 30 min. The reaction mixture was evaporated *in vacuo* to near dryness; water was added, and the resultant viscous oil was converted to a tan solid by scratching with a glass rod. The solid was filtered and washed with water to afford 0.117 g, mp 140–220°, red melt. This material was dissolved in methylene chloride (*ca.* 10 ml) and adsorbed on Florisil (12 g). Elution with 5% acetone–petroleum ether (bp 60–70°; ten 50-ml fractions) gave, in the initial 200 ml of eluate, equilenin (III, 0.024 g) as indicated by infrared spectrum and thin-layer chromatogram. Crystallization from acetone–hexane afforded 0.017 g of III, mp 239–245°, red melt. The remaining 300 ml of eluate on evaporation afforded 0.088 g of a mixture of III and one or more by-products as indicated by infrared spectrum and thin layer chromatography. The mixture was combined with the evaporated mother liquor above and chromatographed on Celite[46] using a solvent system consisting of *n*-heptane saturated with methanol. In contrast with the absorption chromatography, the more polar by-products (by thin layer chromatography) were obtained in the earlier fractions from the partition system (2.5–4.5 hold-back volume) but were not sufficiently separated to permit isolation of pure compounds. The solid (0.037 g) obtained on evaporation of hold-back volumes 5–6.5 was crystallized from acetone–hexane to give an additional 0.020 g of III, mp 242.5–250°. The latter was combined with the fraction obtained from the absorption chromatography above and recrystallized from the same solvent pair to give 0.024 g, mp 244.5–250°. One additional crystallization from ethanol–water afforded 0.015 g of equilenin (III), mp 246.5–250°; $[\alpha]^{25}D$ +89° (dioxane). The infrared spectrum was identical with that of an authentic sample.

19-Norpregna-1,3,5(10),6,8-pentaene-3,17α,20ξ,21-tetrol (i). A solution of 3,17α,21-trihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIc, 0.024 g) and sodium borohydride (0.024 g) in absolute ethanol (2 ml) and one drop of water was allowed to stand at room temperature for 1 hr. It was then neutralized with dilute sulfuric acid, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated saline, dried, and evaporated under reduced pressure to afford crude i (0.019 g), mp 208–214° with previous softening. The infrared spectrum showed essentially no carbonyl absorption.

3,20ξ,21-Triacetoxy-19-norpregna-1,3,5(10),6,8-pentaen-17α-ol (ii). A solution of crude 19-norpregna-1,3,5(10),6,8-pentaene-3,17α,20ξ,21-tetrol (i, 230 mg) in pyridine (2 ml) and acetic anhydride (1 ml) was acetylated at room temperature for 41 hr. Cracked ice was added, and the precipitate was filtered and washed with water to afford ii (294 mg, mp 184–194°). Three crystallizations from acetone–hexane gave 213 mg, mp 198.5–203°; λ_{max} 232 mμ (ε 79,200), 270 (5000), 280 (5750), 292 (4450), 312 (1360), 318 (1090), and 325 (1680); $[\alpha]^{25}D$ +61° (chloroform).

Anal. Calcd for $C_{26}H_{30}O_7$ (454.50): C, 68.70; H, 6.65. Found: C, 68.16; H, 6.94.

7-Iodoestra-1,5(10),6,8-tetraene-3,4,17-trione (iii). A solution of crude 19-norpregna-1,3,5(10),6,8-pentaene-3,17α,20ξ,21-tetrol (i, 0.23 g) in methanol (10 ml) was treated with a solution of periodic acid (0.40 g) in water (2 ml) and allowed to stand at room temperature for 22 hr. Water was added, and the resultant orange precipitate was filtered and washed with water to give 0.20 g, mp 105–129°. A portion (100 mg) was placed on a preparative thin layer chromatography plate (silica gel, 20 × 20 cm × 1 mm) and developed 1 hr in the system benzene–acetone–water (2:1:2) (upper phase). The orange band containing the product (*ca.* 11–12.5 cm from the origin) was scraped from the plate, eluted with methylene chloride, and evaporated to afford 27 mg, mp 179–184°. Recrystallization from acetone–hexane and a few drops of ether gave iii (22 mg, mp 189–193°); λ_{max} 267 mμ (ε 18,300) and 275 mμ (ε 16,100) (I); ν_{max} 1738, 1670, and 1562 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}O_3I$ (406.20): C, 53.22; H, 3.72; I, 31.24. Found: C, 54.78; H, 4.76; I, 30.44.

Maleic Anhydride Adduct of 21-Acetoxy-17α-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (VI). A suspension of 21-acetoxy-17α-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (V, 0.2 g) and maleic anhydride (0.2 g) in xylene (10 ml) was refluxed 6 hr, the steroid going into solution when the boiling point was reached. The solution was cooled to room temperature and diluted with ether. Scratching induced crystallization, but thin layer chromatography indicated that there was considerable starting material in this product. The solid was further refluxed with maleic anhydride (0.5 g) in xylene (10 ml) for 17 hr. Dilution with ether after cooling and scratching gave a solid (0.09 g), mp 215–228°. Recrystallization from acetone–hexane and methylene chloride–ether gave the desired product, mp 230–237° (bubbles); λ_{max} 241 mμ (ε 17,300); $[\alpha]^{25}D$ +209° (chloroform).

Anal. Calcd for $C_{27}H_{28}O_5$ (480.49): C, 67.49; H, 5.87. Found: C, 67.09; H, 5.89.

A further quantity of adduct (0.03 g) was accumulated by chromatography of the mother liquors on Florisil. The desired material was eluted at 20% acetone–hexane.

(45) We wish to thank Dr. T. F. Gallagher for providing us with an authentic sample of equilenin for infrared spectral comparison.

(46) Celite (Johns-Manville Co.), a diatomaceous silica product.

1,21-Diacetoxy-17α-hydroxy-4-methyl-19-norpregna-1,3,5(10),-8,14-pentaen-20-one (iv). Anhydrous hydrogen chloride was passed through an ice-cold solution of 21-acetoxy-17α-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (V, 0.5 g) in methylene chloride (100 ml) for 1 min. The solution was allowed to remain at 0° for 3 hr. Evaporation of the solvent at ice-bath temperature *in vacuo* gave a solid which seemed to be unstable. This was treated in pyridine (5 ml) with acetic anhydride (2.5 ml) for 17 hr at room temperature. Removal of the solvent *in vacuo* and crystallization of the residue from acetone–hexane gave iv (0.347 g), mp 181.5–184°. The analytical sample had mp 184–186°; λ_{max} 222 mμ (ε 12,100), 238 (12,200), 246 (10,300) (I), 292 (21,800), 304 (25,700), and 319 (18,200); $[\alpha]^{25}D$ −43° (chloroform).

Anal. Calcd for $C_{25}H_{28}O_6$ (424.47): C, 70.74; H, 6.65. Found: C, 70.40; H, 6.59.

An additional amount (0.052 g), mp 183–186°, of product was recovered upon chromatography of the mother liquors on Florisil (5% ether–benzene).

3,21-Diacetoxy-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5-(10),6,8-pentaen-20-one (VIIIa). A solution of 21-acetoxy-9α-chloro-11β-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione (VIIa, 0.50 g) in dimethylformamide (25 ml) was heated under reflux for 22.5 hr. The yellow solution was evaporated under reduced pressure to a brown oil which was dissolved in a small amount of acetone and precipitated by the addition of a large volume of water. The resultant solid was collected and washed with water to afford 0.29 g of crude 3-monool, mp 110–130°; λ_{max} 230 mμ (ε 54,500), 270 (5750), 281 (5730), 292 (4300), 328 (2290), and 340 (2580). The crude product was dissolved in methylene chloride (*ca.* 5 ml) and adsorbed on Florisil (15 g). Elution with 4% acetone–hexane (12 50-ml fractions) gave 185 mg of a white amorphous solid which was dissolved in pyridine (4 ml), treated with acetic anhydride (2 ml), and allowed to stand at room temperature for 64 hr. The reaction mixture was poured into ice water, and the diacetate was filtered and washed with water to give VIIIa (190 mg), mp 201–214°. Four recrystallizations from acetone–hexane afforded pure VIIIa (115 mg), mp 222.5–225.5°; λ_{max} 230 mμ (ε 77,000), 281 (5600), 293 (4300) (shoulder), 312 (1500), and 326 (1500); $[\alpha]^{25}D$ +107° (chloroform).

Anal. Calcd for $C_{27}H_{30}O_7$ (466.51): C, 69.51; H, 6.48. Found: C, 69.45; H, 6.63.

3-Acetoxy-21-chloro-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (VIIIb). A. From 9α,11β-Dichloro-1,4-diene IX. A solution of 9α,11β-dichloro-16α,17α-isopropylidenedioxy-21-methanesulfonyloxypregna-1,4-diene-3,20-dione (IX, 0.50 g) and lithium chloride (0.14 g) in dimethylformamide (25 ml) was heated under reflux for 0.5 hr. The yellow solution was evaporated under reduced pressure to near dryness; water was added, and the product was filtered and washed with water to afford an amorphous yellow solid (0.38 g), mp 90–150°. The product was soluble in 10% sodium hydroxide solution and exhibited an equilenin-type absorption in the ultraviolet. A portion (0.365 g) was dissolved in benzene (*ca.* 10 ml) and adsorbed on Florisil (14.5 g). Elution with 3% acetone–petroleum ether (bp 60–70°) gave a solid (0.264 g); λ_{max} 231 mμ (ε 68,900), 269 (6570), 281 (6570), 293 (4800), 328 (3200), and 342 (3200). The product was apparently labile to air or light. A solution of this solid (0.13 g) in pyridine (2 ml) and acetic anhydride (1 ml) was allowed to stand at room temperature for 19 hr. The solution was poured into ice water, and the precipitate was filtered and washed with water to afford VIIIb (0.127 g), mp 200–203.5°. Two crystallizations from acetone–hexane gave the analytical sample (0.109 g), mp 205–207°; λ_{max} 231 mμ (ε 80,200), 263 (4950), 282 (6420), 293 (5320), 312 (1990), 319 (1550), and 326 (1780); $[\alpha]^{25}D$ +99° (chloroform).

Anal. Calcd for $C_{25}H_{27}O_5Cl$ (442.92): C, 67.79; H, 6.14; Cl, 8.01. Found: C, 67.98; H, 6.49; Cl, 8.01.

B. From 1,4,6,9(11)-Tetraene (XI). A mixture of 21-chloro-16α,17α-isopropylidenedioxypregna-1,4,6,9(11)-tetraene-3,20-dione (XI, 0.14 g), lithium chloride (0.07 g), one drop of concentrated hydrochloric acid, and dimethylformamide (5 ml) was refluxed 0.5 hr. The yellow solution was evaporated to an oil *in vacuo;* water was added, and the oil was worked into an amorphous solid (0.122 g), mp 115–130°. Chromatography of this sample on Florisil (5 g) gave an amorphous solid (0.063 g) from 3% acetone–hexane. This was acetylated overnight with pyridine (2 ml) and acetic anhydride (1 ml) to give after crystallization from acetone–hexane the product VIIIb (0.052 g), mp 205–207°. The infrared spectrum was identical with that of the previously prepared material.

21-Acetoxy-17α-hydroxypregna-1,4,7,9(11)-tetraene-3,20-dione (XIV). A suspension of 21-acetoxy-11β,17α-dihydroxypregna-1,4,8-triene-3,20-dione (X, 1.0 g), concentrated hydrochloric acid (0.5 ml), and acetone (20 ml) was stirred a 0° for 40 min when almost all starting material was in solution. Water was added and a solid collected (0.90 g), mp 90–200°. Two crystallizations from acetone–hexane gave material (0.258 g), mp 205–208°, which was still impure by thin layer chromatography. This material was chromatographed on a Florisil column with increasing concentrations of acetone in hexane. Elution with 10% acetone–hexane and crystallization from acetone–hexane afforded the tetraene XIV (0.157 g), mp 212–218.5°. The analytical sample had mp 221–226°; λ_{max} 234 mμ (ε 27,000) and 254 mμ (ε 14,900) (I); $[\alpha]^{25}D$ +136° (chloroform).

Anal. Calcd for $C_{23}H_{26}O_5$ (383.44): C, 72.23; H, 6.85. Found: C, 72.48; H, 7.19.

21-Acetoxy-9α,11β-dichloro-17α-hydroxypregn-4-ene-3,20-dione (XVI). To a solution of 21-acetoxy-17α-hydroxypregna-4,9(11)-diene-3,20-dione[19a] (3.0 g) and lithium chloride (12.0 g) in acetic acid (400 ml) was added tetrahydrofuran saturated with hydrogen chloride (6 ml) and N-chlorosuccinimide (1.14 g). The solution was allowed to stand in the dark at room temperature for 20 min. The solution was poured into water and the precipitate collected. The solid was dissolved in methylene chloride, the solution was dried, and the solvent was removed *in vacuo.* Recrystallization from acetone and acetone–hexane seemed to give material consisting mostly of the $\Delta^{4,9(11)}$ starting material. Crystallization of mother liquors from methylene chloride–ether afforded XVI (0.267 g); mp 235–236° dec; λ_{max} 239 mμ (ε 17,100); $[\alpha]^{25}D$ +155° (chloroform).

Anal. Calcd for $C_{23}H_{30}O_5Cl_2$ (457.38): C, 60.39; H, 6.61; Cl, 15.50. Found: C, 60.98; H, 6.74; Cl, 15.61.

21-Acetoxy-17α-hydroxypregna-4,8,14-triene-3,20-dione (XVII) **and 21-Acetoxy-17α-hydroxypregna-4,6,8-triene-3,20-dione** (XVIII). A solution of the 9α,11β-dichloropregn-4-ene XVI (0.1 g) in dimethylformamide (5 ml) was refluxed 0.5 hr. The solution was evaporated *in vacuo* to a brown gum. Solution of the gum in a small amount of acetone was followed by the addition of a large amount of water. The precipitate was collected to give a brown powder (0.058 g). The material (0.053 g) was placed on a thin-layer preparative plate and developed as in the preparation of IIa (method E) for 1.66 hr. The less polar band (10–11 cm from the origin) was eluted with acetone to give XVII (0.019 g), mp 190–194°; λ_{max} 243 mμ (ε 30,400). Crystallization from acetone–hexane gave 0.0114 g, mp 193.5–196.5°.[47]

Elution of the more polar band (8.5–9.5 cm from the origin) gave XVIII (0.017 g), mp *ca.* 160–170°; λ_{max} 243 mμ (ε 11,100), 295 mμ (ε 4570), and 384 mμ (ε 7200). Recrystallization of this sample from acetone–hexane yielded 0.0033 g, mp *ca.* 175–215°.[48]

Acknowledgment. We wish to thank Professor Howard E. Zimmerman of the University of Wisconsin for some stimulating discussions concerning this work.

(47) Reference 19b reported that XVII has mp 188–192°, λ_{max} 242 mμ (ε 37,400). The infrared spectrum was identical with that of an authentic specimen. We wish to thank Dr. N. Wendler for providing the infrared spectrum for comparison.

(48) Reference 19a reported that XVIII has mp 188–190°; λ_{max}^{EtOH} 244 mμ (ε 14,300), 285–300 mμ (ε 3100), and 385 mμ (ε 6700).