ether,[34] the nicely crystalline prisms had a melting point range of 78–104°. Thin layer chromatographic examination of the product showed the presence of unchanged desoxycholic acid.[35]

16. **3α,12α-Dihydroxycholanic (Desoxycholic) Acid (I).**—(Methyl desoxycholate) diacetate,[9] m.p. 118.0–119.5°, was hydrolyzed to the acid as in part 4. The acid was dried and successively recrystallized three times from freshly distilled butanone; the melting point, after drying at 140° (0.1 mm.) for 24 hr., was 173.8–174.4°. The melting point of the acid before the third crystallization was essentially the same (see text): $[\alpha]_D$ +49.8 (dioxane), +40.3 ($CHCl_3$ and trace of CH_3OH), +54.1° (EtOH); lit.[2] $[\alpha]_D$ +49 (butanone), +48 (dioxane), +53° (alcohol)]; λ_{max}^{KBr} 2.95, 9.65 (OH), and 5.80 μ (COOH).

Anal. Calcd. for $C_{24}H_{40}O_4$ (392.56): C, 73.43; H, 10.27. Found: C, 73.35; H, 10.12.

(34) B. Riegel, R. B. Moffett, and A. V. McIntosh, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 237.

(35) Examination by t.l.c. of methyl cholanates prepared by the methanol–hydrochloric acid method[28] show that in all instances traces of acid remain, even after recrystallization.

Acknowledgment.—This investigation was supported in part by Public Health Service Research Grant CA-05011 from the National Cancer Institute. Terry Richardson and Jo Thedford contributed valuable technical assistance.

Substitution at Unactivated Carbon. The Synthesis of 18- and 19-Substituted Derivatives of 11β-Hydroxyprogesterone*,[1,2]

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A series of optically active 18- and 19-substituted 11-oxygenated progesterones has been prepared using as a key step the Barton reaction. Included in this series are 21-desoxyaldosterone, 11β,18-epoxyprogesterone, 11β,18-dihydroxyprogesterone 18-acetate, 11β-hydroxyprogesteron-18-oic 11,18-lactone, 11β,19-dihydroxyprogesterone, 11β-hydroxy-19-oxoprogesterone 11,19-cyclohemiacetal, 11β-hydroxyprogesteron-19-oic 11,19-lactone, and 11β,19-epoxyprogesterone. The values for the molecular rotations of these steroids are dependent on the nature of the oxygen function at C-18 or -19 and are characteristic for each series. The presence of an 11,19-oxide bridge retards the proton-catalyzed migration of the $\Delta^{5,6}$ double bond into conjugation with the 3-ketone. In the presence of mild acid, 11β,18-dihydroxyprogesterone 3,20-bisketal is converted into 11β,18-epoxyprogesterone. A mechanism is proposed for this surprising transformation.

The interesting chemical and biological properties of 18- and 19-substituted steroids have focused considerable attention on the problem of chemical reactions at "unactivated" carbon atoms. Recent efforts toward this end have resulted in a number of methods for introducing substituents at "unactivated" carbon.[3–10] One method of considerable scope and utility is the Barton reaction.[3–5]

As one aspect of our studies of the Barton reaction, we have undertaken the preparation of a series of 11,18-substituted progesterones as potential biosynthetic precursors of *d*-aldosterone. The corresponding 11,19-oxygenated isomers were also prepared, since it was felt that a series of isomeric 18- and 19-substituted compounds would be useful for the study of physical properties as well as chemical reactivity and biological activity.

Nitrosolation of 11β-hydroxyprogesterone 3,20-bisethylene ketal (**1**)[11] gave a crystalline nitrite **2** which on irradiation underwent rearrangement to yield the isomeric 18- and 19-oximes **3** and **4**. Oxime **3** was shown to be the 18-substituted isomer by acid-catalyzed conversion into the nitrone **5**.[12] The other oxime was shown to be the 19-substituted isomer by transformation to the known 11β-hydroxy-19-norprogesterone (**6**).[13] (See Scheme I.)

Treatment of the 18-oxime **3** with acetic acid and aqueous sodium nitrite[14] gave an oily product which showed considerable carbonyl absorption at 1710 $cm.^{-1}$ in the infrared. This suggested a cleavage of the 20-ketal.[15] The 18-oxime bisketal **3** was therefore treated with dry sodium nitrite in glacial acetic acid to give a small yield of the desired 11→18-hemiacetal bisketal **8**. The major product of this reaction was a gummy solid with a strong ester band at 1740 $cm.^{-1}$. Since this material, on treatment with sodium hydroxide in methanol, was converted into the 11→18-hemiacetal bisketal **8**, it was formulated as the hemiacetal acetate **7**.[16,17]

* To Professor Louis F. Fieser.

(1) Communication No. 33 from the Research Institute for Medicine and Chemistry. For No. 32, see N. Basu and D. H. R. Barton, *Tetrahedron Letters*, 3151 (1964).

(2) A preliminary account of this work was presented at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, Abstracts p. 22C.

(3) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960).

(4) M. Akhtar, D. H. R. Barton, J. M. Beaton, and A. G. Hortmann, *ibid.*, **85**, 1512 (1963).

(5) M. Akhtar, "Advances in Photochemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1964, p. 263.

(6) P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959).

(7) G. Cainellio, M. L. Mihailovic, P. Arigoni, and O. Jeger, *ibid.*, **42**, 1124 (1959).

(8) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 2213 (1961).

(9) Ch. Meystre, K. Heusler, J. Kalvoda, P. Weiland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961).

(10) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **80**, 2903 (1958).

(11) B. J. Magerlin and R. H. Levin, *ibid.*, **75**, 3654 (1953).

(12) The same nitrone had previously been obtained by J. M. Beaton in this institute by treatment of the nitrone from aldosterone acetate oxime with zinc and acetic acid.

(13) A. Bowers, C. Casas-Campillo, and C. Djerassi, *Tetrahedron*, **2**, 165 (1958).

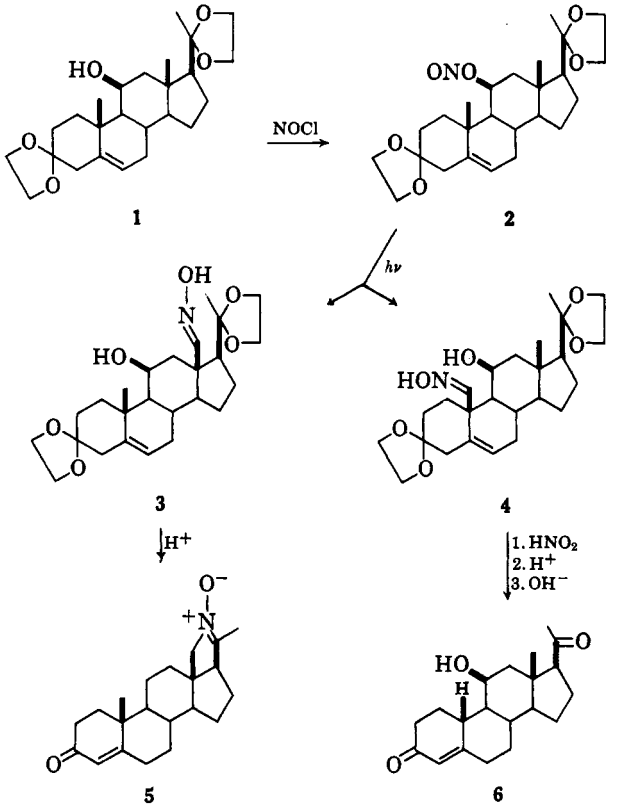
(14) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958).

(15) The 20-ketal in this series is quite labile and is cleaved by prolonged contact with acid-washed alumina or by 60% aqueous acetic acid at room temperature.

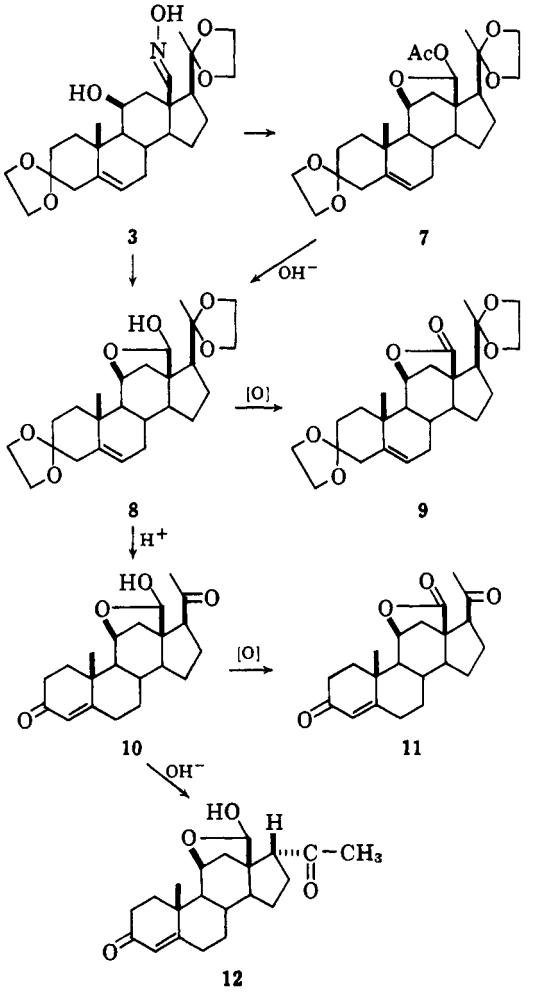
(16) There is evidence[17] that the 11β-hydroxyl participates in this reaction to give an 11β,18-oxonium ion intermediate. This intermediate may be trapped by a variety of internal or external nucleophiles; see, for instance, ref. 4.

(17) Participation of the 11β-hydroxyl is indicated by the rapidity of the reaction (<2 min. at 5°) and by the observation of A. G. Hortmann of this institute that 11-keto 18-oximes, on treatment with nitrous acid, give nitrimines rather than aldehydes.

SCHEME I



SCHEME II



Oxidation of the 11→18-hemiacetal **8** with chromic anhydride in pyridine[18] gave the 11→18-lactone bisketal **9**.[19] Reduction of the 11→18-hemiacetal **8** with lithium aluminum hydride gave the 11,18-diol bisketal **13**. Treatment of the 11→18-hemiacetal bisketal **8** with sulfuric acid in aqueous acetone gave 21-desoxyaldosterone (**10**). Although the infrared spectrum of 21-desoxyaldosterone did not exhibit the diminished absorption of the 20-carbonyl characteristic of aldosterone,[21] the 17β-orientation of the methyl ketone side chain was demonstrated by base-catalyzed isomerization to the more stable 17α epimer **12**.[22] This transformation was accompanied by an appropriately large negative rotatory shift.[24,25] The presence of a hemiacetal in 21-desoxyaldosterone (**10**) was demonstrated by oxidation of **10** to the lactone **11**. (See Schemes II and III.)

Treatment of the 11β,18-diol bisketal **13** with mild acid removed the ketals and effected an unexpected cyclodehydration to yield 11β,18-epoxyprogesterone (**14**). This transformation has been reported for the corresponding racemic compound by Wettstein and Schmidlin.[28] These authors suggest that the epoxy product arises by a simple nucleophilic attack of the 11-oxygen upon C-18. Displacement of a primary hydroxyl is unlikely under these conditions, and this theory does *not* account for the failure of the 18-acetoxy compound **15** or the 11β,19-diol **19** (*vide infra*) to undergo a similar cyclodehydration.

An alternate mechanism consonant with all the observations is shown in Scheme IV. Cleavage of the 20-ketal, known to be rapid under these conditions, would lead to the 18→20-cyclohemiketal (partial structure **29**). Ionization of the hemiketal,[4,21,29] followed by attack of the 11β-hydroxyl in the sense indicated, would result in the observed product **14**.

In order to avoid the cyclodehydration reaction, the 11β,18-diol bisketal **13** was acetylated to give the 11β-hydroxy-18-acetoxy bisketal **15** characterized by oxidation to the corresponding 11-keto compound **16**. Treatment of the 18-acetoxy compound **15** with acid gave a nearly intractable mixture from which it was possible to isolate, in small yield, a compound tentatively characterized as 11β-hydroxy-18-acetoxyprogesterone (**17**). Although satisfactory analytical data have not been obtained owing to the difficulty of obtaining **17** free from occluded solvent, the physical

(18) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(19) Jones oxidation[20] was accompanied by cleavage of the 20-ketal.

(20) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(21) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163, 1200 (1954).

(22) Although the 17β side chain lies in the normally stable pseudo-equitorial conformation, the interaction between the 18-substituent and the 20-ketone renders this configuration unstable in this series.[23]

(23) J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **40**, 2291 (1957).

(24) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 566.

(25) Since the completion of this work and its communication in preliminary form,[2] both a partial[26] and a total[27] synthesis of 21-desoxyaldosterone have been reported.

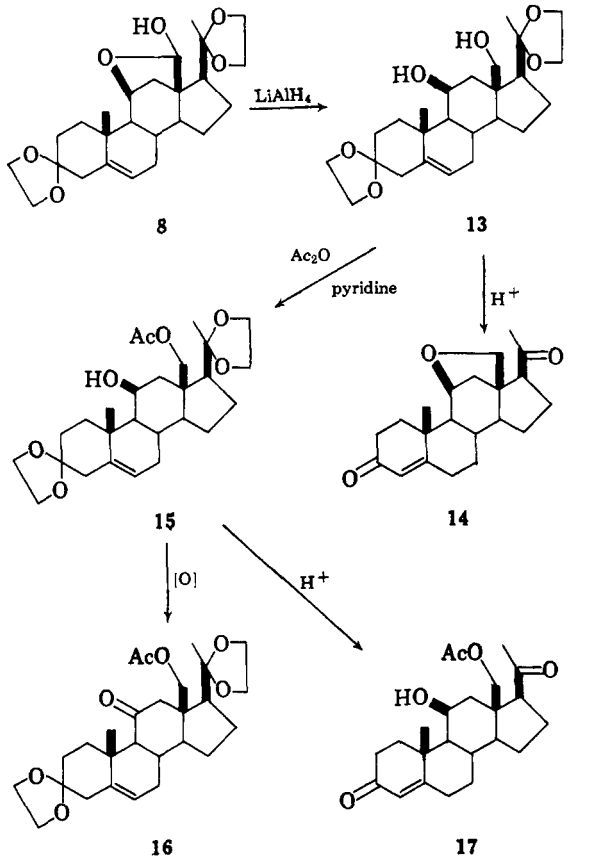
(26) A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

(27) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **45**, 331 (1962).

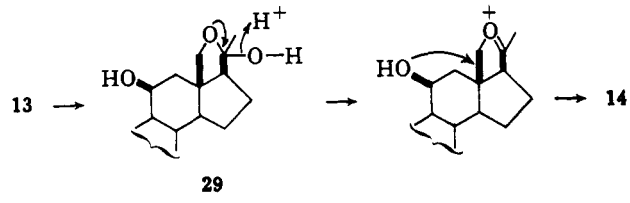
(28) J. Schmidlin and A. Wettstein, *ibid.*, **42**, 2637 (1959).

(29) W. H. Kelly, L. Bondi, and S. Lieberman, *Biochemistry*, **1**, 792 (1962).

SCHEME III



SCHEME IV



properties and mode of formation of **17** support the assigned structure.

Treatment of the 19-oxime bisketal **4** with sodium nitrite and glacial acetic acid, followed by saponification of the intermediate hemiacetal acetate, gave the 11→19-hemiacetal bisketal **18**, which on oxidation with chromium trioxide–pyridine[18] gave the 11→19-lactone bisketal **23**.[19] Either **18** or **23**, upon reduction with lithium aluminum hydride, gave the 11,19-diol bisketal **19**. Treatment of the 11β,19-diol bisketal **19** with acid afforded the expected 11β,19-dihydroxyprogesterone (**20**) (see Scheme V). There was no indication of products arising from cyclodehydration (*vide supra*).

The 11→19-hemiacetal bisketal **18**, on treatment with sulfuric acid–acetone, afforded a crystalline product with the expected composition, $C_{21}H_{28}O_4$. This compound, on treatment with mild base, was quantitatively converted into 11β-hydroxy-19-norprogesterone (**6**). This behavior is consistent with the facile vinylogous β-elimination observed in these laboratories for the 11→19-hemiacetal of 19-oxocorticosterone.[30] Although the composition of the cleavage product and its conversion into the 19-nor **6** were compatible with the expected 11→19-hemiacetal of 11β-hydroxy-19-oxoprogesterone (**21**), the ultraviolet extinction coefficient of this material was only 7.8×10^3, one-half the expected value. Thin layer chromatography showed this material to be a mixture of two interconvertible compounds of similar polarity. One of these exhibited the characteristics of an α,β-unsaturated ketone; the other exhibited *no* conjugated chromophore. The ketal cleavage product was therefore formulated as a mixture of 11β-hydroxy-19-oxoprogesterone (**21**) and its $\Delta^{5,6}$ isomer **22**. Although further treatment of this mixture with sulfuric acid–aqueous acetone under reflux increased the ε of the product to 1.28×10^4, a detectable amount of the unconjugated isomer still remained.

Treatment of the 11→19-lactone bisketal **23** with sulfuric acid–acetone gave a similar mixture of $\Delta^{4,5}$ and $\Delta^{5,6}$ isomers **25** and **26**. The predominant component was the $\Delta^{5,6}$ unconjugated isomer **26** (ε of mixture is 3×10^3). Further treatment of this mixture with sulfuric acid–acetone effected no change.

The *electronic* interaction of the 19-substituent with the α,β-unsaturated carbonyl (estimated by the bathochromic shift of the ultraviolet absorption maximum) *decreases* in the order: hemiacetal (λ_{max} 246 mμ), 19-OH (λ_{max} 243.5 mμ), lactone (λ_{max} 242 mμ). Therefore, the abnormal behavior of the 11→19-hemiacetal bisketal **18** and the 11→19-lactone bisketal **23** under ketal cleavage conditions was presumed due to a steric effect of the 11→19-oxide bridge present in these compounds. To test this hypothesis the 11→19-oxide bisketal **24** was prepared by the action of tosyl chloride on the 11,19-diol bisketal **19**. Treatment of the 11→19-oxide bisketal **24** with sulfuric acid–acetone gave 11-19-epoxypregnene-3,20-dione as the expected mixture of Δ^4 conjugated **27** and $\Delta^{5,6}$ unconjugated **28** isomers. The abnormal behavior of this series of compounds thus appears to be an effect, probably steric, of the 11→19-oxide bridge.

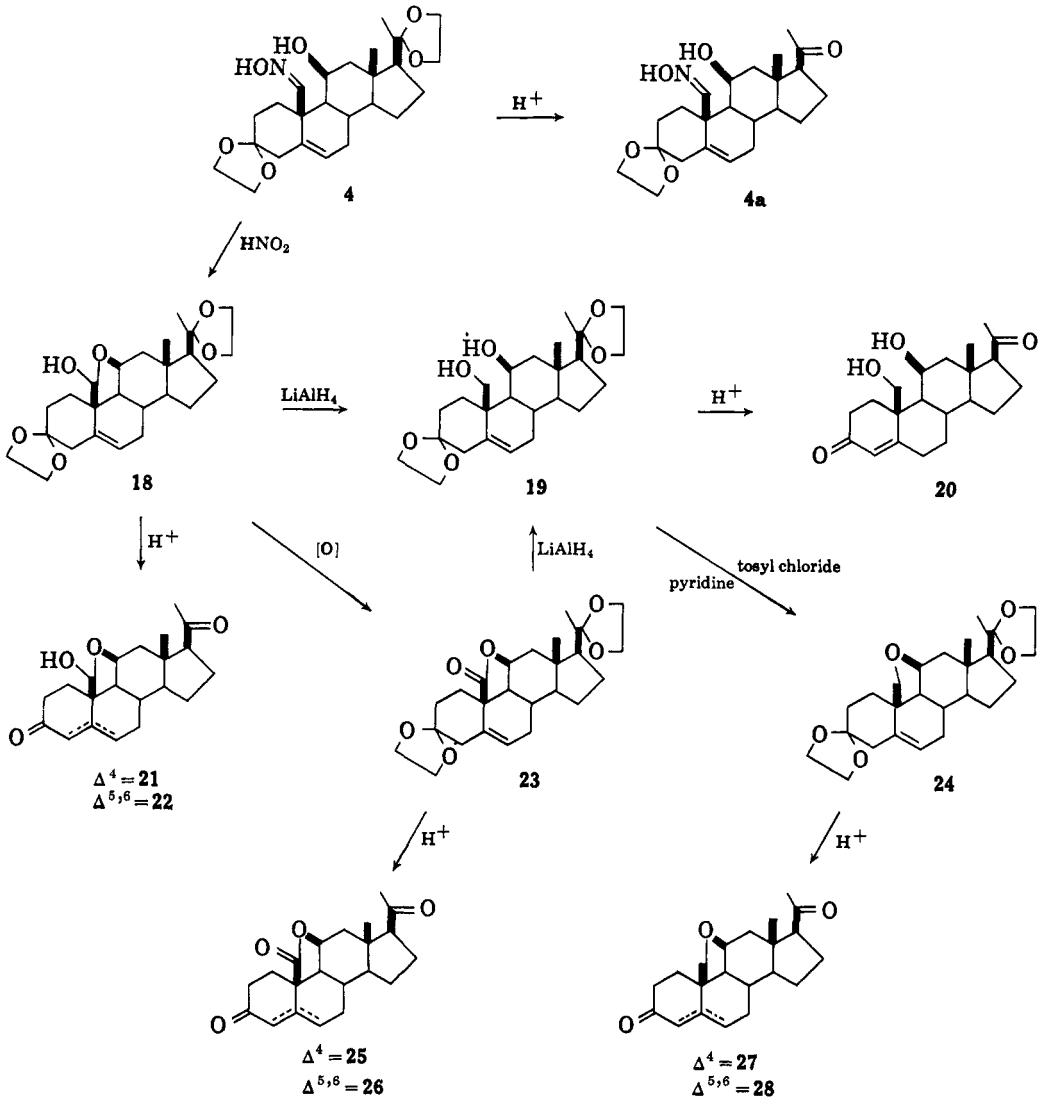
During a previous investigation in these laboratories, Barton and Beaton had not encountered this phenomenon while preparing an analogous 11→19-hemiacetal and 11→19-lactone in the corticosterone series.[30] Since these authors had effected ketal cleavage with hydrochloric acid in aqueous dioxane, the 11→19-lactone bisketal **23** was submitted to these conditions. The product isolated from this reaction consisted of nearly pure Δ^4-3-keto **25**. Furthermore, when a mixture rich in the $\Delta^{5,6}$ unconjugated isomer **26** was subjected to the same conditions, it also was converted into the nearly pure Δ^4-3-keto **25**.

When sulfuric acid was used in place of hydrochloric acid in this system, either the Δ^4 conjugated isomer **25** or the $\Delta^{5,6}$ isomer **26** could be recovered unchanged after 24-hr. incubation. In fact, both forms remained inert even after a tenfold increase in the sulfuric acid concentration. However, when a stable solution of the $\Delta^{5,6}$ unconjugated isomer in aqueous dioxane containing sulfuric acid was treated with lithium chloride, the ultraviolet absorption of the reaction mixture rapidly increased and nearly pure Δ^4-3-keto compound was isolated.

These data indicate that the observed migration of the $\Delta^{5,6}$ double bond into the 4,5 position is catalyzed

(30) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962).

SCHEME V



by hydrogen chloride rather than by a proton.[31] This might proceed by attack of a proton on the double bond *concerted* with the removal of a proton at C-4 by chloride. Such a process could proceed through a cyclic, six-membered transition state.

Since this relatively facile hydrochloric acid catalyzed isomerization of the double bond does not yield a product completely free from unconjugated isomer,[32] it appears that the 11→19-oxide bridge causes a slight departure from the normal relative stabilities of Δ^4- and $\Delta^{5,6}$-3-keto steroids.[33]

The more striking effect of the oxide bridge is the retardation of the *proton*-catalyzed migration of the $\Delta^{5,6}$ double bond into conjugation. The major *initial* ketal cleavage product from compounds with the 11→19-oxide bridge is in each case the $\Delta^{5,6}$ unconjugated isomer. In the case of the 11→19-hemiacetal, the unconjugated isomer **22** is slowly converted by proton into the more stable conjugated isomer **21**. In the case of the 11→19-lactone, this conversion does not proceed at a measurable rate.

Although the use of optical rotatory contributions has largely been superceded by other physical methods, there are a number of obvious rotatory correlations among this series of isomeric 18- and 19-substituted compounds. Each of the 19-substituted compounds is more dextrorotatory than its 18-substituted isomer; each of the cyclohemiacetals or oxides is more strongly dextrorotatory than the corresponding oxime, diol, or lactone. These correlations, if general, may be of use in distinguishing between alternative structures.

Whereas *d*-aldosterone induces tubular reabsorption of sodium, *d*-21-desoxyaldosterone exerts very little influence on the transport of sodium. Thus, although the presence of the 11→18-cyclohemiacetal group bestows a remarkably high activity upon aldosterone,[34] this group is virtually without effect on a steroid lacking oxygen at C-21.

Although 21-desoxyaldosterone appears attractive as a possible precursor of aldosterone, and its formation from progesterone by adrenal tissue has been reported,[35] we have not been able to demonstrate any

(31) This isomerization of the $\Delta^{5,6}$ double bond to the 4,5 position is not due to addition of hydrochloric acid to give the 5-chloro compound, followed by β-elimination during the work-up, since the reaction mixture showed an ultraviolet absorption at 242 mμ which gradually increased to a value of 1.22×10^4, the same as that of the isolated product.

(32) When either the Δ^4 or the $\Delta^{5,6}$ isomer of 19-oxo-11β-hydroxyprogesterone, each chromatographically pure, was treated with hydrochloric acid, a mixture of both was obtained.

(33) K. Otto and M. Ehrenstein, *J. Org. Chem.*, **26**, 2871 (1962).

(34) Aldosterone is approximately 25 times more active than 11-desoxycorticosterone in inducing tubular reabsorption of sodium.

(35) A. Wettstein, *Experientia*, **17**, 329 (1961).

conversion of 21-desoxyaldosterone into aldosterone by bovine adrenal homogenates.

Experimental

All melting points were taken on the Kofler hot stage and are reported uncorrected. Infrared spectra were obtained on a Perkin-Elmer 137 Infracord. Optical rotations are reported for a 0.5% solution in chloroform using a 1-dm. cell except where otherwise noted. Microanalyses were performed by Drs. Alfred Bernhardt of the Max Planck Institut, Manheim, Germany, and Stephen Nagy of the Microanalytical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass. The "usual work-up" refers to extractions with dichloromethane, washing with sodium bicarbonate to remove excess acid, washing with sodium dihydrogen phosphate to remove base, or with phosphoric acid to remove pyridine, and drying of the organic solvent over sodium sulfate.

11β-Nitrosylprogesterone 3,20-Bisketal (2).—Excess nitrosyl chloride was passed through a solution of 4 g. of 11β-hydroxyprogesterone 3,20-bisketal (**1**) in 40 ml. of pyridine at 4°. Ice was added, followed by water, to precipitate the crude nitrite. The product was crystallized from hexane; m.p. 130–134°, $[\alpha]^{24}D$ +5°. This compound was unstable and satisfactory analytical data were not obtained; $\tilde{\nu}_{max}^{KBr}$ 2995 (s), 1625 (s), 1600 (m) cm.$^{-1}$ (ONO); yield 77%.

18-Oximino-11β-hydroxyprogesterone 3,20-Bisketal (3) and 19-Oximino-11β-hydroxyprogesterone 3,20-Bisketal (4).—A solution of 10 g. of nitrite **2** in 300 ml. of toluene was irradiated for 1.5 hr. using a 200-w. mercury vapor lamp. The toluene was removed under reduced pressure; the 18-oxime **3** was precipitated with ethyl acetate and recrystallized from the same solvent; m.p. 263–265°; $[\alpha]^{20}D$ −23°; $\tilde{\nu}_{max}^{KBr}$ 3300, 3200 (s) (OH), 2995 (s), 1650 (w) cm.$^{-1}$ (C=N); yield 18%.

Anal. Calcd. for $C_{25}H_{37}NO_6$: C, 67.39; H, 7.92; N, 3.14. Found: C, 67.22; H, 8.14; N, 3.16.

Treatment of the photolysis mother liquors with ether, followed by prolonged storage at room temperature, gave a moderate yield of the 19-oxime **4**: m.p. 186–189°; $[\alpha]^{23}D$ +10°; $\tilde{\nu}_{max}^{KBr}$ 3500 (s) (OH), 3000 (s), 1650 (w) cm.$^{-1}$ (C=N). This material did not analyze well and was therefore characterized as the 3-monoketal (**4a**), obtained by chromatography on acid-washed alumina; m.p. 211–219°; $[\alpha]D$ +33°; $\tilde{\nu}_{max}^{KBr}$ 3600, 3450 (s) (OH), 2995 (s), 1720 (s) (C=O), 1650 (w) cm.$^{-1}$ (C=N); typical yield 20%.

Anal. Calcd. for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.51; H, 8.11; N, 3.65.

Both were converted into the same unprotected hemiacetal and lactone derivatives.

Nitrone 5.—To a solution of the 18-oxime **3** in 20 ml. of acetone was added 4 ml. of water and 0.4 ml. of concentrated hydrochloric acid. After storage at room temperature for 18 hr., followed by the usual work-up, the nitrone **5** was obtained crystalline from acetone; m.p. 235–280° (dec. 235°); $[\alpha]^{20}D$ +170°; $\tilde{\nu}_{max}^{KBr}$ 2995 (s), 1660 (s) (C=C—C=O), 1660, 1570 (s) cm.$^{-1}$ (nitrone); yield 65%.

Anal. Calcd. for $C_{21}H_{27}NO_4$: C, 73.77; H, 7.97. Found: C, 73.87; H, 7.91.

Hemiacetal of 11β-Hydroxy-18-oxoprogesterone 3,20-Bisketal (8) and Its 18-Acetate (7).—To 10 ml. of glacial acetic acid cooled to 5° was added 500 mg. of sodium nitrite, followed by 500 mg. of the 18-oxime **3**. The suspension was stirred vigorously for 2 min. Following the usual work-up, the crude product was crystallized from acetone to give a small yield of the 11→18-hemiacetal **8**: m.p. 195–197°; $[\alpha]^{22}D$ +0; $\tilde{\nu}_{max}^{KBr}$ 3500 (s) (OH), 2995 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.52; H, 8.35.

Concentration of the mother liquors yielded the hemiacetal acetate **7** as a gum. When a solution of 300 mg. of the acetate in 12 ml. of 1% methanolic sodium hydroxide was allowed to stand for 20 min., a good yield of material identical with the hemiacetal **8** crystallized from the reaction mixture; total yield of **8**, 77%.

Lactone of 11β-Hydroxyprogesteron-18-oic Acid 3,20-Bisketal (9).—To a solution of 200 mg. of chromium trioxide in 2 ml. of pyridine was added a solution of 100 mg. of hemiacetal **8** in 2 ml. of pyridine. The mixture was stored overnight at room temperature, then partitioned between ether and water. The excess pyridine was removed by washing with 10% aqueous phosphoric acid and the organic layer was worked up in the usual fashion. The 11→18-lactone bisketal **9** was obtained from methanol; m.p. 247–249°; $[\alpha]^{20}D$ −35°; $\tilde{\nu}_{max}^{KBr}$ 3000 (s), 1770 (s) cm.$^{-1}$ (lactone); yield 60%.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 70.28; H, 7.81. Found: C, 69.74; H, 7.96.

21-Desoxyaldosterone (10).—A solution of 100 mg. of the 11→18-hemiacetal bisketal **8** in 4.5 ml. of actone and 1.25 ml. of water containing 0.05 ml. of concentrated sulfuric acid was refluxed for 10 min. and allowed to stand at room temperature for an additional 40 min. The usual work-up, followed by crystallization of the product from acetone–ether, gave *d*-21-desoxyaldosterone (**10**): m.p. 159–167°; $[\alpha]^{20}D$ +195°; $\tilde{\nu}_{max}^{CHCl_3}$ 3700, 3500 (w) (OH), 3000 (s), 1700 (s) (C=O), 1660 (s) cm.$^{-1}$ (C=C—C=O); yield 74%.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.14; H, 8.20.

Base-Catalyzed Isomerization of 10.—A solution of 15 mg. of 21-desoxyaldosterone (**10**) in 1 ml. of methanol and 1 ml. of 1 *N* sodium hydroxide was stored at room temperature for 3.5 hr. The usual work-up, followed by crystallization from methanol, gave 17-iso-21-desoxyaldosterone (**12**): m.p. 185–190°; $[\alpha]^{20}D$ +73°; $\tilde{\nu}_{max}^{CHCl_3}$ 3700, 3460 (w) (OH), 2995 (s), 1700 (s), 1660 (s) cm.$^{-1}$; yield 60%.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.53; H, 8.08.

11β-Hydroxyprogesteron-18-oic 11→18-Lactone (11).—A solution of 75 mg. of 21-desoxyaldosterone (**10**) in 3 ml. of acetone was treated with 0.2 ml. of chromic acid–sulfuric acid.[20] After 25 min. the excess oxidant was decomposed with methanol. Following the usual work-up, the product was obtained from ether–hexane; m.p. 193–198°; $[\alpha]^{23}D$ +180°; $\tilde{\nu}_{max}^{KBr}$ 3000 (s), 1780 (s) lactone, 1710 (s) (20-C=O); 1660 (s), 1610 (m) cm.$^{-1}$ (C=C—C=O); yield 62%.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 74.04; H, 7.63.

11β,18-Dihydroxyprogesterone 3,20-Bisketal (13).—To a solution of 400 mg. of the 11→18-hemiacetal bisketal **8** in 50 ml. of tetrahydrofuran was added 150 mg. of lithium aluminum hydride. The suspension was refluxed for 3 hr. After the usual work-up, crystallization from propanol afforded the 11→18-diol bisketal **13**: m.p. 169–172°; $[\alpha]^{24}D$ −24°; $\tilde{\nu}_{max}^{KBr}$ 3300 (s) (OH), 3000 (s) cm.$^{-1}$; yield 86%.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.82. Found: C, 69.36; H, 8.65.

11β,18-Epoxyprogesterone (14).—A solution of 100 mg. of the 11β,18-diol bisketal **13** in 4.5 ml. of acetone and 1.25 ml. of water containing 0.05 ml. of sulfuric acid was refluxed for 15 min. After an additional 30 min. at room temperature, the usual work-up, followed by crystallization from acetone–ether, gave 11β,18-epoxyprogesterone (**14**): m.p. 167–169°; $[\alpha]^{24}D$ +258°; $\tilde{\nu}_{max}^{KBr}$ 3000 (s), 1720 (s) (C=O), 1675 (s), 1610 (m) cm.$^{-1}$ (C=C—C=O); yield 90%.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.78; H, 8.68.

The same product was obtained when the diol bisketal **13** was digested with 90% aqueous acetic acid.

11β-Hydroxy-18-acetoxyprogesterone 3,20-Bisketal (15).—To a solution of 400 mg. of the 11β,18-diol bisketal **13** in 15 ml. of benzene and 18 ml. of pyridine was added 8 ml. of acetic anhydride. The solution was stored at room temperature for 20 hr. Then the acetic anhydride was decomposed with methanol and water. The product was extracted with benzene, washed with 10% phosphoric acid, water, and sodium bicarbonate, and dried, and the benzene was removed *in vacuo*. The product was crystallized from acetone–ether; m.p. 154–155°; $[\alpha]^{20}D$ −15°; $\tilde{\nu}_{max}^{KBr}$ 3600 (m) (OH), 2995 (s), 1725 (s), 1250 (s) cm.$^{-1}$ (OAc); yield 73%.

Anal. Calcd. for $C_{21}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.59; H, 8.45.

11-Keto-18-acetoxyprogesterone Bisketal (16).—To a solution of 200 mg. of chromium trioxide in 2 ml. of pyridine was added 25 mg. of the monoacetate **15**. The mixture was stored overnight at room temperature. After the usual work-up, the product was crystallized from methanol; m.p. 168–173°; $[\alpha]^{23}D$ +11°; $\tilde{\nu}_{max}^{CHCl_3}$ 3000 (s), 1740 (s), 1240 (s) (OAc), 1720 (s) cm.$^{-1}$ (C=O); yield 73%.

Anal. Calcd. for $C_{21}H_{38}O_7$: C, 68.35; H, 8.07. Found: C, 68.54; H, 7.96.

11β-Hydroxy-18-acetoxyprogesterone (17).—A solution of 100 mg. of the 18-monoacetate **15** in 4.5 ml. of acetone and 1.25 ml.

of water containing 0.05 ml. of concentrated sulfuric acid was refluxed for 10 min. and allowed to stand at room temperature for 30 min. After the usual work-up, the product was obtained as an oil. Thin layer chromatography indicated the presence of two compounds with an α,β-unsaturated carbonyl. One minor component had no carbonyl at 1710 cm.$^{-1}$ and was presumably the 11β-acetoxy-18-hydroxy compound.[28] The desired 11β-hydroxy-18-acetoxyprogesterone (**17**) was obtained as a white solid from ethyl acetate–ether containing a trace of methanol; m.p. 95–110°; $[\alpha]^{20}D$ +175°; $\tilde{\nu}_{max}^{KBr}$ 3700, 3600, 3450 (s) (OH), 1740 (s), 1250 (s) (OAc), 1710 (s) (C=O); 1660 (s), 1610 (m) cm.$^{-1}$ (C=C—C=O); yield 50%. Thin layer chromatography indicated homogeneity.

11→19-Hemiacetal of 11β-Hydroxy-19-oxoprogesterone 3,20-Bisketal (18).—To 4 ml. of cold glacial acetic acid was added 200 mg. of sodium nitrite followed by 200 mg. of the 19-oxime **4**. The mixture was stirred for 2.5 min. at 5°. After the usual work-up, the resulting oil was taken up in 3 ml. of 1% methanol–sodium hydroxide. Upon standing, the product crystallized from the reaction mixture; m.p. (recrystallized from methanol) 245–256°; $[\alpha]^{23}D$ +52°; $\tilde{\nu}_{max}^{KBr}$ 3700 (s) (OH), 3000 (s) cm.$^{-1}$; yield 74%.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 68.92; H, 8.46.

11β,19-Dihydroxyprogesterone 3,20-Bisketal (19).—To a solution of 450 mg. of 11→18-hemiacetal bisketal **18** in 50 ml. of tetrahydrofuran was added 400 mg. of lithium aluminum hydride. The mixture was refluxed for 1.5 hr.; then, after work-up in the usual fashion, the product was crystallized from methanol–ether; m.p. 200–207°; $[\alpha]^{24}D$ −12°; $\tilde{\nu}_{max}^{KBr}$ 3600 (s) (OH), 3000 (s) cm.$^{-1}$; yield 78%.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.35; H, 8.79.

11β,19-Dihydroxyprogesterone (20).—A solution of 150 mg. of the diol bisketal **19** in 4.5 ml. of acetone and 1.25 ml. of water containing 0.05 ml. of concentrated sulfuric acid was refluxed for 15 min. and allowed to stand at room temperature for an additional 30 min. After the usual work-up, the product was obtained as large crystals from ethyl acetate–hexane; m.p. 122–155°; $[\alpha]^{24}D$ +185°; λ_{max}^{MeOH} 243.4 mμ (ϵ 14,600); $\tilde{\nu}_{max}^{KBr}$ 3400 (s) (OH), 3000 (s), 1710 (s) (C=O), 1660 (s), 1610 (m) cm.$^{-1}$ (C=C—C=O); yield 72%.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.79; H, 8.67.

11→19-Lactone of 11β-Hydroxyprogesteron-19-oic Acid 3,20-Bisketal (23).—To 500 mg. of the 11→19-hemiacetal bisketal **18**, dissolved in 10 ml. of pyridine, was added 10 ml. of pyridine containing 1 g. of chromium trioxide. The reaction mixture was stored at room temperature overnight. Following the usual work-up, the product was crystallized from methanol; m.p. 185–190°; $[\alpha]^{21.5}D$ +27°; $\tilde{\nu}_{max}^{KBr}$ 2950 (s), 1775 (s) cm.$^{-1}$ (lactone); yield 80%.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 70.28; H, 7.81. Found: C, 69.97; H, 7.82.

11→19-Hemiacetal of 11β-Hydroxy-19-oxoprogesterone (21) and Its $\Delta^{5,6}$ Isomer (22).—A suspension of 115 mg. of the 11→19-hemiacetal bisketal **18** in 4.5 ml. of acetone and 1.25 ml. of water containing 0.05 ml. of concentrated sulfuric acid was heated under reflux for 15 min. to effect solution and allowed to stand at room temperature for an additional 30 min. After the usual work-up, a mixture of the products was obtained from methanol; m.p. 210–222°; $[\alpha]^{24}D$ +227°; λ_{max}^{MeOH} 246 mμ (ϵ 7800); $\tilde{\nu}_{max}^{KBr}$ 3600 (s) (OH), 3000 (s), 1715 (s) (20-C=O), 1693 (s) (β,γ-unsaturated C=O), 1660 (s), 1610 (m) cm.$^{-1}$ (C=C—C=O); yield 99%.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.94; H, 8.05.

When the above product was heated under reflux in sulfuric acid–acetone (*vide supra*) for 45 min., the ϵ increased to 12,800. When either product was treated with dilute sodium hydroxide, the ultraviolet absorption disappeared and later reappeared at 242 mμ (ϵ 15,800) (*vide infra*).

11β-Hydroxy-19-norprogesterone (6).—A solution of 200 mg. of the isomeric 11→19-hemiacetals **21** and **22** in 10 ml. of 1% methanolic sodium hydroxide was allowed to remain at room temperature for 25 min. The product which had been deposited was collected and recrystallized from methanol; m.p. 218–223°, $[\alpha]^{24}D$ +177°, λ_{max}^{MeOH} 242 mμ (ϵ 15,800), yield 88%; lit.[6] m.p. 215–217°, $[\alpha]D$ +158°, λ_{max}^{EtOH} 242 mμ (ϵ 15,800).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.05; H, 8.98.

11→19-Lactone of 11β-Hydroxyprogesteron-19-oic Acid (25) and Its $\Delta^{5,6}$ Isomer (26). A.—To a solution of 50 mg. of the 11→19-lactone bisketal **23** in 16 ml. of dioxane was added 0.75 ml. of 1 *N* aqueous hydrochloric acid. The solution was stored at room temperature overnight. The usual work-up afforded an isomeric mixture rich in the conjugated isomer **25**: m.p. 212–224°; $[\alpha]^{27}D$ +271°; λ_{max}^{MeOH} 242 mμ (ϵ 12,200); $\tilde{\nu}_{max}^{KB}$ 3000 (s), 1770 (s) (lactone), 1710 (s) (20-C=O), 1680 (s), 1610 (m) cm.$^{-1}$ (C=C—C=O); yield 79%.

B.—A solution of 100 mg. of the 11→19-lactone bisketal in 4.5 ml. of acetone containing 1.25 ml. of water and 0.05 ml. of concentrated sulfuric acid was heated under reflux for 45 min. The usual work-up afforded an isomeric mixture rich in the nonconjugated isomer **26**: m.p. 229–235°; $[\alpha]^{27}D$ +109°; λ_{max}^{MeOH} 242 mμ (ϵ 3000); $\tilde{\nu}_{max}^{KBr}$ 3000 (s), 1700 (s) (lactone), 1720 (s), 1700 (s), 1675 (s), 1610 (w) cm.$^{-1}$ (C=C—C=O); yield 83%.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.47; H, 7.52.

11β,19-Epoxyprogesterone 3,20-Bisketal (24).—To a solution of 120 mg. of the 11β,19-diol bisketal **19** in 3 ml. of pyridine was added 400 mg. of tosyl chloride. The stoppered flask was stored at room temperature for 5 days. At the end of the reaction period, ice was added, the mixture was diluted with water, and the crude product was collected. Recrystallization from methylene chloride–methanol gave **24**: m.p. 187–189°; $[\alpha]^{23}D$ +42.9°; $\tilde{\nu}_{max}^{KBr}$ 2995 (s), 1650 (w) cm.$^{-1}$ (C=C); yield 79%.

Anal. Calcd. for $C_{25}H_{33}O_5$: C, 72.08; H, 8.71. Found: C, 71.99; H, 8.72.

11β,19-Epoxyprogesterone (27) and Its $\Delta^{5,6}$ Isomer (28).—A solution of 60 mg. of the 11β,19-epoxy bisketal **24** in 4.5 ml. of acetone and 1.25 ml. of water containing 0.05 ml. of concentrated sulfuric acid was heated under reflux for 15 min. and allowed to cool for 30 min. After the usual work-up, the product was recrystallized from methanol to give, as a mixture, **27** and **28**: m.p. 169–172°; $[\alpha]^{29}D$ +180°; λ_{max}^{MeOH} 242 mμ (ϵ 98,400); $\tilde{\nu}_{max}^{KBr}$ 2995 (s), 1720 (s) (20C=O), 1695 (s) (β,γ-unsaturated C=O), 1660, (s), 1610 (m) cm.$^{-1}$ (C=O—C=O); yield 75%.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.67; H, 8.50.