$\times 10^{-5}\mu$c./mmole, or approximately 0.1% of the calculated specific activity of the hydrogens in the ammonia used.

Attempted Exchange of IIa-3-*t* with Sodium Amide in Liquid Ammonia.—To a stirred slurry of 2.5 g. (0.064 mole) of sodium amide and 300 ml. of liquid ammonia was added dropwise in 30 min. 24 g. (0.25 mole) of IIa-3-*t*, b.p. 104–107°, containing 7% IVa. When the mixture had stirred for 2 hr., 100 ml. of ether and 5 ml. of water were added cautiously. The ammonia was allowed to evaporate and the ether solution was separated, dried over sodium hydroxide and distilled through the Podbielniak-type column. A 5.0-g. portion of the fraction (17.0 g., 71%) with b.p. 104–106° was freed of IVa by treatment with lithium aluminum hydride, as shown by v.p.c. analysis, and hydrogenated in 80% aqueous ethanol over platinic oxide. The di-*n*-propylamine was isolated as the hydrochloride (4.9 g., 69%). The hydrochloride (0.53 g.) was converted in 85% yield to the *p*-bromobenzenesulfonamide derivative, m.p. 55.0–55.7° after 2 recrystallizations from ethanol, which had a specific activity of $(1.64 \pm 0.03) \times 10^{-2}\mu$c./mmole.

Chromic Acid Oxidation of IX in Tritium-enriched 14 *N* Sulfuric Acid.—Compound IX (0.50 g., 1.9 mmoles) was oxidized with chromic acid as described earlier except the solvent contained 1.0 mc. of tritium oxide. About 5 ml. of water was allowed to co-distil with the propionaldehyde into a solution containing 0.75 g. (5.4 mmoles) of methone. The methone derivative, m.p. 154–155°, weighed 0.50 g. (40%) and had a specific activity of $(1.42 \pm 0.02) \times 10^{-3}\mu$c./mmole. After one recrystallization from dilute ethanol, the methone derivative, m.p. 154.5–155.0°, had a specific activity of $(1.5 \pm 1.5) \times 10^{-5}\mu$c./mmole.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

The Synthesis of 19-Noraldosterone Acetate and Related 19-Substituted Steroids[1]

BY D. H. R. BARTON AND J. M. BEATON

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Corticosterone 3,20-bisethylene ketal 21-acetate 11β-nitrite affords on photolysis a mixture of isomeric 18- and 19-substituted oximes. By further processing the former has been converted into aldosterone acetate. The 19-oxime has been transformed into the 19-substituted isomer of aldosterone (XXIII), into 19-hydroxycorticosterone, into 19-norcorticosterone and finally into 19-noraldosterone acetate. 19-Substituted steroids bearing 11β-hydroxyl groups thus become readily available. Starting with cortisol 3,20-bisethylene ketal 21-acetate 11β-nitrite the derived 18- and 19-oxo-derivatives have been prepared through the oximes in the usual way. The former has been transformed into 17α-hydroxy-18,21-anhydroaldosterone; the latter into the 19-isomer of 17α-hydroxyaldosterone.

Recent work[2] has shown that the photochemically induced exchange of H and NO within nitrite esters, discovered in this Institute,[3] can provide a useful synthetic method for steroids as well as for other types of compound. We have applied[4] the reaction specifically to the synthesis of aldosterone acetate. Photolysis of corticosterone acetate 11β-nitrite (I) gave the C_{18}-oxime II which, on deoximation with nitrous acid, furnished aldosterone acetate III. The same procedure could not be used for the synthesis of the C_{19}-isomer of aldosterone. This was because that moiety of the photolysis product which involved formation of the C_{19}-carbon radical IV involved also intramolecular cyclization to V which, on capture by nitric oxide, afforded the oxime VI. The present paper describes experiments designed to overcome this difficulty. The success that we have attained also has enabled us to prepare 19-noraldosterone acetate.

We reasoned that the cyclization of radical IV to radical V must be facilitated by the fact that the latter radical is resonance stabilized through distribution over oxygen as well as carbon. If, therefore, the 4(5)-ethylenic linkage of I could be moved to 5(6)-, this facilitation would no longer be present and there might be a reasonable chance of securing the true 19-substituted compounds that we desired. This argument was found to be correct by the facts outlined in the sequel.

Corticosterone 3,20-bisethylene ketal 21-acetate[5] (VII, R = H) was converted to the nitrite (VII, R = NO) and photolyzed according to our general method.[3] This afforded two isomeric oximes[6] (VIII) and (X). The 18-oxime VIII was characterised by dehydration with phosphorus oxychloride and pyridine to the nitrile XII. Its constitution was proved by deoximation with nitrous acid to give aldosterone 21-acetate bisethylene ketal (IX) which, on hydrolysis with 90% aqueous acetic acid,[7] afforded aldosterone 21-acetate (III). This procedure amounts to an alternative partial synthesis of the latter.

The 19-oxime X, which at first[1] resisted crystallisation, was characterized by dehydration with phosphorus oxychloride and pyridine which furnished, instead of the expected nitrile, the iminolactone XI. The latter may, of course, have been formed by the working up procedure. Deoximation of the 19-oxime X with nitrous acid afforded the expected masked aldehyde XIII which, on chromic acid oxidation, gave the γ-lactone XIV. Treatment of the latter with dioxane-hydrochloric acid at room temperature gave the mono-ketal XV. This compound was also obtained by similar acid treatment of the bis-ketal XIII under the same conditions to give the monoketal masked aldehyde XVI which on chromic acid oxidation afforded XV.

(1) This paper is Communication No. 14 from the Research Institute for Medicine and Chemistry. For a preliminary report see D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 750 (1961). The article by M. Akhtar and D. H. R. Barton, *ibid.*, **83**, 2213 (1961), is Communication No. 13.

(2) For summary see A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, in press (1961).

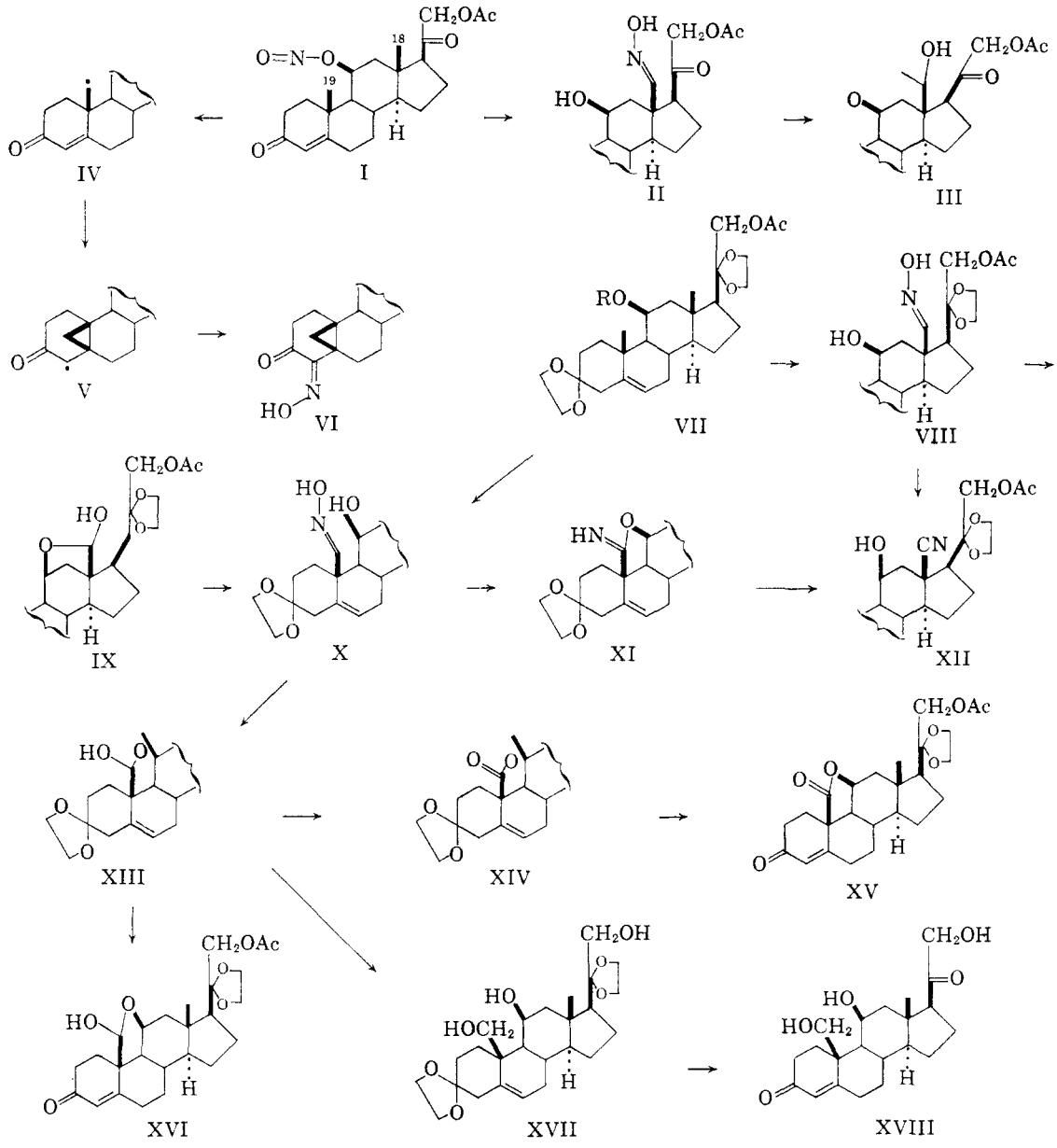
(3) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961).

(4) D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960); **83**, 4083 (1961).

(5) S. Bernstein and R. H. Lenhard, *ibid.*, **77**, 2331 (1955).

(6) For convenience we write these compounds as true oximes, but without commitment on our part as to whether this constitution or the alternative cyclized hydroxylamino-tautomer is correct. We have made this reservation[4] before in analogous compounds.

(7) J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta*, **40**, 2318 (1957).

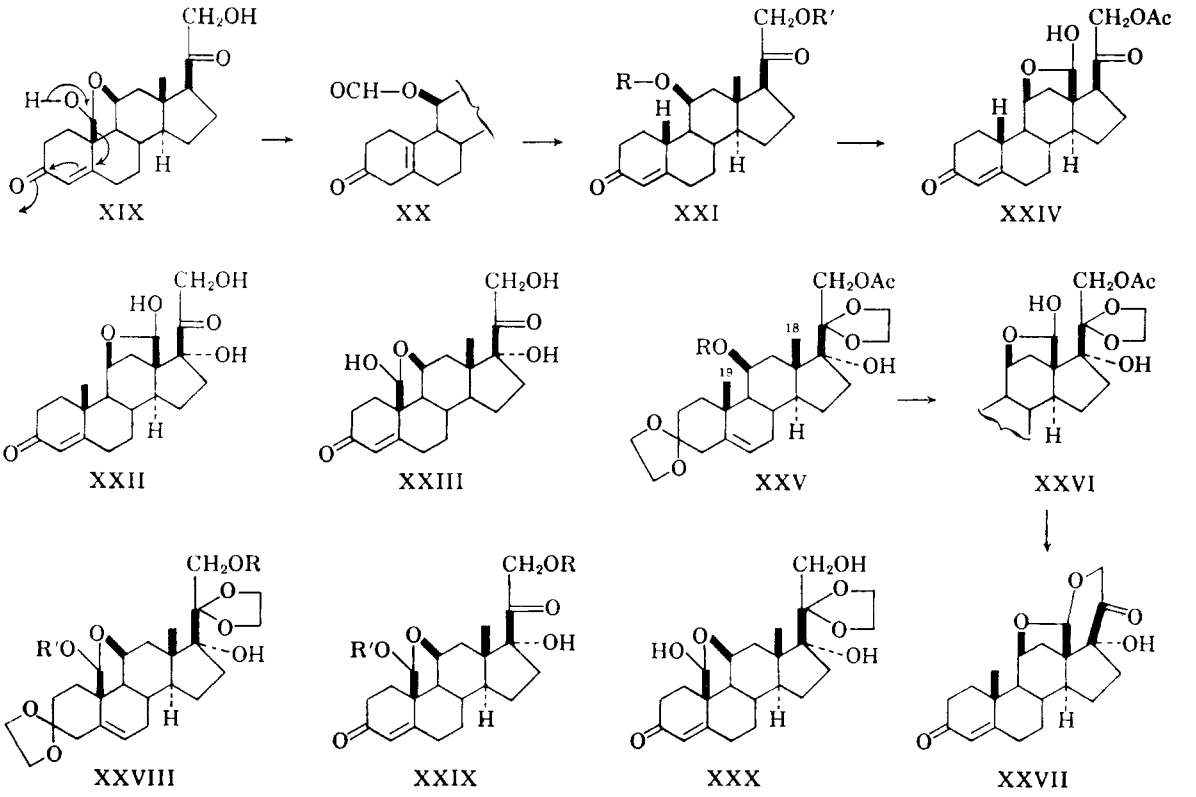


Reduction of the bis-ketal XIII with excess of lithium aluminum hydride afforded the triol XVII which with the dioxane–hydrochloric acid reagent at room temperatures gave, without difficulty, 19-hydroxycorticosterone (XVIII). The constants that we record for this compound are in good agreement with those reported recently by Barber, Peterson and Ehrenstein[8] for a specimen prepared by a microbiological procedure.

Reference already has been made above to the monodeketalization of XIII to give the 20-ketal XVI. In order to remove both ketal groups, the 21-acetate of XIII was first hydrolyzed to give the 21-ol (as XIII). Treatment of this compound with the dioxane–hydrochloric acid reagent then afforded the desired 19-isomer XIX of aldosterone. We expected (XIX, see arrows) that this compound should be a convenient source of 19-nor-derivatives. In the event, treatment of XIX under very mild basic conditions for a short time afforded the isomeric formate XX. Obviously α-protonation at C_4 of the intermediate anion is favored over γ-protonation at C_{10}. Further treatment of XX with mild base then furnished the expected 19-norcorticosterone (XXI, R = R′ = H) with constants in good agreement with those in the literature.[9] This process makes 19-norcorticosterone so easily available that we could consider its conversion into the 19-nor analog of aldosterone acetate. Mild acetylation of 19-norcorticosterone gave the 21-monoacetate (XXI, R = H, R′ = Ac) which on nitrosation and photolysis of the derived nitrite in the usual way[3] gave a product containing the desired 18-oxime. Deoximation with nitrous acid then afforded 19-noraldosterone acetate (XXIV) in satisfactory yield.

(8) G. W. Barber, D. H. Peterson and M. Ehrenstein, *J. Org. Chem.*, **25**, 1168 (1960).

(9) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6110 (1958).



We were now in a position to consider the synthesis of 17α-hydroxyaldosterone (XXII) and of its 19-isomer XXIII. The cortisol bis-ketal 21-acetate (XXV, R = H) was converted to its nitrite (XXV, R = NO) and photolyzed in the usual way.[3] From the product it was possible to crystallize out the 18-oxime which, on deoximation, gave the 17α-hydroxyaldosterone bis-ketal 21-acetate (XXVI). The constitution of this series of compounds was proved by treatment with acid which gave a compound whose composition and functional group content require that it be formulated as 17α-hydroxy-18,21-anhydroaldosterone (XXVII). The conversion of this compound (which is obtained more easily by an alternative synthetic route) into 17α-hydroxyaldosterone (XXII) will be described in a later communication from this Institute.

The isomeric 19-oxime formed in the above-mentioned photolysis could not be obtained easily in pure form, but this was not essential for further progress because on deoximation it gave a highly crystalline and easily isolated masked aldehyde (XXVIII, R = Ac, R′ = H). In practice it was most convenient to deoximate the mixed 18- and 19-oximes obtained from the photolysis and then separate the two masked aldehydes by chromatography. The 19-isomer (XXVIII, R = Ac, R′ = H) could be reduced to the corresponding 11β,17α,19,21-tetrol by lithium aluminum hydride. Acetylation gave the 19,21-diacetate (XXVIII, R = R′ = Ac). Alkaline hydrolysis of the 21-acetate furnished the alcohol (XXVIII, R = R′ = H). On treatment with dioxane–hydrochloric acid this afforded a mixture of the 20-monoketal XXX and the desired 19-isomer XXIII of 17α-hydroxyaldosterone. Treatment of (XXVIII, R = R′ = H) with dioxane–hydrochloric acid containing methanol afforded a monomethyl ether (XXIX, R = H, R′ = Me).

The action of mild base on the 19-isomer XXIII paralleled exactly the behavior observed with 19-oxocorticosterone (XIX, see arrows). The ultraviolet spectrum (maximum at 246 mμ) at first disappeared, due to conversion to the analog of XX, and then reappeared (maximum at 241 mμ) with the same intensity due to the formation of the analog of XXI (R = R′ = H). The monomethyl ether (XXIX, R = H, R′ = Me) and the anhydro-compound XXVII had, as expected, spectra which were stable in basic solution. The constitutions assigned to these 18- and 19-substituted cortisols are thus confirmed.

The biological properties of the compounds described in this paper have been investigated[10]; a report will be presented elsewhere in due course.

Acknowledgments.—We express our thanks to Dr. M. M. Pechet for his interest and encouragement and to Misses L. T. Gendron, R. A. Holland and M. A. Kennedy for their able assistance throughout the course of this work.

Experimental

Microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim (Ruhr), Germany. Infrared spectra were determined using an Infracord model 137 spectrophotometer. Ultraviolet spectra were measured in methanol by means of a Cary model 11 spectrophotometer. Unless otherwise stated, optical rotations were determined in chloroform and m.p.s. on a Kofler-type hot-stage.

Corticosterone 3,20-Bisethylene Ketal 21-Acetate 11-Nitrite (VII, R = NO).—Corticosterone 3,20-bisethylene ketal[5] (23 g.) in pyridine (70 ml.) and acetic anhydride (35 ml.) was kept at room temperature for 20 hr. The gummy

(10) Personal communication from Dr. M. M. Pechet.

product, which had infrared spectrum indicative of 21-acetylation, was taken up in pyridine (75 ml.) and treated with nitrosyl chloride as for corticosterone acetate.[4] Addition of water (4 l.) gave a light brown gum which was separated by decantation, taken up in CH_2Cl_2, dried (Na_2SO_4) and isolated by evaporation *in vacuo*. Chromatography over Florisil (1 kg.) gave the desired 11-nitrite (VII, R = NO) as needles (17.95 g.) from methylene dichloride–hexane, m.p. 134–137°, $[\alpha]_D$ +2°, +6° (*c* 1.2, 1.1); λ_{max} 238, 346, 358, 372 and 386 mμ (ε 1,500, 59, 77, 80 and 60, respectively); λ_{max}^{KBr} 1745(s), 1630(s), 1260(s) and 770(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}O_8N$: C, 64.14; H, 7.78; O, 25.32; N, 2.77. Found: C, 64.15; H, 7.70; O, 25.55; N, 2.84.

Photolysis of Corticosterone 3,20-Bisethylene Ketal 21-Acetate 11-Nitrite (VII, R = NO).—A solution of the nitrite (18.9 g.) in toluene (200 ml.) was irradiated at 30° with a 200 w. mercury arc lamp[3] for 2 hr. (disappearance of the nitrite infrared bands after 1.5 hr.). Concentration of the solution under reduced pressure and cooling gave crystals (2.21 g., m.p. 240–252°) later shown to be the 18-oximino-derivative VIII. Chromatography of the total residual material over alumina (500 g.) afforded first crystalline material (2.3 g.) consisting mainly of 11-dehydrocorticosterone 3,20-bisethylene ketal 21-acetate and then 18-oximinocorticosterone 3,20-bisethylene ketal 21-acetate (VIII) [0.85 g., total yield 3.06 g. (16%)]. The 18-oxime, crystallized for analysis from acetone, formed needles, m.p. 246–252°, $[\alpha]_D$ −44° (*c* 1.1), ε at 207 mμ 3,800; γ_{max}^{KBr} 3200(s), 1745(s), 1650(w) and 1230(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}O_8N$: C, 64.14; H, 7.78; O, 25.32; N, 2.77. Found: C, 63.84; H, 7.47; O, 25.65; N, 3.12.

The mother liquors from crystallization of the 18-oxime were combined with the later oily fractions from the column. Initially[1] the 19-oximino-derivative contained in this material could not be crystallized. In a later experiment two fractions (5.3 g., obtained from 37.5 g. of nitrite), coming from the column immediately after the 18-oximino-derivative, crystallized on standing. Recrystallization from ethyl acetate–hexane afforded 19-oximino-corticosterone 3,20-bisethylene ketal 21-acetate (X) (3.65 g., 9.7%). The analytical sample (2.65 g.) formed needles, m.p. 169–171°, $[\alpha]_D$ −11° (*c* 2.0), ε at 207 mμ 6,200; γ_{max}^{KBr} 3600(m), 3450(s), 1745(s), 1640(w), and 1240(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}O_8N$: C, 64.14; H, 7.78; O, 25.32; N, 2.77. Found: C, 64.04; H, 7.63; O, 25.48; N, 2.88.

In the earlier experiment the combined non-crystalline material (11.5 g., from 18.9 g. of the nitrite), obtained as specified above, was taken up in glacial acetic acid (170 ml.) and treated with aqueous sodium nitrite (85 ml., 5%) at room temperature for 10 min. Extraction into methylene dichloride and crystallization from acetone gave 19-oxocorticosterone 3,20-bisethylene ketal 21-acetate (XIII) as needles (6.27 g., 34%), m.p. 269–275°, $[\alpha]_D$ +47° (*c* 1.1), ε at 206 mμ 2,000; γ_{max}^{KBr} 3600(s), 1745(s) and 1230(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81; O, 26.09. Found: C, 66.04; H, 7.94; O, 26.16.

In the later experiment (based on 37.5 g. of nitrite) nitrous acid treatment of the non-crystalline fractions and mother liquors gave the same 19-aldehyde (10.2 g., 28%). The same compound (165 mg., 85%) was also obtained when the crystalline 19-oximino-derivative (see above; 200 mg.) in glacial acetic acid (20 ml.) was treated with aqueous sodium nitrite (10 ml., 5%) at room temperature for 5 min.

The 18-oximino-derivative VIII (400 mg.) in acetic acid (26 ml.) was similarly treated with aqueous sodium nitrite (13 ml., 5%) at room temperature for 15 min. After neutralization with sodium hydrogen carbonate, dilution with water, extraction into methylene dichloride and crystallization of the product from ethyl acetate, aldosterone 3,20-bisethylene ketal 21-acetate (IX) was obtained as needles, m.p. 189–194°, $[\alpha]_D$ +2°, +3° (*c* 1.2 and 1.0, respectively), ε at 207 mμ 2,030; γ_{max}^{KBr} 3550(m), 1745(s) and 1260(s); $\gamma_{max}^{CHCl_3}$ 3500(m), 1740(s), 1660(w) and 1250(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81; O, 26.09. Found: C, 66.26; H, 7.74; O, 25.74.

Treatment of this bisketal acetate (133 mg.) with aqueous acetic acid (20 ml., 90%) on the steam-bath for 20 min. gave, after removal of the solvent *in vacuo* and chromatography over alumina, aldosterone 21-acetate (9 mg., crystallized from ethyl acetate) identical with material prepared earlier in this Laboratory.[4]

The 18-oximino-derivative VIII was further characterized in the following way. The derivative (200 mg.) in pyridine (4 ml.) and phosphorus oxychloride (0.4 ml.) was heated on the steam-bath for 4 min. Chromatography of the product over alumina and crystallization from ethyl acetate–hexane afforded 18-nitrilocorticosterone 3,20-bisethylene ketal 21-acetate (XII) as prismatic needles (92 mg.), m.p. 127–130°, $[\alpha]_D$ −11°, −13° (*c* 0.9, 1.0, respectively), ε at 208 mμ 2,100; $\gamma_{max}^{CHCl_3}$ 3700(w), 2250(w), 1750(s), 1670(w) and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}O_7N$: C, 66.51; H, 7.65; O, 22.97; N, 2.87. Found: C, 66.39; H, 7.58; O, 23.18; N, 3.11.

Similarly the 19-oximino-derivative X was further characterized in the following way. The crude derivative (1.7 g.) in pyridine (50 ml.) and phosphorus oxychloride (5 ml.) was heated on the steam-bath for 5 min., cooled and poured into ice-water (1 l.). Saturation with sodium chloride, extraction into methylene dichloride and chromatography over alumina (50 g.), gave the iminolactone XI. Recrystallized from ethyl acetate–hexane this formed needles (350 mg.), m.p. 205–210°, $[\alpha]_D$ +29° (*c* 1.1), ε at 206 mμ 3,200; γ_{max}^{KBr} 3500(w), 3300(m), 1740(s), 1680(s) and 1240(s); $\gamma_{max}^{CHCl_3}$ 3300(w), 1750(s), 1685(s) and 1250(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}O_7N$: C, 66.51; H, 7.65; O, 22.97; N, 2.87. Found: C, 66.03, 66.72; H, 7.52, 8.02; O, 23.35, 22.28; N, 2.69, 3.46.

Derivatives of 19-Oxocorticosterone 3,20-Bisethylene Ketal 21-Acetate (XIII). (a) Hydrolysis to the Corresponding Alcohol.—The acetate (250 mg.) in methanol (50 ml.) containing aqueous sodium hydroxide (10 ml., 5%) was refluxed for 15 min. Crystallization of the product from ethyl acetate gave 19-oxocorticosterone 3,20-bis-ethylene ketal as needles (190 mg.), m.p. 259–260°, $[\alpha]_D$ +60°, +61° (*c* 1.1, 1.0), ε at 206 mμ 3,050, γ_{max}^{KBr} 3600(s) and 1660(w) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; O, 24.97. Found: C, 66.66; H, 8.60; O, 24.52.

(b) **Conversion to 19-Oxocorticosterone (XIX).**—The alcohol described above (derived from 2.03 g. of the parent acetate) was kept in dioxane (133 ml.) containing aqueous hydrochloric acid (1 *N*, 15 ml.) at room temperature overnight. Crystallization of the product from ethyl acetate afforded 19-oxocorticosterone (XIX) as needles (1.04 g.), m.p. 180–195°. The analytical sample had m.p. 195–199°, $[\alpha]_D$ +218° (*c* 1.0), λ_{max} 246 mμ (ε 13,100); γ_{max}^{KBr} 3400(s), 1700(s), 1665(s) and 1610(m); $\gamma_{max}^{CHCl_3}$ 3700(w), 3500(m), 1715(s), 1670(s) and 1615(m) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.84; O, 22.19. Found: C, 70.27; H, 7.86; O, 21.70.

(c) **Conversion to 19-Oxocorticosterone 21-Acetate 20-Monoethylene Ketal (XVI).**—19-Oxocorticosterone 3,20-bisethylene ketal 21-acetate (XIII) (2.00 g.) in dioxane (133 ml.) containing aqueous hydrochloric acid (15 ml., 1 *N*) was kept at room temperature for 20 hr. Crystallization of the product from ethyl acetate furnished the 20-monoethylene ketal 21-acetate XVI as prisms (1.05 g.), m.p. 170–185°. The analytical sample had m.p. 170–186°, $[\alpha]_D$ +164° (*c* 1.1), λ_{max} 246 mμ (ε 14,500); γ_{max}^{KBr} 3450(s), 1740(s), 1660(s), 1600(m) and 1240(s) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67; O, 25.08. Found: C, 67.31; H, 7.81; O, 24.67.

(d) **Conversion to the Lactone XIV.**—The bis-ketal acetate XIII (500 mg.) in acetone (300 ml.) was treated at 30° with 8 *N* chromium trioxide (3 equiv.) in aqueous (2 *N*) sulfuric acid with stirring. After 5 min., methanol and water in excess were added and the product was isolated by extraction into methylene dichloride. Filtration through alumina and crystallization from ethyl acetate–hexane gave the lactone XIV as prisms (410 mg.), m.p. 188–191°, $[\alpha]_D$ +19° (*c* 1.1). The analytical sample had m.p. 195–197°, $[\alpha]_D$ +20° (*c* 1.1), ε at 206 mμ 2,700; γ_{max}^{KBr} 1770(s), 1745(s) 1670 (w) and 1240(s); $\gamma_{max}^{CHCl_3}$ 1750(s) and 1240(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43; O, 26.2. Found: C, 66.33; H, 7.25; O, 26.37.

(e) **Conversion to the Lactone Mono-ketal XV.**—19-Oxocorticosterone 21-acetate 20-ethylene ketal (XVI) (150 mg.)

was treated with 8 *N* chromium trioxide solution as detailed above. Crystallization of the product from ethyl acetate–hexane gave the lactone mono-ketal XV as prisms, m.p. 224–234°. The analytical sample had m.p. 225–238°, $[\alpha]_D$ +191° (*c* 1.2), λ_{max} 241 mμ (ε 13,400); γ_{max}^{KBr} 1770(s), 1740(s), 1660(s), 1610(w) and 1230(s); $\gamma_{max}^{CHCl_3}$ 1765(s), 1675(s) and 1620(w) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26; O, 25.20. Found: C, 67.57; H, 7.11; O, 25.10.

The same compound was obtained by treating the bisethylene ketal lactone XIV with dioxane–hydrochloric acid under the conditions exemplified above.

Synthesis of 19-Hydroxycorticosterone.—19-Oxocorticosterone 3,20-bisethylene ketal 21-acetate (XIII) (510 mg.) in dry tetrahydrofuran (200 ml.) was treated with lithium aluminum hydride (500 mg.) and the solution refluxed for 3 hr. Crystallization of the product from acetone–hexane gave 19-hydroxycorticosterone 3,20-bisethylene ketal (XVII) as needles (400 mg.), m.p. 156–162°, $[\alpha]_D$ +4° (*c* 1.0), ε at 207 mμ 2,600, γ_{max}^{KBr} 3450(s), $\gamma_{max}^{CHCl_3}$ 3650(w) and 3450(m) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50; O, 24.86. Found: C, 66.88, 66.97; H, 8.91, 8.31; O, 24.46, 24.61.

The 19-hydroxy-bisketal (from 2.0 g. of the 19-oxo-compound) was taken up in dioxane (135 ml.) containing aqueous hydrochloric acid (15 ml., 1 *N*) and left at room temperature for 20 hr. Crystallization from acetone–hexane gave 19-hydroxycorticosterone (XVIII) (620 mg.) as needles, m.p. 145–152°. The analytical sample, crystallized from ethyl acetate, had m.p. 152–159°, $[\alpha]_D$ +214°, +209° (*c* 1.0, 1.2), λ_{max} 243 mμ (ε 12,300); γ_{max}^{KBr} 3400(s), 1705(s), 1640(s) and 1610(w); $\gamma_{max}^{CHCl_3}$ 3400(s), 1700(s), 1655(s) and 1610(m) cm.$^{-1}$. Barber, Peterson and Ehrenstein[8] report m.p. 163–164°, $[\alpha]_D$ +210°, λ_{max} 243 mμ (ε 12,900) for this compound.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34; O, 22.07. Found: C, 69.70; H, 8.48; O, 22.32.

The Synthesis of 19-Norcorticosterone (XXI, R = R′ = H).—19-Oxocorticosterone (XIX) (500 mg.) in methanol (100 ml.) was treated at room temperature with methanolic sodium hydroxide (0.3 ml., 0.5 *N*) and the disappearance of the 246 mμ band followed spectroscopically. After 10 min., when the absorption had reached a minimum, acetic acid (0.2 ml.) was added and the solvents removed *in vacuo*. Chromatography over alumina and crystallization from methylene dichloride–ethyl acetate–hexane gave the 19-nor-11-formate XX as prisms (375 mg.), m.p. 155–159°, $[\alpha]_D$ +196° (*c* 1.1), ε at 210 mμ 3,100; γ_{max}^{KBr} 3600(s), 1720(s) and 1180(s); $\gamma_{max}^{CHCl_3}$ 3550(m), 1720(s) and 1180(s) cm.$^{-1}$. It gave a yellow color with tetranitromethane.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.84; O, 22.19. Found: C, 69.92; H, 7.85; O, 22.88.

In an analogous experiment 19-oxocorticosterone (XIX) (3.08 g.) in methanol (300 ml.) was treated at room temperature with methanolic sodium hydroxide (60 ml., 0.5 *N*). After 15 min. glacial acetic acid (3 ml.) was added and the solution worked up as above. Crystallization of the product from ethyl acetate gave 19-norcorticosterone (XXI) as prisms (2.57 g.), m.p. 180–195°. The analytical sample had m.p. 191–196°, $[\alpha]_D$ +151° (*c* 1.0), λ_{max} 242 mμ (ε 16,600); γ_{max}^{KBr} 3450(s), 1700(s), 1650(s) and 1620(m); $\gamma_{max}^{CHCl_3}$ 3650(w), 3550(m), 1705(s), 1660(s) and 1620(m) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 72.03; H, 8.32; O, 19.07.

The same compound was obtained by treating the 19-nor 11-formate XX with the same concentration of alkali. Zaffaroni, Ringold, Rosenkranz, Sondheimer, Thomas and Djerassi[9] report m.p. 195–197°, $[\alpha]_D$ +155° (in ethanol), λ_{max} 241 mμ (ε 16,200) for 19-norcorticosterone.

The Synthesis of 19-Noraldosterone Acetate (XXIV). 19-Norcorticosterone (XXI, R = R′ = H) (480 mg.) in pyridine (1.0 ml.) containing acetic anhydride (0.150 ml.) was heated on the steam-bath for 15 min. Crystallization of the product from methylene dichloride–hexane gave 19-norcorticosterone 21-acetate (XXI, R = H, R′ = Ac) as prisms (460 mg.), m.p. 214–219°, $[\alpha]_D$ + 155° (*c* 1.1), λ_{max} 242 mμ (ε 17,000); γ_{max}^{KBr} 3550(s), 1755(s), 1730(s), 1655(s), 1620(m) and 1240(s); $\gamma_{max}^{CHCl_3}$ 3700(w), 3550(w), 1745(s), 1720(s), 1660(s), 1620(m) and 1240(s) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07; O, 21.36. Found: C, 70.36; H, 7.88; O, 21.52.

19-Norcorticosterone acetate (XXI, R = H, R′ = Ac) (2.93 g.) in pyridine (55 ml.) was treated at 0° with excess nitrosyl chloride until a dark green color persisted. Addition of water (1 l.) gave a gum which crystallized on standing. This solid (m.p. 75–90°) had the correct infrared spectrum for the desired 11-nitrite 21-acetate. After drying *in vacuo* at room temperature the nitrite was taken up in benzene (120 ml.) and irradiated at 25° for 1 hr. using a 200 watt mercury arc lamp as detailed earlier.[8] Removal of the benzene *in vacuo* gave a noncrystalline material. This was taken up in acetic acid (200 ml.) and treated with aqueous sodium nitrite (100 ml., 5%) at room temperature for 5 min. The product was chromatographed over alumina (90 g.) to give 19-noraldosterone acetate (XXIV). Recrystallized from ethyl acetate–hexane this formed needles (585 mg., 19.3% overall), m.p. 146–153°. The analytical sample had m.p. 155–163°, $[\alpha]_D$ +79° (*c* 1.2), λ_{max} 239 mμ (ε 17,400); γ_{max}^{KBr} 3550 (s), 1740(s), 1665(s) and 1615(m) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.37; H, 7.30; O, 24.84. Found: C, 68.07; H, 7.10; O, 24.98.

The earlier fractions from the chromatography consisted of unchanged 19-norcorticosterone acetate (160 mg.).

Cortisol 3,20-Bisethylene Ketal 11-Nitrite 21-Acetate (XXV, R = NO).—Cortisol 3,20-bisethylene ketal 21-acetate[11] (XXV, R = H) (800 mg.) in dry pyridine (10 ml.) was cooled to −20° and treated with an excess of nitrosyl chloride in the usual way. Water (3 ml.) was added, the mixture heated on the steam-bath for 2 min. and then more water added gradually to incipient cloudiness. After 5–10 min. crystallization commenced. Recrystallization from methylene dichloride–hexane afforded the desired 11-nitrite (XXV, R = NO) as needles (670 mg.), m.p. 158–160°. The analytical sample had m.p. 160–163°, $[\alpha]_D$ −5°, −7° (*c* 1.0, 1.1), ε at 207 mμ 3,200; λ_{max} 236, 347, 358, 372 and 386 mμ (ε 1,600, 37, 50, 53 and 32, respectively); γ_{max}^{KBr} 3550(s), 3300(w), 1745(s), 1640(s), 1590(m), 1240(s) and 760–785(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}O_9N$: C, 62.17; H, 7.54; O, 27.61; N, 2.69. Found: C, 62.16; H, 7.66; O, 27.56; N, 3.12.

Treatment of this nitrite (200 mg.) with acetic acid (4 ml.) at 90° for 30 min. gave back cortisol 3,20-bisethylene ketal 21-acetate (XXV, R = H).

Photolysis of Cortisol 3,20-Bisethylene Ketal 11-Nitrite 21-Acetate (XXV, R = NO). (a) **Isolation of 18-Oximino-derivative.**—The nitrite (10.0 g.) in benzene (130 ml.) was irradiated at 10° under nitrogen for 1.25 hr. according to our general technique.[8] The benzene was removed *in vacuo* and the residue triturated with acetone to give 18-oximinocortisol 3,20-bisethylene ketal 21-acetate (1.48 g.). The analytical sample, recrystallized from acetone, had m.p. 235–242°, $[\alpha]_D$ −59°, −61° (*c* 1.0, 1.0), ε at 208 mμ 5,600; γ_{max}^{KBr} 3500 (s), 3200(s), 3100(s), 1745(s), 1660(w) and 1645(w) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}O_9N$: C, 62.17; H, 7.54; O, 27.61; N, 2.69. Found: C, 62.67; H, 7.60; O, 26.99; N, 2.92.

This oxime (200 mg.) in glacial acetic acid (13 ml.) was treated with aqueous sodium nitrite (6.5 ml., 5%) at room temperature for 15 min. Crystallization of the product from ethyl acetate–hexane gave 18-oxocortisol 3,20-bisethylene ketal 21-acetate (XXVI) as prisms, m.p. 218–239°, $[\alpha]_D$ −1°, −4° (*c* 0.9, 0.9), ε at 209 mμ 1,500; γ_{max}^{KBr} 3500(s), 1745(s) and 1250(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{36}O_9$: C, 64.01; H, 7.56; O, 28.43. Found: C, 63.34, 64.86; H, 7.60, 7.46; O, 29.07, 27.69.

The isolation of the 19-oxime in a state of purity could not be effected satisfactorily from experiments of this type. Preliminary experiments showed, however, that the derived 19-oxo-compound was easily obtained crystalline and separated from the 18-oxo-derivative. The procedure outlined below was therefore adopted.

(b) **Isolation of 19-Substituted Derivatives.**—The nitrite (XXV, R = NO) (23.6 g.) was photolyzed as above, the benzene removed *in vacuo* and the total product taken up in glacial acetic acid (200 ml.) and treated with aqueous sodium nitrite (100 ml., 5%) at room temperature for 10 min. The product was chromatographed over alumina (200 g.). The early fractions contained small amounts of cortisone and cortisol 3,20-bisethylene ketal 21-acetates and were dis-

(11) W. S. Allen, S. Bernstein and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954), and references there cited.

carded. Later fractions contained the 18-oxo-derivative XXVI (2.25 g.) already described above, whilst further elution afforded the desired 19-oxocortisol 3,20-bis-ethylene ketal 21-acetate (XXVIII, R = Ac, R′ = H) (8.01 g.) as needles from ethyl acetate, m.p. 283–301°. The analytical sample had m.p. 294–302°, $[\alpha]D$ +30° (*c* 0.9), ϵ at 207 mμ 2,100; γ_{max}^{KBr} 3600(s), 1750(s) and 1240(s); $\gamma_{max}^{CHCl_3}$ 3650(m), 1740(s) and 1240(s) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_9$: C, 64.01; H, 7.56; O, 28.43. Found: C, 64.14; H, 7.71; O, 28.21.

The above 19-oxo-21-acetate (XXVIII, R = Ac, R′ = H) (500 mg.) in methanol (100 ml.) and benzene (25 ml.) was refluxed with aqueous sodium hydroxide (20 ml., 5%) for 15 min., then diluted with water (50 ml.) and extracted with methylene dichloride (450 ml.). The product, crystallized from ethyl acetate, gave 19-oxocortisol 3,20-bisethylene ketal (XXVIII, R = R′ = H) (420 mg.), m.p. 311–328°. The analytical sample had m.p. 309–331°, ϵ at 208 mμ 2,200, γ_{max}^{KBr} 3600(s) and 1660(w) cm.$^{-1}$. The compound was too insoluble for determination of $[\alpha]D$.

Anal. Calcd. for $C_{25}H_{36}O_8$. C, 64.63; H, 7.81; O, 27.55. Found: C, 64.51; H, 7.74; O, 27.55.

19-Oxocortisol 3,20-bisethylene ketal 21-acetate on treatment with pyridine–acetic anhydride on the steam-bath for 15 min. gave, after crystallization from ethyl acetate–hexane, the 19,21-diacetate (XXVIII, R = R′ = Ac) as needles, m.p. 236–245°, $[\alpha]D$ −23° (*c* 1.0) ϵ at 208 mμ 2,700; γ_{max}^{KBr} 3550(m), 1745(s) and 1250(s) cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{40}O_{10}$: C, 63.52; H, 7.35; O, 29.16. Found: C, 63.43; H, 7.55; O, 29.07.

19-Oxocortisol (XXIII) and Related Compounds.—19-Oxocortisol 3,20-bisethylene ketal (XXVIII, R = R′ = H) (see above) (1.63 g.) was taken up in dioxane (80 ml.) and water (20 ml.) and treated with water (20 ml.) and aqueous hydrochloric acid (40 ml., 2 *N*) at room temperature for 12 hr. The solution was concentrated *in vacuo* and the solid product filtered off. Chromatography over alumina in methylene dichloride containing increasing amounts of methanol gave first 19-oxocortisol 20-monoethylene ketal (XXX) (700 mg.). Crystallized from ethyl acetate–methanol this had m.p. 205–209°, λ_{max} 246 mμ (ϵ 13,000) (the max. disappeared on addition of a trace of alkali); γ_{max}^{KBr} 3500(s), 1665(s) and 1615(m) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67; O, 26.64. Found: C, 65.78; H, 7.74; O, 26.69.

Further elution afforded 19-oxocortisol (XXIII) as needles (180 mg.) from ethyl acetate–methanol or ethyl acetate–hexane, m.p. 208–241°, λ_{max} 246 mμ (ϵ 13,000), disappearing on addition of trace of alkali and reappearing (at 241 mμ) with the original intensity on the addition of more alkali; γ_{max}^{KBr} 3500(s), 1705(s), 1655(s) and 1610(m) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50; O, 25.50. Found: C, 66.70; H, 7.60; O, 25.67.

In a related experiment 19-oxocortisol 3,20-bisethylene ketal (XXVIII), R = R = H) (4.0 g.) in dioxane (200 ml.), methanol (70 ml.) and aqueous hydrochloric acid (90 ml., 1 *N*) was warmed briefly to effect dissolution and then kept at room temperature for 24 hr. Chromatography of the product over alumina (120 g.) gave, as major crystalline product, 19-oxocortisol 19-methyl ether (XXIX, R = H, R′ = Me). Crystallized from ethyl acetate this formed needles (600 mg.), m.p. 220–241, $[\alpha]D$ +73° (*c* 1.0), λ_{max} 244 mμ (ϵ 15,600), unchanged on addition of alkali; γ_{max}^{KBr} 3550(s), 1660(s) and 1615(m) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74; O, 24.59; OMe, 7.95. Found: C, 67.73; H, 7.66; O, 24.99; OMe, 9.44.

19-Oxocortisol 3,20-bisethylene ketal 21-acetate (XXVIII, R = Ac, R′ = H) (3.96 g.) in tetrahydrofuran (800 ml.) was refluxed with lithium aluminum hydride (4.5 g.) for 3 hr. Crystallization of the product from aqueous methanol furnished 19-hydroxycortisol 3,20-bisethylene ketal (2.34 g.). The analytical sample, crystallized from ethyl acetate–methanol, had m.p. 248–251°, γ_{max}^{KBr} 3600(s), 3500(s), 3400(s), 3250(s) and 1670(w) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_8$: C, 64.36; H, 8.21; O, 27.44. Found: C, 64.01; H, 8.01; O, 27.58.

18,21-Anhydro-17α-hydroxyaldosterone (XXVII).—18-Oxocortisol 3,20-bisethylene ketal 21-acetate (XXVI) (300 mg.) in dioxane (18 ml.) containing water (42 ml.) and concd. sulfuric acid (3.6 ml.) was heated under nitrogen on the steam bath for 105 min. Addition of water and extraction into methylene dichloride gave, on crystallization from ethyl acetate, 18,21-anhydro-17α-hydroxyaldosterone (XXVII) as needles (95 mg.), m.p. 201–210°. The analytical sample had m.p. 203–214°, $[\alpha]D$ +200° (*c* 1.0), λ_{max} 239 mμ (ϵ 16,500); γ_{max}^{KBr} 3550(s), 1730(s), 1670(s), and 1620(m); $\gamma_{max}^{CHCl_3}$ 3600(m), 1730(s), 1665(s) and 1620(m) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31; O, 22.32. Found: C, 70.18; H, 7.35; O, 22.46.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO., KALAMAZOO, MICH.]

Nuclear Magnetic Resonance Studies on Some Hydrocarbon Side Chains of Steroids

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Nuclear magnetic resonance spectra of some common steroids with hydrocarbon side chains have been studied. The methyl regions have been factored and assigned. The results are applied to the identification of an unknown methylated steroid.

Chemists often perform exploratory reactions on sterols because they offer a convenient source of rigid molecules with known stereochemistry. However, the structural analysis of the products by proton magnetic resonance spectroscopy is quite difficult. The methyl–hydrogen region of the spectrum is so cluttered with absorptions from the side chains that those from the angular methyls[1] or from other methyl substitutents[2] have been difficult to identify. A study of the methyl absorptions of some of the common sterols, which is reported herein, has clarified this region of the spectrum to the point where useful structural data can be obtained from it.

The absorption frequencies of the angular methyls in the steroid molecule vary[1] depending on the nature and position of other substituents nearby and the anisotropy corrections form the basis for many structural assignments. Hydrocarbon chains at the 17β-position caused the 18-methyl absorption frequency for most steroids to be about 2 c.p.s.[3] lower than those for the corresponding 20-keto analogs. There was no contribution from the 22,23-double bond.

(1) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(2) G. Slomp and B. R. McGarvey, *ibid.*, **81**, 2200 (1959).

(3) All absorption frequencies are recorded in c.p.s. at 60 megacycles (unless otherwise noted) to obviate the need for analyzing unknown multiplets.