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A Partial Synthesis of 11β,17α,21-Trihydroxy-A-nor-3(5)-pregnene-2,20-dione, an A-Nor Homolog of Hydrocortisone

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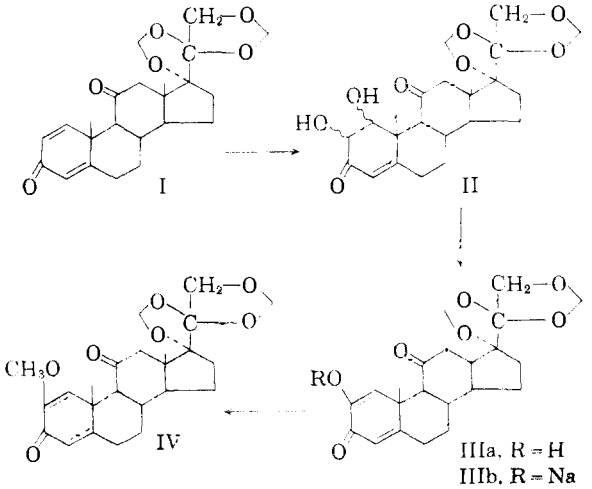
RECEIVED NOVEMBER 25, 1958

The conversion of prednisone to 11β,17α,21-trihydroxy-A-nor-3(5)-pregnene-2,20-dione is described. The ring contraction was effected by a benzilic acid rearrangement on a 2,3-diketo-Δ^4-steroid.

The preparation and biological activities of compounds closely related to hydrocortisone have appeared in numerous publications in recent years. In these studies the effects upon pharmacological activity resulting from the introduction of halogen atoms,[1] double bonds,[2] methyl[3] and hydroxy[4] groups as well as combinations of these functions[5] have been examined. Modifications in the hydrocortisone molecule whereby the cortical side-chain becomes part of 4-[5g,6] or 5-membered[7] rings are also known. Two further homologs of hydrocortisone or cortisone, a 19-nor compound[8a] and a D-homo compound[8b] have been described.

While several A-nor-steroids including 2α-hydroxy-A-nor-androstan-17-one have been reported,[9] they are not closely related to the cortical steroids. Jacobs and Takahashi[10] recently described the preparation of A-nor-3(5)-cholesten-2-one *via* the saturated A-nor ketone. They reported unsuccessful attempts to prepare 2-keto-4-nor-$\Delta^{3(5)}$-steroids from the corresponding unsaturated 6-membered ketones.

In this paper we report the conversion of prednisone to 11β,17α,21-trihydroxy-A-nor-3(5)-pregnene-2,20-dione (XIII). We effected the contraction of the A-ring by a benzilic acid rearrangement using the α-diketone III which was prepared as shown in Chart I. Prednisone-BMD (I)[11] reacted readily with osmium tetroxide in pyridine solution. Decomposition of the osmate ester with hydrogen sulfide[12] followed by fractional crystallization afforded a substance which reduced tetrazolium reagent and which retained an α,β-unsaturated ketone system as shown by its ultraviolet and infrared spectra. The selective hydroxylation must have been effected at C-1 and C-2 as desired, since only this course will be consistent with the conversion of the resulting diol II to a β,γ-unsaturated-2-keto-A-nor-steroid as described below. Dehydration of II with methanolic alkoxide solution resulted in the formation of the diosphenol IIIa which gave a negative tetrazolium test but a strong ferric chloride test.



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(4) E. J. Agnello, B. L. Bloom and G. D. Laubach, *ibid.*, **77**, 4684 (1955); W. S. Allen and S. Bernstein, *ibid.*, **78**, 1909 (1956); G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957); A. L. Nussbaum, G. Brabazon, T. L. Popper and E. P. Oliveto, THIS JOURNAL, **80**, 2722 (1958).

(5) (a) R. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *ibid.*, **77**, 3166 (1955); (b) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956); (c) G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider and J. A. Hogg, *ibid.*, **79**, 1515 (1957); (d) A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik and E. B. Hershberg, *ibid.*, **77**, 4184 (1955); (e) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955); (f) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman, *ibid.*, **77**, 4438 (1955); (g) J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *ibid.*, **78**, 4813 (1956); (h) S. Bernstein, M. Heller, R. Littell, S. Stolar, R. Lenhard and W. Allen, *ibid.*, **79**, 4555 (1957).

(6) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker and J. M. Chemerda, *ibid.*, **78**, 4814 (1956).

(7) W. S. Allen and S. Bernstein, *ibid.*, **78**, 3223 (1956).

(8) (a) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954); B. J. Magerlein and J. A. Hogg, *ibid.*, **79**, 1508 (1957); **80**, 2226 (1958); (b) R. O. Clinton, H. C. Neumann, A. J. Mason, S. C. Laskowski and R. G. Christiansen, *ibid.*, **80**, 3305 (1958).

(9) See, *e.g.*, A. Georg, "Elsevier's Encyclopedia of Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1954, Series III, Vol. 14, Suppl., pp. 1371S–1738S.

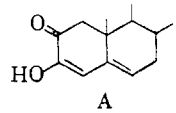
(10) T. L. Jacobs and N. Takahashi, THIS JOURNAL, **80**, 4865 (1958).

(11) R. E. Beyler, R. M. Moriarty, F. Hoffman and L. H. Sarett, *ibid.*, **80**, 1517 (1958). The designation "BMD" signifies "bismethylenedioxy."

(12) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085 (1956).

It was found most convenient to precipitate the diosphenol from the reaction mixture directly as the sodio derivative IIIb. The structure assigned to III is also consistent with its spectral characteristics[13] ($\lambda_{max}^{CH_3OH}$ 249 mμ, infl. 295 mμ). It was converted by treatment with methyl iodide in refluxing acetone to the monomethyl ether IV.

The sodium salt of the diosphenol had only limited solubility in water or in aqueous alkali, but heating a dilute solution of IIIb in aqueous sodium hydroxide on a steam-bath overnight effected chemical changes. The fraction of the reaction mixture which was soluble in bicarbonate[14] afforded two



A

carboxylic acids V and VI. The lower melting acid (Acid A) (V) analyzed for $C_{23}H_{32}O_9$ and afforded a methyl ester $C_{24}H_{34}O_9$ which gave a negative tetranitromethane test. N. Trenner and B. Arison of these laboratories[15] found the compound to be devoid of olefinic protons. The higher melting acid (Acid B) (VI), however, analyzed for $C_{23}H_{30}O_8$ and gave a strong tetranitromethane test. These formulations, which imply that the 3-keto-Δ^4-steroid III does not undergo the benzilic acid rearrangement *per se*, are also in accord with the transformations described below. The two acids were separated readily by fractional crystallization, the lower melting isomer A being the less soluble compound. When barium hydroxide[16] was the base employed in the benzilic acid rearrangement a higher proportion of acid B was isolated.

Reduction of acid A with lithium aluminum hydride gave a mixture of two tetrols which was not separated but oxidized directly with periodate at a *p*H of about 6. The crude product showed no selective absorption in the ultraviolet. The infrared spectrum revealed strong absorption at 5.77 μ, indicative of a saturated five-membered ketone, as well as absorption at 2.85–2.95 μ (OH) and at 9.1–9.2 μ (BMD). Accordingly the hydride reduction product was formulated as a mixture of the tetrols VII and VIII and the periodate oxidation product as a mixture of the β-hydroxy ketones IX and X. These structure assignments are consistent with the facile conversion of IX and X with alkoxide into the conjugated ketones XI and XII which were separated by partition chromatography. The nature of the isomerism of compounds XI and XII was shown to be epimerism of the secondary hydroxyl group (C-11) because XI and XII could be oxidized to a common ketone XIV. The less mobile isomer XII was assigned the equatorial[17] 11α-configuration. Since a configurational assignment based on comparative mobility is not infallible,[18] additional chemical support was desired. The proposed 11α-isomer was readily acetylated with pyridine and acetic anhydride at room temperature, whereas the 11β-epimer was recovered unchanged under these conditions. Rotation data were also in accord with the assigned configurations. The levorotatory shift brought about by ring contraction is of interest. Treatment of XI with dilute formic acid at room temperature for three days afforded the desired A-norhydrocortisone XIII. The position of the absorption maxima in compounds XI and XII at 233–234 mμ further supports the 2-keto-4-nor-$\Delta^{3(5)}$-structures over their 3-keto-4-nor-Δ^1-isomers.

Acid A also was treated with lead tetraacetate in methanol–benzene. The product showed no selective absorption in the ultraviolet and contained no olefinic protons,[15] but it revealed a strong hydroxy peak in the infrared. The analysis was consistent with a 2-keto-5-hydroxy structure analogous to X. Treatment with alkoxide readily afforded A-norcortisone BMD (XIV) which shows an absorption maximum at 229 mμ. Thus the 11-keto-compound XIV absorbs at shorter wave lengths than XI and XII. The 11-oxygenated 3-keto-4-pregnenes follow a similar pattern. Treatment of A-norcortisone BMD with dilute acetic acid on a steam-bath for fourteen hours gave A-norcortisone XV.

When acid B was similarly cleaved with lead tetraacetate, the crude product showed no selective absorption in the ultraviolet, but it contained one olefinic proton[15] and gave a strong tetranitromethane test. It showed no hydroxy peak in the infrared. On treatment with alkoxide the double bond was readily isomerized to give XIV. Hence the double bonds in Acid B and in its lead tetraacetate cleavage product are in the 5,6-position. It is apparent that the formation of a β,γ-unsaturated ketone requires that the osmylation of I occurred at positions 1 and 2. An aliquot of the total crude acidic fraction also was cleaved with lead tetraacetate. The product was essentially devoid of absorption at 229 mμ indicating that no significant amounts of a $\Delta^{3(5)}$-steroid are formed during the benzilic acid rearrangement.

The infrared spectra of the α,β-unsaturated ketones are noteworthy. A-Norhydrocortisone BMD, *e.g.*, in addition to the double bond peak at 6.12 μ showed *two* distinct *carbonyl* peaks (5.86 and 5.94 μ) in chloroform solution which are assigned the single carbonyl group at C-2. The unexpected peak at 5.94 μ was the more intense one. In toluene the intensity relationship of the two maxima was

(13) The same A-ring chromophore has been described recently by J. S. Baran [THIS JOURNAL, **80**, 1687 (1958)] who prepared it by different synthetic schemes from that described above.

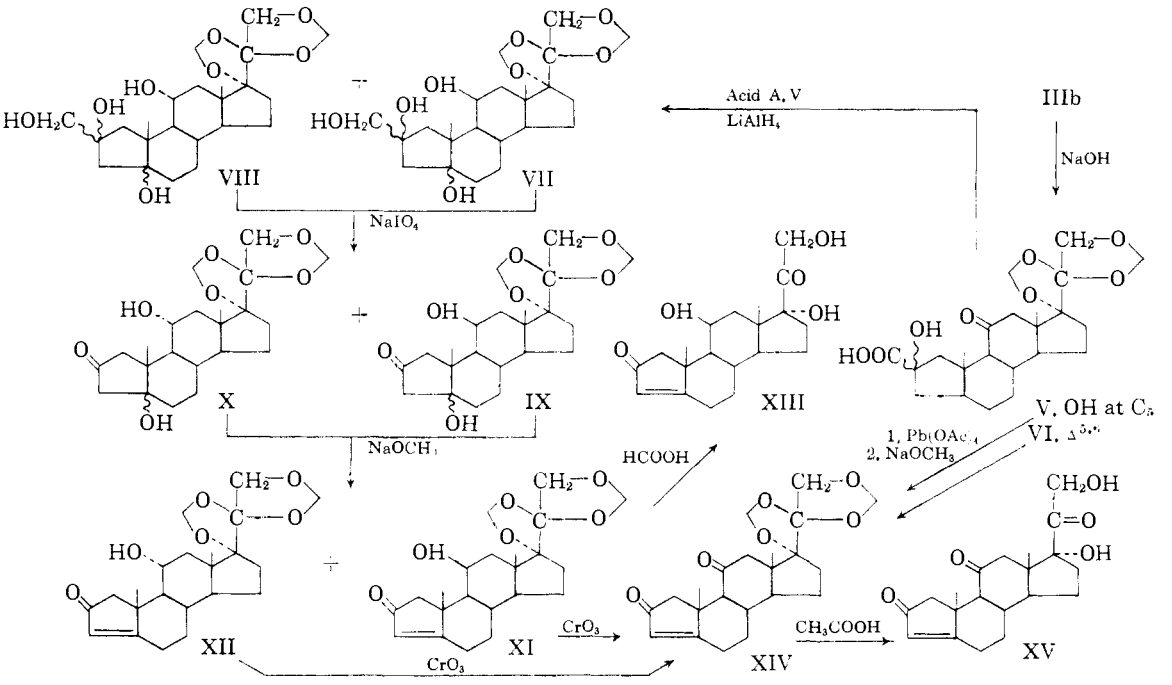
(14) The bicarbonate-insoluble fraction gave a strong ferric chloride test. This material was not fully characterized. It showed a strong absorption maximum at 315 mμ, which may be due to the isomeric diosphenol of structure A for which the calculated absorption maximum is at 321 mμ (*cf.* L. F. Fieser, M. Fieser and S. Rajagopalan [*J. Org. Chem.*, **13**, 800 (1948)].

(15) We are very much indebted to N. Trenner and B. Arison for the nuclear magnetic resonance studies.

(16) E. Pfeil, G. Geissler, W. Jacquemin and F. Lömkes, *Ber.*, **89**, 1210 (1956).

(17) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953).

(18) C. Sannie and H. Lapin [*Bull. soc. chim. France*, 1008 (1952)] as well as W. J. McAleer and M. A. Kozlowski [*Arch. Biochem. & Biophys.*, **66**, 120 (1957)] found rockogenin to be less polar than epirockogenin. The former compound had been shown to be the equatorial 12β-hydroxy isomer [R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, THIS JOURNAL, **76**, 4013 (1954)]. A similar situation exists with 7-hydroxy steroids [W. J. McAleer and M. A. Kozlowski, T. Stoudt and J. M. Chemerda, *J. Org. Chem.*, **23**, 958 (1958)]; see also S. G. Brooks, J. S. Hunt, A. G. Long and B. Mooney, *J. Chem. Soc.*, 1175 (1957).



reversed. These results are, however, not without precedent.[19,20,21]

Bioassay: A-norhydrocortisone and A-norcortisone were inactive in the liver glycogen deposition and the granuloma inhibition tests. These assays were kindly performed by Dr. R. Silber and Dr. H. Stoerk and their collaborators of these laboratories.

Experimental[22]

Hydroxylation of Prednisone BMD.—A solution of 100 g. of prednisone BMD[11] (I) in 720 ml. of pyridine was cooled to 5° and treated with a solution of 69.9 g. of osmium tetroxide in 408 ml. of pyridine. The mixture, which turned black within five minutes, was allowed to stand at room temperature for five days when it was added with stirring to 13.4 l. of petroleum ether. The crude osmate ester was isolated by filtration and washed with petroleum ether to remove most of the residual pyridine. The crude product was then dissolved in 8 l. of dioxane and kept in an ice-bath while a slow stream of hydrogen sulfide[12] was bubbled through the reaction mixture. The precipitated osmium dioxide was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residual foam was dissolved in 2 l. of acetone, decolorized with activated carbon, filtered and concentrated to a volume of 1 l. Addition of 1 l. of Skellysolve B afforded 38 g. of 1ζ,2ζ-dihydroxycortisone BMD (II), $\lambda_{max}^{CH_3OH}$ 236 mμ (log ε 4.15); $\lambda_{max}^{CHCl_3}$ 2.85, 5.95, 6.15, 5.85–5.90sh μ; λ_{max} 9–9.2 μ. When inserted into a m.p. bath at 200°, the compound underwent an immediate change in crystal structure and melted at 232–234°. Paper chromatography showed this did not involve a chemical change such as dehydration to the diosphenol III. The mother liquor afforded two further crops, m.p. 228–230° and 227–228.5°, amounting to 3.48 and 10.55 g., respectively. Further recrystallization of the first crop from the same solvent pair raised the m.p. to 244–245° (70% recovery). An analytical sample was obtained by paper chromatography using methanol–formamide (2:1) as the stationary phase and chloroform as the mobile phase.[23] Isolation by crystallization from acetone–Skellysolve B did not give a sample of improved m.p. *Anal.* Calcd. for $C_{27}H_{30}O_8 \cdot C_3H_6O$: C, 63.40; H, 7.37. Found: C, 63.84; H, 7.35. The compound gave a positive tetrazolium test and a negative ferric chloride test. The extinction of the former was about two-thirds that given by cortisone.

2-Carboxy-2ξ,17α,21-trihydroxy-A-nor-pregnene-11,20-dione BMD (VI) and its 5ξ-hydroxy-A-nor-pregnane analog V. (a) Sodium Salt IIIb of the Diosphenol.—To a solution of 3.09 g. of the above glycol in 75 ml. of hot methanol was added 52 ml. of a solution of sodium methoxide in methanol (0.14 *N*). The mixture was heated on a steam-bath until a tetrazolium test was essentially negative. The bulk of the methanol was removed *in vacuo*, about 250 ml. of ether was added and the product was isolated by filtration affording 3.15 g. of a very hygroscopic solid; $\lambda_{max}^{0.1N\ NaOH}$ 227 mμ (log ε >4.18), 352 mμ (>3.41); 252sh mμ (>3.86); $\lambda_{max}^{CHCl_3}$ 5.86, 6.05, 6.2, 6.32, 9.05–9.2 μ (BMD). In another experiment (14.5-g. scale), treatment of I with a 5% excess of sodium methoxide afforded 11.39 g. of the sodio derivative IIIb. The latter sample was dried at 100° for two hours, resulting in a weight loss of 8%. *Anal.* Calcd. for $C_{23}H_{27}O_7Na \cdot (H_2O)_{1/2}$: C, 61.73; H, 6.31; Na, 5.14. Found: C, 61.94; H, 6.39; Na, 4.93. This preparation decomposed to a large extent on standing at room temperature for three months. In methanol the sodium salt showed the characteristic ultraviolet absorption pattern of the free diosphenol IIIa (λ_{max} 252 mμ, infl. 292 mμ, see below).

(b) Benzilic Acid Rearrangement. Acid A (V).—A mixture of 5.05 g. of the above sodio-derivative of the diosphenol was heated on a steam-bath overnight in a nitrogen atmosphere with 240 ml. of a 1.55 *N* aqueous solution of sodium hydroxide. The solution was acidified in the cold, the resulting acid extracted into ethyl acetate and washed with a saturated salt solution. The acid was purified *via* its sodium salt by extraction into sodium bicarbonate fol-

(19) See *e.g.*, (a) R. N. Jones, T. Ito and C. L. Angell, *Angew Chem.*, **69**, 645 (1957); (b) P. Wieland, K. Heusler, H. Ueberwasser and A. Wettstein, *Helv. Chim. Acta*, **41**, 74 (1958); (c) P. Yates, N. Yoda, W. Brown and B. Mann, THIS JOURNAL, **80**, 202 (1958).

(20) To dispel all doubt that the chromophore is anything but a five-membered α,β-unsaturated ketone, we hydrogenated the double bond. The resulting product showed the typical maxima of a 5-membered ketone at 5.76 μ. Therefore the size of ring A in the final product is fully verified.

(21) After this manuscript was submitted P. Yates and L. L. Williams (*ibid.*, **80**, 5896 (1958)) provided strong evidence that in simpler cyclopentenones the unexpected peak results from Fermi resonance[19a] between the true carbonyl stretching vibration and an overtone of the out of plane bending vibration of the ethylenic α-hydrogen. Our α,β-unsaturated cyclopentenones absorb at 11.65 μ in accord with this concept.

(22) All melting points are uncorrected. We are greatly indebted to Mr. R. Boos and his collaborators for C and H analyses reported herein.

(23) A. Zaffaroni, R. B. Burton and E. H. Keutmann, *Science*, **111**, 6 (1950).

lowed by reacidification and extraction into ethyl acetate. Removal of the solvent gave an amorphous solid which was decolorized with activated carbon and crystallized from acetone–Skellysolve B. The product (965 mg.) melted at 197–199.5° dec. and was further recrystallized from methanol–water, then from acetone–Skellysolve B and dried at 80° to give the colorless, analytically pure acid, m.p. 202–203°, $[\alpha]^{Py}D$ −75.5°. *Anal.* Calcd. for $C_{23}H_{32}O_9$: C, 61.05; H, 7.13. Found: C, 60.91; H, 7.03. Treatment with diazomethane gave the methyl ester, m.p. 253–256°, which gave a negative tetranitromethane test and contained no olefinic protons.[15] *Anal.* Calcd. for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 62.02; H. 7.31.

Acid B (VI).—The mother liquor from the initial crystallization of acid A (see above) was taken to dryness. Dissolution in acetone, followed by the addition of Skellysolve B gave only a red oil. The supernatant was separated by decantation and afforded, after the addition of more Skellysolve B, a crystalline solid, m.p. *ca.* 220°. Repeated recrystallization from the same solvent pair gave an analytical sample, m.p. 250–252°, $[\alpha]^{Py}D$ −98.3° which gave a positive tetranitromethane test. *Anal.* Calcd. for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.63; H, 6.89.

In another experiment 2.0 g. of the sodio-derivative IIIb was suspended in a solution of 38.6 g. of barium hydroxide in 265 ml. of water and heated on a steam-bath with vigorous stirring in a nitrogen atmosphere overnight. The mixture was filtered, the filtrate made acid to congo red and the acid extracted with ethyl acetate. The A-nor-acid was purified *via* its sodium salt as described above. Crystallization from acetone–Skellysolve B gave acid B (210 mg.), m.p. *ca.* 240–245°.

(c) Alternate Preparation of A-Nor-acid from II.—A 2.65-g. sample of the glycol II was dissolved in 35 ml. of methanol, 5 ml. of a 2.5 *N* solution of sodium hydroxide was added and the mixture was refluxed for about three minutes (negative tetrazolium test). The bulk of the solvents was removed *in vacuo*. The residue, which proved insoluble in water, was acidified with hydrochloric acid, the diosphenol was extracted into ethyl acetate and the resulting solution was washed twice with a saturated salt solution. An aliquot was taken to dryness to afford the crude diosphenol, $\lambda_{max}^{CH_3OH}$ 252 mμ (log ε 4.05), infl. 292 mμ (3.43); addition of one drop of 2.5 *N* aqueous sodium hydroxide solution produced a marked change in the spectrum, λ_{max} 226 mμ (log ε 4.24), 345 mμ (3.23), infl. 250 mμ (3.89). This change could be reversed with acid.

The bulk of the organic layer, which still contained mineral acid, was repeatedly extracted with a dilute solution of sodium hydroxide causing the sodium salt of the diosphenol (IIIb) to separate at the interface. The combined solids were heated on a steam-bath with 300 ml. of 1.1 *N* sodium hydroxide overnight. The isolation of the A-nor-acid "A" (200 mg., m.p. 197–200°) was carried out essentially as described above. The bicarbonate-insoluble fraction from the benzilic acid rearrangement was washed free of bicarbonate, dried over magnesium sulfate and taken to dryness to give 60 mg. of a brown solid which gave a strong ferric chloride test[14]; $\lambda_{max}^{CH_3OH}$ 315 mμ (log ε 3.69), infl. 235 mμ (3.57).

After separation of the interface-solids from the dehydration step, as described above, the ethyl acetate layer was washed until neutral, dried and taken to dryness. The residue, which left no residue on burning, was shown to be the free diosphenol IIIa on the basis of its ultraviolet absorption spectrum. In the infrared it showed λ_{max}^{Nj} 2.99, 5.85, 6.07 μ; $\lambda_{max}^{CHCl_3}$ 2.9, 5.85, 5.96, 6.08, 6.18, 9, −9.2 μ.

5,11β,17α,21-Tetrahydroxy-4-nor-5ξ-pregnane-2,20-dione BMD (IX) and its 11-Epimer X. (1) Lithium Aluminum Hydride Reduction of Acid A.—About 615 mg. of lithium aluminum hydride, suspended in 29 ml. of dry dioxane, was heated to reflux in a nitrogen atmosphere. A solution of 525 mg. of acid A, m.p. 196–198°, in 40 ml. of dioxane was added over a period of 25 minutes. After refluxing was continued for an additional hour, the mixture was cooled, excess hydride was decomposed with ethyl acetate, and a saturated solution of sodium chloride was added. The mixture was filtered and the inorganic residue was washed with more ethyl acetate. The combined ethyl acetate extracts were washed with a solution of sodium bicarbonate and then with a saturated salt solution, dried and taken to dryness to give 480 mg. of an amorphous foam consisting of a mixture of the 11-epimeric tetrols VII and VIII.

(2) Periodate Oxidation and Isomerization.—A 465-mg. aliquot of the above mixture was dissolved in 61 ml. of ethanol and treated with a solution of 1.02 g. of sodium metaperiodate in about 20 ml. of water, followed by 19 drops of sodium bicarbonate (5% aqueous solution) which raised the *p*H of the mixture to about 6. The mixture was stirred overnight and the alcohol as well as the bulk of the water were removed *in vacuo*. The residue was distributed between ethyl acetate and water and the aqueous layer was back-extracted with ethyl acetate. The combined organic extracts were washed with water and a saturated salt solution to afford, after drying, an amorphous foam which showed no selective absorption in the ultraviolet and absorbed at 2.85–2.95 μ (OH), 5.77 μ (saturated 5-membered ketone) 9.1–9.2 μ (BMD) in the infrared.

The bulk of the 5ξ-hydroxy-2-ketones was dissolved in 100 ml. of methanol and allowed to react with 10.4 ml. of an alkoxide solution (prepared by dissolving 9.2 g. of sodium methoxide in 200 ml. of methanol) at room temperature for two hours. The base was neutralized with acetic acid and the solvent was removed *in vacuo*. Water was added and the resulting solid (285 mg.) removed by filtration. The product showed λ_{max}^{NaOH} 233 mμ (log ε 4.16).

The epimeric mixture was purified by partition-chromatography on Super-Cel[24] using methanol–formamide (III) as the stationary phase and benzene as the mobile phase[23] and taking 50-ml. fractions. Fraction 12, after crystallization from acetone–Skellysolve B, gave 42 mg. of **11β,17α,21-trihydroxy-A-nor-3(5)-pregnene-2,20-dione BMD (XI)**, m.p. 241–243°, $[\alpha]^{CHCl_3}D$ −73.6°, $\lambda_{max}^{CH_3OH}$ 234 mμ (log ε 4.18); $\lambda_{max}^{CHCl_3}$ 2.75–2.95, 5.86(strong), 5.94(stronger), 6.12(strong), 9.05–9.15 μ; λ_{max}^{tol} 2.77, 5.86(strong), 5.95(moderate), 6.14 μ (moderate). *Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.78; H, 7.80.

Fractions 10 and 11 afforded an additional 109 mg. of the 11β-isomer which was single spot material by paper chromatography but which melted at 217–220°; a mixed m.p. with a sample, m.p. 241–243°, was 239–241°.

Cuts 15 and 16 were similarly crystallized from acetone–Skellysolve B to give 37 mg. of **11α,17α,21-trihydroxy-A-nor-3(5)-pregnene-2,20-dione BMD (XII)**, m.p. 248–251°, $[\alpha]^{CHCl_3}D$ −111°, $\lambda_{max}^{CH_3OH}$ 233 mμ (log ε 4.20); $\lambda_{max}^{CHCl_3}$ 2.75, 2.9, 5.85 (pronounced shoulder), 5.94(strong), 6.12(strong), 9.05–9.2 μ (strong); λ_{max}^{tol} 2.76, 2.9, 5.92(strong), 5.84-(stronger), 6.13(strong), 9.05–9.25 μ. *Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.78; H, 7.80.

Fractions 13 and 14 afforded an additional 33 mg. of the 11α-isomer, m.p. 247–251°.

Acetylation Studies.—A 17-mg. sample of the more polar isomer X, m.p. 248–251°, was dissolved in a mixture of 0.3 cc. of pyridine and 0.3 cc. of acetic anhydride and kept at room temperature overnight. Removal of the solvents and addition of water gave 18 mg. of the 11α-acetate. An analytical sample, m.p. 272–274.5°, was obtained from Acetone–Skellysolve B. *Anal.* Calcd. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.79; H, 7.56.

Treatment of the 11β-isomer XI (m.p. 217–220°) with pyridine and acetic anhydride as described above gave only unchanged starting material.

11β,17α,21-Trihydroxy-A-nor-3(5)-pregnene-2,20-dione (XIII).—A total of 96 mg. of compound XI, described above, was treated with 4.8 ml. of 60% formic acid at room temperature for three days. The mixture was distributed between chloroform and water and the aqueous layer was back-extracted with chloroform. The combined organic layers were washed with water, with sodium bicarbonate solution, and with a saturated solution of sodium chloride. The desired product was isolated by paper chromatography on Whatman paper #4 using methanol–formamide (1:1) as the stationary phase and chloroform as the mobile phase.[23] An analytical sample, m.p. 235–237°, had the same mobility in the above system as prednisolone. *Anal.* Calcd. for $C_{20}H_{28}O_5 \cdot {}^1/_2H_2O$: C, 67.24; H, 8.17. Found: C, 67.75; H, 8.17.

17α,21-Dihydroxy-A-nor-3(5)-pregnene-2,11,20-trione BMD (XIV). (a) **From Acid B.**—To a solution of 150 mg. of acid B (m.p. 238–240°) in a mixture of 10 ml. of benzene and 20 ml. of methanol was added 500 mg. of lead tetraacetate. The mixture was allowed to stand at room tem-

(24) We are greatly indebted to Messrs. W. J. McAleer and M. A. Kozlowski for numerous helpful suggestions in connection with this chromatogram.

perature overnight. The bulk of the solvents was removed *in vacuo* and the residue was distributed between ether–benzene (3:2) and water. The aqueous layer was back-extracted with benzene and the combined organic layers were extracted with a bicarbonate solution and then with a saturated solution of sodium chloride. The crude product contained only a small amount of the conjugated ketone as evidenced by log ϵ 3.45 at 228 mμ. Addition of a dilute solution of sodium methoxide immediately raised the log ϵ to 4.12. An aliquot (75 mg.) was, therefore, dissolved in 15 ml. of methanol and isomerized for two hours by the addition of 1.5 ml. of a 0.86 *N* solution of sodium methoxide in methanol. Neutralization with acetic acid, removal of the solvent and addition of water gave 55 mg. of crude XIV. An analytical sample (m.p. 208–212°, λ_{max} 229 mμ (log ϵ 4.16); λ_{max}^{Nj} 5.86, 5.94(shoulder), 6.11 μ; $\lambda_{max}^{CHCl_3}$ 5.85, 5.93, 6.11 μ) was prepared from acetone–Skellysolve B. *Anal.* Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.14; H, 7.00. In another experiment (40 mg. scale) the crude lead tetraacetate product did not show an absorption maximum at 228 mμ but the product gave a strong tetranitromethane test and showed one olefinic proton.[15] Isomerization afforded XIV.

(b) **From Acid A.**—The lead tetraacetate oxidation was carried out on the lower melting acid (m.p. 198–200°) as described above for acid B on a 260-mg. scale. The crude product showed no selective absorption in the ultraviolet. Repeated recrystallization from acetone–Skellysolve B gave **5ξ,17α,21-trihydroxy-A-nor-pregnane-2,11,20-trione BMD**, m.p. 259.2–260.2°, λ_{max}^{Nj} 2.91, 5.73, 5.92 μ which had no olefinic protons[15] and gave a negative tetranitromethane test. *Anal.* Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.23; H, 7.76. Treatment with alkoxide carried out essentially as described above gave 205 mg., λ_{max} 228 mμ (log ϵ 4.14). One recrystallization from acetone–Skellysolve B gave XIV, m.p. 207–210°, identical with the specimen described above.

(c) **From XI and XII.**—The same compound XIV was obtained when 11.4 mg. of the 11α-isomer XII or 9.4 mg. of the 11β-isomer XI was treated, respectively, with 21 mg. and with 17.2 mg. of chromic oxide in aqueous acetic acid.

17α,21-Dihydroxy-A-nor-3(5)-pregnene-2,11,20-trione (XV).—A solution of 160 mg. of the A-norcortisone BMD XIV in 58 ml. of dilute acetic acid (50% v./v.) was heated on a steam-bath for about 14 hours. The mixture was poured on ice and extracted with chloroform. Removal of the solvent and crystallization from acetone–Skellysolve B gave crude XV which was purified further by paper chromatography on Whatman paper #4 using the solvent system employed in the purification of XIII. An analytical sample, m.p. *ca.* 200°, λ_{max} 229 mμ (log ϵ 4.12) was obtained from acetone–Skellysolve B. *Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.07; H, 7.35.

17α,21-Dihydroxy-2-methoxy-1,4-pregnadiene-3,11,20-trione BMD (IV).—A solution of the sodio-derivative IIIb in a mixture of 100 ml. of acetone and 3 ml. of methyl iodide was refluxed in a nitrogen atmosphere. Solvents were removed *in vacuo* and the residue distributed between dilute aqueous sodium hydroxide and chloroform. The neutral fraction was recrystallized from acetone–Skellysolve B to give material melting at 262–264° dec. *Anal.* Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.60; H, 7.00.

Acknowledgment.—The authors are pleased to acknowledge the able technical assistance of Mr. Nathan G. Steinberg.

RAHWAY, N. J.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. LI. Reaction of Steroidal Olefins with Acetyl Hypobromite[2a,b]

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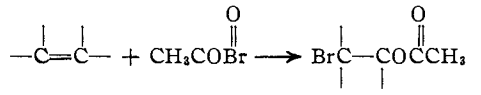
RECEIVED NOVEMBER 17, 1958

Treatment of various steroidal olefins with acetyl hypobromite has yielded stable bromohydrin acetate adducts which, on saponification, produced the corresponding β-oxides. This method is compared with certain alternative routes with regard to scope, limitations and possible general advantages.

In the course of studies on the conversion of steroidal sapogenins to cortical hormones it was necessary to prepare a number of β-oxides from the corresponding steroidal olefin. Conventionally, hypobromous acid has been the reagent used for this purpose[3a-f] giving predominantly diaxial α-bromo-β-hydroxy compounds which yield the β-oxide on treatment with base. Several features of the hypobromous acid procedure seemed undesirable. This reaction is conducted in an acidic medium which, frequently, is incompatible with a spiroketal or other acid-labile functional grouping and at times other side reactions (*e.g.*, bromination) occur. Most important, in some cases, our wish to carry a stable intermediate through several stages before closure to the β-oxide was precluded by the lability of bromohydrins toward oxidation or even the mildest base treatment. For these reasons, we have explored the olefin addition of acetyl hypobromite as a one-step method of preparing steroidal bromohydrin *acetates* as our epoxide precursors.



1,2-Addition of an acyl hypohalite is thought to be the first step of the familiar Prévost oxidation[4] which, in cyclic olefins, leads to the corresponding *trans*-diol. The Winstein–Woodward modification leading to *cis*-diols has been similarly interpreted.[5] In these cases, the intermediate iodohydrin ester is not ordinarily isolated[6]; such addition products have been obtained, though, from a variety of aliphatic and monocyclic olefins.[4] However, the addition of acyl hypobromites to unsaturated polycyclic systems has received little attention.

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) (a) Presented in part at the 135th National A.C.S. Meeting, Boston, Mass., April 5–10, 1959; (b) Paper L, Walens and Wall, THIS JOURNAL, **81**, in press (1959).

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(6) See, however, W. S. Knowles and Q. E. Thompson, *ibid.*, **79**, 3212 (1957).