edge the benefit of a stimulating discussion with Professor R. B. Woodward (Harvard University) and with Dr. K. Gerzon (Eli Lilly and Co.).
DETROIT, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

11-Oxygenated Steroids. XVI. The Preparation of Hydrocortisone from Cortisone Acetate[1]

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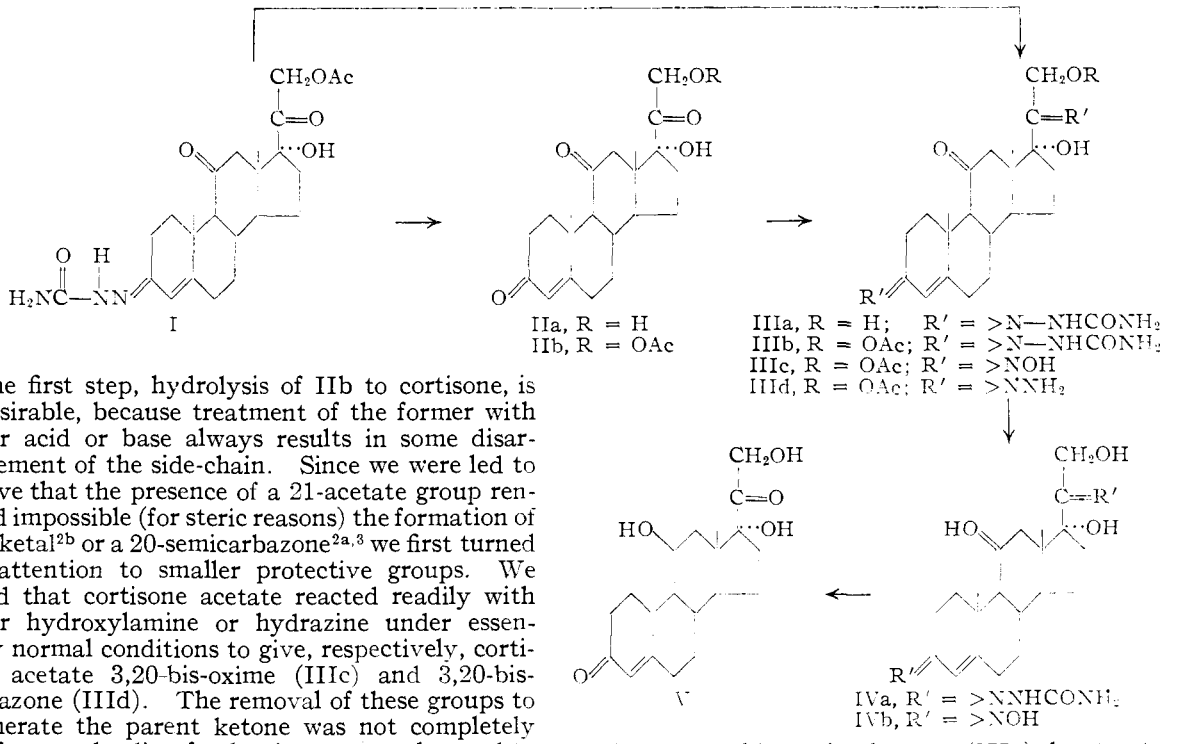
Cortisone acetate (IIb) has been converted into its 3,20-bis-oxime, bis-hydrazone and bis-semicarbazone. The latter, upon reduction with potassium borohydride followed by cleavage of the semicarbazone groups with nitrous acid, gave hydrocortisone (V) in 65–70% over-all yield from IIb.

The published[2] syntheses of hydrocortisone (V) from cortisone acetate (IIb) involve hydrolysis of the latter to cortisone, selective protection of the C-3 and C-20 carbonyls by semicarbazone[2a] or ketal[2b] formation, reduction of the 11-ketone by a suitable metal hydride, and removal of the protective groups. Although these processes give low yields, the ready availability of IIb made attractive a re-investigation of its conversion to V.

The first step, hydrolysis of IIb to cortisone, is undesirable, because treatment of the former with either acid or base always results in some disarrangement of the side-chain. Since we were led to believe that the presence of a 21-acetate group rendered impossible (for steric reasons) the formation of a 20-ketal[2b] or a 20-semicarbazone[2a,3] we first turned our attention to smaller protective groups. We found that cortisone acetate reacted readily with either hydroxylamine or hydrazine under essentially normal conditions to give, respectively, cortisone acetate 3,20-bis-oxime (IIIc) and 3,20-bis-hydrazone (IIId). The removal of these groups to regenerate the parent ketone was not completely satisfactory, lending further impetus to the need to form the 3,20-bis-semicarbazone of IIb.

When IIb was refluxed overnight in aqueous methanol with *unbuffered* semicarbazide hydrochloride a product was obtained, in modest yield, which was not identical with cortisone acetate 3-monosemicarbazone or cortisone 3,20-bis-semicarbazone. Its nitrogen content indicated the presence of two semicarbazone groups, and its infrared spectrum disclosed the retention of the 21-acetate group but the loss of the 20-carbonyl group. This new compound was therefore formulated as cortisone acetate 3,20-bis-semicarbazone (IIIb). This same material also could be obtained from cortisone 3,20-bis-semicarbazone (IIIa) by treatment with acetic anhydride and pyridine at room temperature. The use of pyridine as solvent also gave IIIb, but the best yields (99–100%) were obtained in aqueous methanol upon the addition of a small amount of pyridine.[4] Semicarbazide base



(1) Paper XV, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik, E. B. Hershberg, A. Nobile, W. Charney, C. Federbush, D. Sutter and P. L. Perlman.

(2) (a) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951); (b) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(3) O. Mancera, THIS JOURNAL, **72**, 5752 (1950); G. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 556 (1951).

(4) The use of pyridine and semicarbazide hydrochloride in the formation of semicarbazones has been noted before [I. Hopper, *J. Roy. Tech. Coll. Glasgow*, **2**, 52 (1929); *C. A.*, **23**, 3903 (1929)]. Using this technique H. Reich and B. Samuels [*J. Org. Chem.*, **19**, 1041 (1954)] prepared 21-acetoxypregnenolone semicarbazone, but they did not attempt to prepare the semicarbazone of a 20-keto-17α-hydroxy-21-acetoxysteroid.

and pyridine hydrochloride in aqueous methanol gave the same result.

Now, with the 20-carbonyl group in the form of its semicarbazone, the conditions for the removal of the 21-acetate group were no longer critical. In fact, the hydrolysis of this group could be combined into one step with the subsequent reduction of the 11-ketone to the 11β-hydroxyl group. Using sodium or potassium borohydride in aqueous tetrahydrofuran, the removal of the ester group was assumed to proceed at the faster rate. However, the reduction of the 11-ketone also proceeded fairly rapidly, for seven hours at reflux gave a product which no longer contained an 11-carbonyl. While longer reaction times in the reduction gave slightly inferior results, the addition of alkali during this step gave a markedly inferior product, in contrast to the experience of others[5] who have used an alkali–borohydride mixture. This may be due to attack by the alkali on the semicarbazone group. The reduction product, in theory hydrocortisone 3,20-bis-semicarbazone (IVa), was in fact a variable material, probably because of borate ester formation. This variability was reduced to a minimum by heating the reduction product in water for a short length of time, after which the material behaved consistently in the subsequent regeneration of the diketone.

Because our early studies on the pyruvic acid splitting of the reduction product gave generally poor results, the use of nitrous acid was investigated for the fission of the semicarbazone group.[6]

It was found that conversion of IVa to hydrocortisone could be accomplished in about 70% yield by dissolving the former in dilute hydrochloric acid and treating the resulting solution with an excess of sodium nitrite solution at 5°. The over-all yield from cortisone acetate was 65–70%. The same results can be obtained starting from cortisone acetate 3-mono-semicarbazone (I) (a precursor of IIb) with the advantage of omitting the final step in the preparation of IIb.

The 3,20-bis-oxime could also be split with nitrous acid to the parent ketone, but the reaction times had to be extended and the over-all yields were much lower.

To some extent, the protective groups at C-3 and C-20 could be interchanged. For example, cortisone acetate 3,20-bis-hydrazone (IIId) was converted to cortisone 3,20-bis-oxime by refluxing in aqueous methanol with excess hydroxylamine. Similarly, cortisone acetate 3-monosemicarbazone (I) was converted to cortisone acetate 3,20-dioxime (IIIc).

Experimental[7]

Cortisone Acetate 3,20-Bis-hydrazone (IIId).—A solution of 5.0 g. of cortisone acetate (II) and 5.85 g. of 85% hydrazine hydrate in 250 ml. of 80% ethanol was refluxed with stirring for 18 hours. The ethanol was removed by distillation and water added simultaneously until the vapor temperature reached 99°. The slurry was cooled at 10° for 1 hour and the solids collected by filtration; yield 4.78 g., m.p. > 300°.

Anal. Calcd. for $C_{23}H_{34}O_4N_4$: N, 13.01. Found: N, 13.23.

The infrared spectrum disclosed the presence of a 21-acetate group and the absence of a 20-carbonyl group.

Cortisone Acetate 3,20-Bis-oxime (IIIc).—A solution of 2.0 g. of cortisone acetate, 2.0 g. of hydroxylamine hydrochloride and 4.0 g. of sodium acetate in 400 ml. of 80% aqueous methanol was refluxed for 18 hours. About 150 ml. of water was added, the mixture concentrated at atmospheric pressure until the appearance of crystals, and after cooling, the solids were collected by filtration: yield 1.92 g., m.p. 159–169° dec., $[\alpha]_D$ +203° (HOAc), $\lambda_{max.}^{EtOH}$ 21,250 at 240 mμ.

Anal Calcd. for $C_{23}H_{32}O_6N_2$: N, 6.48. Found: N, 6.22.

The infrared spectrum indicated the presence of the C-21 acetate group and the loss of the C-20 carbonyl group.

Cortisone Acetate 3,20-Bis-semicarbazone (IIIb).—(A) A solution of 2 g. of cortisone 3,20-bis-semicarbazone (IIa), 15 ml. of acetic anhydride and 40 ml. of pyridine was allowed to stand 18 hours at room temperature, then poured into excess water and the solid collected by filtration. After drying, it weighed 1.7 g., had m.p. > 300°, $\lambda_{max.}^{EtOH}$ 32,700 at 270 mμ, and possessed an acetate group as shown by its infrared spectrum. (B) A mixture of 50.0 g. of cortisone acetate, 83.0 g. of semicarbazide hydrochloride, 58.8 g. of pyridine, 500 ml. of water and 2 l. of methanol was refluxed for 15 hours. The slightly turbid solution was concentrated to a volume of *ca.* 600 ml., then poured into 2 l. of cold water. The solid collected by filtration weighed 64.0 g. (99.5%), m.p. > 300°, $[\alpha]_D$ +181.4° (HOAc), $\lambda_{max.}^{EtOH}$ 32,400 at 270 mμ.

Anal. Calcd. for $C_{25}H_{36}O_6N_6$: N, 16.28. Found: N, 16.78.

Its infrared spectrum was identical with that of the material prepared in (A) above and confirmed the presence of C-21 acetate group and the absence of the C-20 carbonyl group. (C) The same product was obtained: (a) in 65% yield by refluxing IIb for 16 hours with semicarbazide hydrochloride in aqueous methanol, (b) in 95+% yield by refluxing cortisone acetate 3-monosemicarbazone (I) for 15 hours with semicarbazide hydrochloride and pyridine in aqueous methanol, and (c) in 74% yield by treating I for 15 hours with semicarbazide hydrochloride in pyridine solution.

Reduction of Cortisone Acetate 3,20-Bis-semicarbazone (IIIb).—A solution of 65.6 g. of IIIb and 33.8 g. of potassium borohydride in 1.97 l. of purified tetrahydrofuran and 984 ml. of water was allowed to react at room temperature for 30 minutes, then refluxed for seven hours. The solution was cooled to *ca.* 40° and acetic acid added to *p*H 5.5. The organic solvent was removed under reduced pressure, the resulting suspension warmed for 30 minutes at 60–70°, cooled to 10°, and the solid collected by filtration; yield 60.0 g. (99.2%), m.p. >290°. Its infrared spectrum confirmed the absence of the 11-carbonyl group and the 21-acetate group, and was very similar to the spectrum of authentic hydrocortisone 3,20-bis-semicarbazone.

Hydrocortisone (17α-Hydroxycorticosterone (V).—Fifty grams of the reduction product obtained above was dissolved at 20° in 2.5 l. of 2.4 *N* hydrochloric acid under a nitrogen atmosphere. The solution was cooled to 5°, and then a solution of 25 g. of sodium nitrite in 250 ml. of water was added over a 15-minute period, maintaining the temperature at 5 ± 1°. It was stirred an additional 30 minutes at this temperature, then treated with a solution of 150 g. of urea in 250 ml. of water over a 15-minute period. The reaction was neutralized below 15° with 20% sodium hydroxide, and the mixture extracted several times with chloroform. Evaporation of the solvent under reduced pressure gave 33 g. of crude hydrocortisone (V), m.p. 197–203°. Crystallization from acetone–Darco gave 26.4 g. (69.5%) of pure V, m.p. 216–221°, $\lambda_{max.}^{EtOH}$ 16,050 at 242 mμ, $[\alpha]_D$ +151.1° (dioxane). Its infrared spectrum matched that of an authentic sample.

Exchange Reactions (A).—A solution of 2.0 g. of cortisone acetate bis-hydrazone (IIId), 9.8 g. of hydroxylamine hydrochloride and 11.4 g. of sodium acetate in 200 ml. of 75%

(5) For example, W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954).

(6) *Cf.* S. Goldschmidt and W. Veer, *Rec. trav. chim.*, **65**, 796 (1946); D. H. Hey and D. S. Morriss, *J. Chem. Soc.*, 2319 (1948).

(7) All m.p.'s are corrected. All rotations were taken in a 1-dm. tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

aqueous methanol was refluxed for 18 hours. The cloudy solution was filtered while hot, then concentrated until turbid, cooled, 50 ml. of water added, and the solids collected by filtration; yield 1.95 g., $\lambda_{max.}^{EtOH}$ 19,680 at 240 mμ. The infrared spectrum indicated the loss of the 21-acetate and substantial replacement of hydrazone groups by oxime group.

Anal. Calcd. for $C_{21}H_{30}O_5N_2$: N, 7.18. Found: N, 8.61.

(B).—A mixture of 9.18 g. of cortisone acetate 3-monosemicarbazone, 2.78 g. of hydroxylamine hydrochloride, 3.28 g. of sodium acetate, 45 ml. of acetic acid and 275 ml. of methanol was refluxed for 15 hours. The methanol was removed by distillation, the residue poured into water and the precipitated solid removed by filtration; yield 6.8 g. (72%), m.p. 165–175° dec., $\lambda_{max.}^{EtOH}$ 20,900 at 240 mμ. Its infrared spectrum was identical with that of authentic cortisone acetate 3,20-bis-oxime (IIIc).

Anal. Calcd. for $C_{23}H_{26}O_6N_2$: N, 6.49. Found: N, 6.76.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S. A.]

Steroids. LXXVII.[1] Synthesis and Reactions of 16β-Oxygenated Pregnan-20-one Derivatives

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Oxidation of $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (I) with alkaline hydrogen peroxide has been shown to give 16β,17β-oxido-17-iso-Δ^5-pregnen-3β-ol-20-one acetate (IIIa) in low yield in addition to 16α,17α-oxido-Δ^5-pregnen-3β-ol-20-one acetate (II). The β-oxide IIIa adds hydrogen bromide with the formation of 17α-bromo-Δ^5-pregnene-3β,16β-diol-20-one 3-monoacetate (V), identical with the product obtained from $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (I) by successive addition of bromine to the Δ^5-double bond, addition of hypobromous acid to the Δ^{16}-double bond and treatment with sodium iodide (I → VI → VII → V). The bromohydrin V on treatment with potassium hydroxide and reacetylation gives back the β-oxide IIIa, whereas catalytic hydrogenation over a palladium–charcoal catalyst produces Δ^5-pregnene-3β,16β-diol-20-one 3-monoacetate (VIIIa), which can be dehydrated to $\Delta^{5,16}$-pregnadien-3β-ol-20-one (I). Lithium aluminum hydride reduction and subsequent acetylation of Δ^5-pregnene-3β,16β-diol-20-one 3-monoacetate (VIIIa) gives Δ^5-pregnene-3β,16β,20β-triol triacetate (IXb), identical with the acetylated lithium aluminum hydride reduction product of the "diosone" XI derived from diosgenin X. Catalytic hydrogenation of the triacetate IXb yields the known allopregnane-3β,16β,20β-triol triacetate (XII) and the stereochemical configuration of the various 16β-oxygenated pregnan-20-one derivatives is therefore fixed.

16β-Hydroxylated pregnan-20-one derivatives such as Δ^5-pregnene-3β,16β-diol-20-one 3-monoacetate (VIIIa) are of interest since their 16-γ-methyl-δ-acetoxyvalerates are the so-called "diosones" (*e.g.*, XI), which are important intermediates in the industrial conversion of steroidal sapogenins (*e.g.*, diosgenin, X) to the adrenal and the sex hormones. In contrast to the 16α-hydroxypregnan-20-ones which may be obtained by several chemical methods[3] as well as by microbiological means,[4] only one synthetic route to 16β-hydroxypregnan-20-ones (unsubstituted at C-17) has been described.[5] This route proceeds from the corresponding Δ^{16}-pregnen-20-one by addition of hypobromous acid to yield the 16β-hydroxy-17α-bromopregnan-20-one, followed by debromination with zinc.[5,6] The stereochemistry at C-16 and C-17 of the resulting 16β-hydroxypregnan-20-one was not, however, rigidly established.

We first became interested in this subject when investigating the oxidation of $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (I) with alkaline hydrogen peroxide. This reaction is known[7] to produce an oxide in about 95% yield, shown to be the 16α,17α-oxide II by its subsequent reactions. The formation of this isomer is in accord with the known predominant α-attack of steroidal 16(17)- and 17(20)-double bonds.[8] We have now isolated a by-product in 1–2% yield, for which the 16β,17β-oxide structure IIIa (16β,17β-oxido-17-iso-Δ^5-pregnen-3β-ol-20-one acetate) was first proposed on the basis of the elemental analysis, the infrared spectrum and the comparatively high negative rotation which was expected for a 17-isopregnane derivative.[8a] This formulation for the substance was subsequently proved to be correct through its further transformations (*vide infra*). Although by-products derived by β-attack of 17-ketoandrostanes (containing a 17-("20")-double bond) have been isolated,[9] the above appears to be the first recorded instance of the formation of a product derived by β-attack of a steroid with a 16(17)-double bond.

The reaction of 16α,17α-oxido-Δ^5-pregnen-3β-ol-20-one acetate (II) with hydrogen bromide in acetic acid is known[10] to yield 16β-bromo-Δ^5-pregnene-3β,17α-diol-20-one 3-monoacetate (IV) by opening of the oxide ring in such wise as to produce the new substituents in the quasi-axial configura-

(1) Paper LXXVI, E. Batres, R. Gómez, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **21**, 240 (1956).

(2) (a) Instituto Centro Americano de Investigaciones y Tecnología Industrial, Guatemala, C.A.; (b) Department of Chemistry, The Weizmann Institute of Science, Rehovoth, Israel.

(3) H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *Federation Proc.*, **12**, 218 (1953); *J. Org. Chem.*, **20**, 572 (1955); H. Hirschmann, F. B. Hirschmann and G. L. Farrel, THIS JOURNAL, **75**, 4862 (1953); W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954); S. Bernstein, M. Heller and S. M. Stolar, THIS JOURNAL, **76**, 5674 (1954).

(4) D. Perlman, E. Titus and J. Fried, *ibid.*, **74**, 2126 (1952); E. Vischer, J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **37**, 321 (1954).

(5) G. Gansau, Doctorate Thesis, Technische Universität, Berlin-Charlottenburg, 1952. ADDED IN PROOF.—S. Bernstein, M. Heller and S. M. Stolar (THIS JOURNAL, **77**, 5327 (1955)) have now described another route to such compounds.

(6) In addition, syntheses of 16β,17α-dihydroxypregnan-20-ones have been described recently (a) by H. H. Inhoffen, F. Blomeyer and K. Brückner [*Ber.*, **87**, 593 (1954)] and (b) by K. Heusler and A. Wettstein [*ibid.*, **87**, 1301 (1954)].

(7) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950).

(8) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(8a) *Cf.* A. Butenandt and L. Mamoli, *Ber.*, **68**, 1847 (1935); A. Butenandt and G. Fleischer, *ibid.*, **70**, 96 (1937).

(9) L. Ruzicka and H. Kägi, *Helv. Chim. Acta*, **19**, 842 (1936); K. Miescher and W. Klarer, *ibid.*, **22**, 962 (1939).

(10) *Cf.* H. J. Ringold, B. Löken, G. Rosenkranz and F. Sondheimer THIS JOURNAL, **78**, 816 (1956).