g., 1.6%) of hexaphenyldisiloxane, m.p. 226–228° (mixed m.p.) could be isolated as one of the products from this run.

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AMES, IOWA

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

Selective Sodium Borohydride Reductions in Aqueous Dimethylformamide Solution. Neighboring Group Effects in the Cortical Side Chain[1]

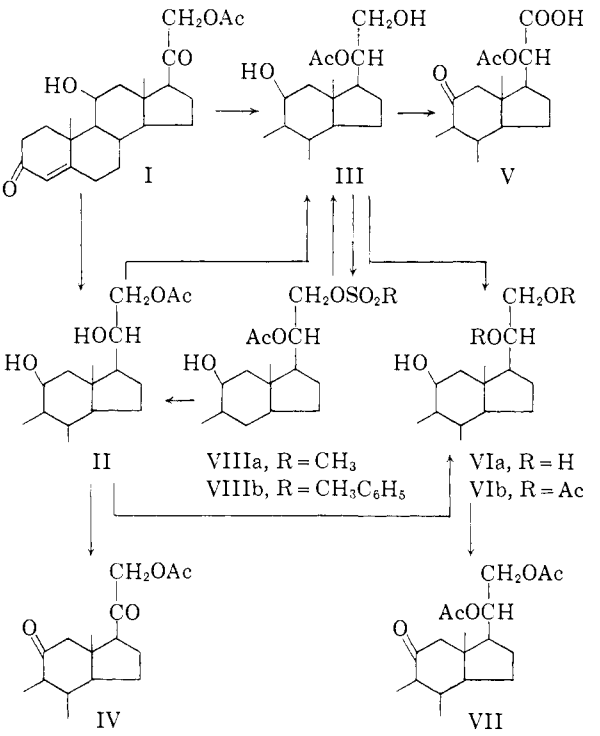
BY D. TAUB, R. D. HOFFSOMMER AND N. L. WENDLER

RECEIVED DECEMBER 20, 1958

Sodium borohydride reduction of corticosterone 21-acetate (I) in aqueous dimethylformamide proceeded largely with acetyl migration to give the 20β-acetate 21-ol III as well as the 20β-ol-21-acetate II. The 21-mesylate-20β-acetate VIIIa on demesylation gave mixtures of II and III in which II predominated. Similar sodium borohydride reductions of hydrocortisone 21-acetate (XI) and cortisone 21-acetate (XIII) led directly to Reichstein's Substances E and U 21-acetates, respectively.

The present work originated in an attempt to modify the procedure of Norymberski and Woods[2] for the preferential reduction of the 20-keto group of cortical steroids in the presence of the Δ^4-3-keto and/or 11-keto groupings, such that concomitant loss of easily hydrolyzable ester functions elsewhere in the molecule would not occur. Under the conditions employed by Norymberski and Woods (1.5 mols of sodium borohydride per mol of steroid in methanol at 0° for one hour) the 21-acetate function of 21-acetoxy-20-keto steroids readily undergoes methanolysis and the principal products, produced in moderate yields, are 20β-21-diols[3] or, following mild acetylation, the corresponding diacetates.[2]

In preliminary studies we found that reduction of 20-ketoacetoxy systems in aqueous dimethylformamide proceeds more slowly than in methanol but without loss of acetate functionality.[3c] These conditions were applied in detail to the reduction of corticosterone acetate (I) in the interest of obtaining the corresponding 21-monoacetate II.[4] When compound I was treated with sodium borohydride in 50% aqueous dimethylformamide, a new substance, m.p. 234–240°, which partly precipitated during the reduction, was formed in 75–80% yield. Its analysis, infrared and ultraviolet absorption spectra were in conformity with those expected for structure II and it readily formed monomesylate and monotosylate derivatives. However, CrO_3 oxidation of the reduction product did not produce 11-dehydrocorticosterone acetate



(IV) as would be expected from II. The oxidation product was an *acetoxy acid* formulated as V on the basis of its properties and analysis.

The substance, m.p. 234–240°, must therefore have a 20-acetate-21-ol part structure.[5] The 20β-acetate-21-ol formulation III was shown to be

(1) Presented in part at the 132nd Meeting of the American Chemical Society, September 1957, New York, N. Y. (Abstracts, p. 23P).

(2) J. K. Norymberski and C. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(3) (a) See for example: C. M. Southcott, H. E. Bandy, S. E. Newsom and M. Darrach, *Can. J. Biochem. Physiol.*, **34** 913 (1956). (b) It should be noted that the 17β-acetoxy function in C_{19}-steroids is stable to sodium borohydride in aqueous methanol (E. Elisberg, H. Vanderhaeghe and T. F. Gallagher, THIS JOURNAL, **74**, 2814 (1952).

(3c) N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(4) 21-Monoacetates may be obtained from the corresponding 20,21-diols of 3-keto-Δ^4-pregnenes in low yield by partial acetylation and chromatography [*e.g.*, L. H. Sarett, THIS JOURNAL, **68**, 2478 (1946)] and similarly from 17α,20,21-triols [*e.g.*, Huang-Minlon and R. H. Pettebone, *ibid.*, **74**, 1562 (1952)]. Catalytic reduction of the 20-carbonyl group, which proceeds in good yield to the corresponding 20β-hydroxy compound without loss of the 21-acetate function [L. H. Sarett, *ibid.*, **71**, 1169 (1949)], is not applicable to Δ^4-3-keto systems since reduction of A-ring functionality would occur also.

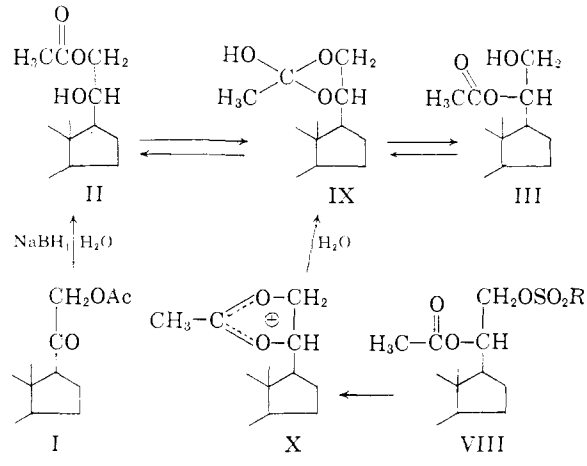
(5) Acetyl migration from C_{18} to C_{17} was recently observed during the sodium borohydride reduction of *d,l*-ethylenedioxy-5-androstene-11β,18-diol-17-one 18-acetate by P. Wieland, K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **41**, 1657 (1958).

correct by hydrolysis to the corresponding diol VIa and acetylation to the diacetate VIb as well as oxidation of the latter to the known Δ^4-pregnene-20β, 21-diol-3,11-dione-20β,21-diacetate (VII) (Reichstein's Substance T-diacetate).[6] The ΔM_D (diacetate VIb − diol VIa) value of +188° is in agreement with that expected for the 20β-configuration and extremely unlikely for the 20α-configuration for which a negative ΔM_D would be expected.[7]

It proved possible to rearrange the 20β-acetate group of III to C-21 *via* the 20β-acetate-21-mesylate VIIIa or tosylate VIIIb. The 21-mesylate in refluxing collidine was converted to a mixture separable by chromatography into the 20β-acetate-21-ol II (46%) and the 20β-ol-21-acetate III (27%) plus mixed fractions.[8] Displacement of sulfonate esters under solvolytic conditions with participation of correctly oriented neighboring acyl groups is a well known phenomenon[9] but to our knowledge has not been reported previously to occur in refluxing collidine or similar weakly basic amines. The reaction generally has been run in acetic acid, and, in the presence of water the intermediate acetoxonium ion is cleaved with retention of configuration.[9] Demesylation of VIIIa in refluxing aqueous acetic acid (70%) containing potassium acetate gave as major products the 21-monoacetate II (35%), the diacetate VIb (35%) and small amounts of impure 20β-monoacetate III. Under generally similar conditions Fukushima and co-workers converted a 17α-acetoxy,20β-tosyloxy pregnane to the corresponding 20α-acetate.[10]

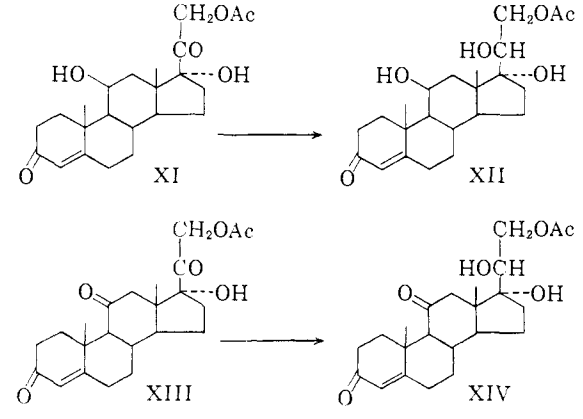
The rearrangements herein described may be depicted as proceeding through an orthoacetate[9,11] intermediate IX which is in equilibrium with II and III, the amounts of each of the latter isolated in any given case being influenced by the reaction conditions. Thus, in the collidine demesylation both II and III were formed in at least 46 and 27% yields, respectively. The results of the aqueous acetic acid demesylation of VIIIa were obscured by the formation of considerable diacetate VIb, which could arise by reaction of the medium with III or the acetoxonium ion X at C_{21} or, less likely, with II. It is of interest that in none of the reactions described have the 20α-hydroxy or acetoxy epimers been observed.

The sodium borohydride reduction of corticosterone 21-acetate (I) in 50% aqueous dimethylformamide produced the 20β-acetate-21-ol III in 75–80% yield and at best only trace amounts of the isomeric 21-acetate-20β-ol II. This may have been a result of the slight solubility of III in the specific aqueous dimethylformamide solvent system used—the precipitation of III from solution displacing the equilibrium in its favor. With these considerations in mind a reduction was carried out under conditions (80% aqueous dimethyl-



formamide) where all the reactants remained in solution. Under these conditions II and III were isolated in roughly equal amounts, indicating that acetyl migration in this system does occur in solution to a large extent. Finally, it was of interest to attempt the direct conversion of the 20β-ol 21-acetate II into the 20β-acetate-21-ol III. This was accomplished by dissolving II in 50% aqueous dimethylformamide containing 1% potassium bicarbonate followed by cooling and seeding with III. The latter crystallized from solution in good yield. Similar results were obtained in 50% aqueous dimethylformamide containing 1% sodium borohydride. However, in the absence of base catalysis II could be recrystallized from aqueous dimethylformamide essentially unchanged even in the presence of seeds of III. Evidently mild base catalysis is strikingly effective in promoting acetyl transfer from C_{21} to C_{20} in the above system.

In contrast to the acetyl migration observed in the reduction of corticosterone acetate (I), hydrocortisone acetate (XI) and cortisone acetate (XIII) were reduced in 80% dimethylformamide without acetyl migration to give, respectively, 4-pregnene-11β,17α-20β,21-tetrol-3-one 21-acetate (XII, Reichstein's Substance E Monoacetate) and



(6) T. Reichstein and J. von Euw, *Helv. Chim. Acta.*, **22**, 1222 (1939).

(7) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); L. H. Sarett, THIS JOURNAL, **71**, 1175 (1949).

(8) Qualitatively similar results but lower yields were obtained in probe demesylations in refluxing dimethylformamide, pyridine, dimethylformamide–pyridine, dimethylformamide–dimethylaniline, dimethylformamide–lithium chloride and even refluxing xylene.

(9) S. Winstein, H. V. Hess and R. E. Buckles, *ibid.*, **64**, 2796 (1942), and subsequent papers by Winstein and collaborators.

(10) D. K. Fukushima, N. S. Leeds, H. L. Bradlow, T. H. Kritchevsky, M. B. Stokem and T. F. Gallagher, *J. Biol. Chem.*, **212**, 449 (1955).

(11) R. Boschan and S. Winstein [THIS JOURNAL, **78**, 4921 (1956)] have postulated an equilibrium involving an orthoacetate intermediate in the reaction of *cis*-glycol monoacetates under acidic conditions with halide ion to yield *trans* halohydrin acetates.

4-pregnene-17α-20β,21-triol-3,11-dione 21-acetate (XIV, Reichstein's Substance U Monoacetate). Products of migration were formed at best in trace amounts.

Experimental[12]

Δ^4-Pregnene-11β,20β,21-triol-3-one 20β-Acetate (III).—A solution of 2.0 g. of sodium borohydride in 100 ml. of water was added dropwise to a stirred solution of 10.0 g. of corticosterone acetate (I) in 100 ml. of dimethylformamide maintained at 20°. Product began to precipitate before the addition was complete. After one hour 70 ml. of 15% aqueous acetic acid was added cautiously followed by 2 liters of 50% saturated sodium chloride solution. The product was filtered, washed with 500 ml. of water and 30 ml. of ether to give 7.70 g. (77%) of the 20β-acetate 21-ol III with m.p. 220–237° which gave a negative tetrazolium test. Trituration with hot acetone raised the m.p. to 238–243, $[\alpha]_D^{HCON(Me)_2}$ + 152°, $\lambda_{max}^{CHCl_3-CH_3OH}$ 1:1 243 mμ (14,800); λ_{max}^{Nujol} 2.87, 2.95, 5.79, 6.02, 6.17, 8.1 μ. The 20β-acetate-21-ol III was nearly insoluble in most of the common organic solvents but was soluble in formamide and dimethylformamide.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.34; H, 8.49.

Extraction of the combined mother liquors with chloroform gave 1.0 g. of amorphous material, $\lambda_{max}^{CH_3OH}$ 244 mμ, E% 55, in which the 3-carbonyl group has been reduced to a major extent as well as the 20-carbonyl group. Paper chromatography (benzene–formamide system) showed the presence of minor amounts of corticosterone acetate (I) and a more polar component which absorbed in the ultraviolet but did not give a tetrazolium test. This substance was shown to be the 20β-hydroxy 21-acetate II (see below).

20β-Acetoxy-Δ^4-pregnene-3,11-dione-21-oic Acid (V).—To a stirred solution of 195 mg. of the 20β-acetate-21-ol III in 10 ml. of acetic acid was added 200 mg. of chromium trioxide in 0.2 ml. of water and 2 ml. of acetic acid. After 40 hours at 25° excess oxidant was destroyed by addition of 1 ml. of methanol. The reaction mixture was partitioned between 50% saturated sodium chloride solution and chloroform. Treatment of the chloroform extract with dilute potassium bicarbonate solution followed by acidification and re-extraction into chloroform, gave 154 mg. (79%) of acid V which was crystallized from acetone–ether; m.p. 240–246°, $[\alpha]_D^{CHCl_3}$ +136°, $\lambda_{max}^{CH_3OH}$ 237.5 mμ (15,300); λ_{max}^{Nujol} 3.2(broad), 5.69, 5.88, 6.00, 6.19 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; neut. equiv., 403. Found: C, 68.44; H, 7.58; neut. equiv., 413.

Δ^4-Pregnene-11β,20β,21-triol-3-one 20β,21-Diacetate (VIb).—The 20β-acetate-21-ol III (100 mg.) was treated with 2 ml. of acetic anhydride and 2 ml. of pyridine at 25° for 18 hours. Concentration of the reaction mixture to dryness *in vacuo* followed by crystallization of the residue from acetone–ether gave the 20β,21-diacetate VIb, m.p. 192–196°, $[\alpha]_D^{CHCl_3}$ +158°, $\lambda_{max}^{CH_3OH}$ 242 mμ (15,800), λ_{max}^{KBr} 2.93, 5.75, 6.02, 6.17 μ.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.69; H, 8.39.

The 20β,21-diacetate VIb was also obtained from the 20β-ol-21-acetate II in the same manner.

Δ^4-Pregnene-11β,20β,21-triol-3-one (VIa).—The 20β-acetate-21-ol III (200 mg.) was suspended in 5 ml. of methanol under nitrogen. Sodium hydroxide (150 mg.) in 0.2 ml. of water and 1 ml. of methanol was added and the mixture stirred 30 minutes. Neutralization followed by concentration, addition of water and chloroform extraction gave a crystalline residue which was crystallized from acetone–ether to give prismatic needles, m.p. 208–210° $[\alpha]_D^{CHCl_3}$ +137°, $\lambda_{max}^{CH_3OH}$ 242 mμ (15,600); λ_{max}^{Nujol} 2.90, 6.03, 6.17 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.31; H, 8.90.

(12) Melting points were taken on a micro hot-stage apparatus and are corrected. Paper chromatograms were run on strips of Whatman No. 1 filter paper using the formamide systems of A. Zaffaroni, R. B. Burton and E. H. Keutmann, *Science*, **111**, 6 (1950). We are indebted to R. N. Boos and associates for the microanalyses and R. W. Walker for the infrared spectra.

Similar treatment of the 20β-ol-21-acetate gave triol VIa identical with that obtained from the 20β-acetate-21-ol III.

Δ^4-Pregnene-11β,20β,21-triol-3-one 20β-Acetate 21-Tosylate (VIIIb).—To a stirred solution of 500 mg. of the 20β-acetate-21-ol III in 25 ml. of pyridine was added 1.2 g. of *p*-toluenesulfonyl chloride. After 18 hours at 25° the mixture was cooled to −5° and 15 ml. of cold water was slowly added followed by 50 ml. of saturated sodium chloride solution. The mixture was extracted with chloroform, the chloroform extract washed with dilute hydrochloric acid, water and dried over magnesium sulfate. Crystallization of the residue from acetone–ether gave the 20β-acetate-21-tosylate VIIIb, m.p. 130–135° dec.

Anal. Calcd. for $C_{30}H_{40}O_7S$: S, 5.85. Found: S, 6.00.

Δ^4-Pregnene-11β,20β,21-triol-3-one 20β-Acetate 21-Mesylate (VIIIa).—The 20β-acetate-21-ol III (200 mg.) was dissolved in 8 ml. of pyridine by warming. The stirred solution was cooled to 0° and 0.2 ml. of methane sulfonyl chloride was added dropwise. After 2 hours, 50 ml. of cold water and 25 ml. of saturated sodium chloride solution were added. The precipitate was filtered, washed with water and dried in air. Crystallization from acetone–ether gave 170 mg. of the 20β-acetate-21-mesylate VIIIa as pearly plates, m.p. 175–177° dec., $[\alpha]_D^{CHCl_3}$ +118°, $\lambda_{max}^{CH_3OH}$ 242 mμ (15,500); λ_{max}^{Nujol} 2.96, 5.79, 6.04, 6.18, 7.42, 8.08, 8.42 μ.

Anal. Calcd. for $C_{24}H_{36}O_7S$: C, 61.52; H, 7.74; S, 6.84. Found: C, 61.62; H, 7.94; S, 6.95.

Collidine Demesylation of Δ^4-Pregnene-11β,20β,21-triol-3-one 20β-Acetate 21-Mesylate (VIIIa). Δ^4-Pregnene-11β,20β,21-triol-3-one 21-Acetate (II).—One gram of the 20β-acetate-21-mesylate VIIIa was dissolved in 25 ml. of γ-collidine and the solution was refluxed under nitrogen for 2.5 hours. The reaction mixture was cooled and partitioned between chloroform and dilute hydrochloric acid. The organic layer was extracted with dilute hydrochloric acid, water, and dried over mangnesium sulfate. Trituration of the residue in benzene gave 215 mg. (27%) of the 20β-acetate-21-ol III, m.p. 226–235°; infrared spectrum identical with that of an authentic sample.

Chromatography of the mother liquors on neutral alumina gave from the 20% chloroform–benzene eluates 365 mg. (46%) of the 20β-ol-21-acetate II, hexagonal prisms from acetone–ether; m.p. 208–211°, $[\alpha]_D^{acetone}$ +116°, $\lambda_{max}^{CH_3OH}$ 242.5 mμ (15,700); λ_{max}^{Nujol} 2.83, 2.95, 5.79, 6.03, 6.19, 8.1 μ.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 71.02; H, 8.84.

Further elution of the column gave mixed fractions containing the 20β-ol-21-acetate II and the 20β-acetate-21-ol III as indicated by melting point and paper chromatographic behavior.

Demesylation of Δ^4-Pregnene-11β-20β,21-triol-3-one-20β-Acetate 21-Mesylate in 70% Aqueous Acetic Acid–Potassium Acetate.—A solution of 410 mg. of the 20β-acetate 21-mesylate VIIIa and 5.00 g. of potassium acetate in 55 ml. of 70% aqueous acetic acid was refluxed for 3.5 hours and kept at room temperature 14 hours. Water was added and the mixture was extracted with chloroform. The latter extract was washed with aqueous potassium bicarbonate, water and dried over magnesium sulfate. Chromatography of the residue on neutral alumina gave 142 mg. (35%) of the 20β,21-diacetate (VIb) crystallized from acetone–ether, m.p. 190–193° and 140 mg. (35%) of the 20β-ol 21-acetate (II) contaminated with a small amount of the 20β-acetate 21-ol III; m.p. 200–208-trace to 240° as evidenced by melting point and paper chromatographic comparisons with authentic samples.

11-Dehydrocorticosterone Acetate (IV) from the 20β-Ol 21-Acetate II.—A solution of 12 mg. of chromium trioxide in one drop of water and 0.5 ml. of acetic acid was added to 21 mg. of Δ^4-pregnene-11β,20β,21-ol-3-one 21-acetate (II) in 0.5 ml. of acetic acid. After 17 hours at 25° water was added and the neutral product isolated by chloroform extraction. The crystalline residue (21 mg.) was crystallized from acetone–ether; m.p. 174–177° undepressed on admixture with authentic 11-dehydrocorticosterone acetate; identical infrared spectra and paper chromatographic mobility.

Sodium Borohydride Reduction of Corticosterone Acetate (I) in 80% Aqueous Dimethylformamide.—A solution of 200 mg. of sodium borohydride in 10 ml. of water was added to a stirred solution of 1.00 g. of corticosterone acetate (I) in 40 ml. of dimethylformamide maintained at 15–20°. The blue tetrazolium test for the ketol side chain was

essentially negative in 2.5 hours. Excess reducing agent was decomposed by the addition of 10% aqueous acetic acid. Additional chloroform and water were added and the mixture extracted with chloroform. The chloroform extract was washed with dilute potassium bicarbonate and water and dried over magnesium sulfate. Crystallization of the residue from acetone gave 200 mg. of the 20β-acetate-21-ol III, m.p. 237–243°. Chromatography of the mother liquors on 20 g. of neutral alumina gave 270 mg. of the 20β-ol-21-acetate II crystallized from acetone–ether, m.p. 206–210°. Paper chromatography (benzene–cyclohexane 2:1—formamide system) of pertinent fractions indicated the presence of minor amounts of corticosterone acetate (I), a non-ultraviolet absorbing component probably resulting from reduction of the 3 as well as the 20-carbonyl group, and mixed fractions of II and III.

Conversion of the 20β-Ol 21-Acetate II into the 20β-Acetate 21-Ol III.—To a solution of 30 mg. of the 20β-ol-21-acetate II in 0.6 ml. of dimethylformamide was added 0.6 ml. of 2% aqueous potassium bicarbonate. The clear solution was seeded with the 20β-acetate-21-ol III. Within 5 minutes a precipitate of small prisms appeared. The mixture was kept at 0° for 30 minutes, filtered, the precipitate washed with water, 50% aqueous acetone and dried in air; 15 mg., m.p. 240–245° undepressed with authentic 20β-acetate-21-ol III. The respective infrared spectra were identical. An additional 4 mg. of III, m.p. 241–245°, was obtained from the mother liquors on standing overnight.

Similar treatment of 50 mg. of II in 1 ml. of dimethylformamide with 1 ml. of 1% aqueous sodium borohydride led to 38 mg. of III, m.p. 238–243°.

However, when a solution of 50 mg. of II in 2 ml. of 50% aqueous dimethylformamide was seeded with III and permitted to cool slowly, essentially unchanged II (35 mg.) was recovered in 2 crops of long needles, m.p. 208–212° with a trace remaining to 245°. The mixed melting point with authentic II was undepressed and the respective infrared spectra were identical.

Δ^4-Pregnene-11β,17α,20β,21-tetrol-3-one 20-Acetate (Reichstein's Substance E Monoacetate) (XII).—To a stirred solution of 2.00 g. of hydrocortisone 21-acetate (XI) in 80 ml. of dimethylformamide at 20° was added 400 mg. of sodium borohydride in 20 ml. of water. Starting material partly precipitated. Stirring was continued at 20° for four hours at which time all the material was in solution and a blue tetrazolium test on an aliquot was negative. Excess cold 10% aqueous acetic acid was added slowly, water and chloroform were added and the mixture extracted with chloroform. The chloroform extract was washed with potassium bicarbonate solution, water and dried over magnesium sulfate. The crystalline residue was chromatographed on 60 g. of neutral alumina. The fractions from 50% benzene–chloroform to 100% chloroform (1.15 g.) were crystalline and consisted primarily of the monoacetate XII. Crystallization from acetone–ether gave prisms, m.p. 225–235° (233–236° capillary m.p.), $\lambda_{max}^{CH_3OH}$ 242 mμ (15,600); undepressed with an authentic sample of Reichstein's Substance E 21-monoacetate.[13] The respective infrared spectra were identical. Acetylation of 50 mg. of XII in acetic anhydride–pyridine at 25° gave the corresponding 20β,21-diacetate, m.p. 212–220°, likewise identical with authentic material.

Paper chromatography (benzene–chloroform 1:2—formamide system) of the individual chromatogram fractions indicated the total yield of the 20-monoacetate XII formed to be about 70%. Also present were small amounts of a more polar ultraviolet absorbing component (negative blue tetrazolium test) which may be the 20β-monoacetate analogous to III and a very polar non-ultraviolet absorbing component (negative blue tetrazolium test) in which the 3- as well as the 20-carbonyl group has been reduced. These substances were not isolated.

Δ^4-Pregnene-17α,20β,21-triol-3,11-dione 21-Acetate (Reichstein's Substance U Monoacetate) (XIV).—Reduction of a suspension of 2.00 g. of cortisone 21-acetate XIII with 380 mg. of sodium borohydride in 100 ml. of 80% aqueous dimethylformamide at 15–20° as in the preceding experiment was complete (negative blue tetrazolium test) in 2.5 hours. The mixture was worked up as above and chromatographed on 60 g. of neutral alumina. The fractions from 30% benzene–chloroform through 50% benzene–chloroform (670 mg.) were crystalline and essentially pure monoacetate XIV. Crystallization from acetone–ether gave prismatic needles, m.p. 181–183°,[14] $[\alpha]_D^{CHCl_3}$ +174°; $\lambda_{max}^{CH_3OH}$ 238 mμ (15,300); $\lambda_{max}^{CHCl_3}$ 2.74, 2.80–2.85, 5.74, 5.84, 5.97, 6.14, 8.0 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.23; H, 7.96.

Paper chromatography (benzene–chloroform 1:1—formamide system) of representative chromatogram fractions indicated the presence of small quantity of a more polar ultraviolet absorbing component that gave a negative blue tetrazolium test and a very polar component (no ultraviolet; negative tetrazolium test). These materials were not characterized.

Acetylation of a sample of the monoacetate XIV in acetic anhydride–pyridine at 25° led to the 20β,21-diacetate, m.p. 245–249°, identical with authentic Reichstein's Substance U-20,21-diacetate by mixed melting point and infrared criteria.

Chromium trioxide–acetic acid oxidation[14] of a sample of the monoacetate XIV led to a neutral product resolved by paper chromatography (benzene–formamide system) into cortisone acetate (XIII) and adrenosterone.

(13) This substance was first prepared by partial acetylation of Reichstein's Substance E by Huang-Minlon and R. H. Pettebone, THIS JOURNAL, **74**, 1562 (1952).

(14) The monoacetate XIV was first obtained by partial acetylation of Reichstein's Substance U by L. H. Sarett [*J. Biol. Chem.*, **162**, 601 (1946)] who reported m.p. 172–174°.

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Oxidation of 1,1-Dibenzylhydrazines[1]

BY R. L. HINMAN[2] AND K. L. HAMM[3]

RECEIVED NOVEMBER 29, 1958

A series of unsymmetrically substituted dibenzylhydrazines (p-$XC_6H_4CH_2N(NH_2)CH_2C_6H_5$, where X = CH_3O–, $(CH_3)_2N$–, CH_3–, Cl–) have been oxidized with yellow mercuric oxide and in each case the only product identified was the unsymmetrical bibenzyl, p-$XC_6H_4CH_2CH_2C_6H_5$. Similarly, 2-(β-phenylethyl)-furan was obtained from the oxidation of 1-benzyl-1-furfurylhydrazine. The oxidation of 1-benzyl-1-(p-methoxybenzyl)-hydrazine by potassium permanganate, Fehling solution, or air also yielded the unsymmetrical bibenzyl, but oxidation of the same hydrazine with mercuric acetate or quinone produced the corresponding tetrazene. The benzenesulfonyl derivatives of 1-benzyl-1-(p-methoxybenzyl)-hydrazine and of 1-benzyl-1-(p-chlorobenzyl)-hydrazine were converted in good yield to the unsymmetrical bibenzyls by treatment with hot aqueous sodium hydroxide.

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A large number of 1,1-disubstituted hydrazines (I) have been oxidized with many commonly used oxidizing agents, including potassium permanganate, bromine, sodium hypochlorite, ferric chloride,