Saponification of Allethrin.—Allethrin, 30 g. (0.1 mole), that had been prepared from pure materials was dissolved in 180 ml. of 75% ethanol containing 4.8 g. (0.12 mole) of sodium hydroxide. After three and a half hours most of the ethanol was removed in vacuum and the residue, after dilution with water, was extracted with petroleum ether. The yield of crude product from which the solvent had been removed in vacuum was 12.7 g., $n^{25}D$ 1.5310. It was dissolved in 80 ml. of 75% ethanol containing 14 g. of semicarbazide hydrochloride and 11 ml. of pyridine. The crystalline material which had separated overnight was filtered off and refluxed with methanol. Three grams of insoluble disemicarbazone was removed by filtration and dried, m.p. 248–250°. The soluble semicarbazone obtained on concentrating the methanol solution melted at 207–210°, and was identical with the monosemicarbazone from allethrolone acid phthalate; yield 3.0 g.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.62; H, 7.91; N, 12.45.

Water was added to the concentrated mother liquor, and the suspended material was extracted with a large volume of ether. On concentration of the washed and dried ether solution, a small amount of monosemicarbazone melting at 185° was obtained.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.25; H, 7.41; N, 13.46.

From another experiment under identical conditions, 12.6 g. of the crude dimer mixture was obtained from 31 g. of pure allethrin. Upon seeding with the dimer (III), 4.35 g. of the crystalline product was obtained on standing, m.p. 66–67° after recrystallization from ligroin. The yield of insoluble disemicarbazone was 3.3 g.

Allethrolone Acetate.—Allethrolone, 12 g., in about 15 ml. of acetic anhydride with a little anhydrous sodium acetate was allowed to stand overnight and then warmed for half an hour on the steam-bath. The excess of anhydride and the acetic acid were removed in vacuum, water was added to the residue, and the ester extracted with about 150 ml. of petroleum ether. The solution was extracted with sodium carbonate solution and dried. The solvent was removed, leaving 12.9 g. of the ester. It was distilled at 0.5 mm., b.p. 96–97°, $n^{25}D$ 1.4902.

Anal. Calcd. for $C_{11}H_{14}O_3$: CH_3CO, 22.2. Found: CH_3CO, 21.2.

Saponification of Allethrolone Acetate.—Allethrolone acetate, 15 g., was allowed to stand overnight in 180 ml. of 75% ethanol containing a small excess of sodium hydroxide. Most of the solvent was removed in vacuum, and the separated oil was extracted with low-boiling petroleum ether in the usual manner to yield 7.0 g. of colorless oil, which, combined with 1.8 g. of the same material from a previous experiment, was dissolved in 40 ml. of methanol. A solution of 3.7 g. of semicarbazide hydrochloride in 14 ml. of 60% methanol and 4 ml. of pyridine was added at intervals of one-half hour. Crystallization began shortly after the first addition. The 3.4 g. of total product, obtained directly and on partial evaporation of the solvents, was still a mixture containing 1.65 g. of the monosemicarbazone of the dimer (III) soluble in hot methanol, m.p. 207–208°, and 0.9 g. of the insoluble disemicarbazone, m.p. 250–252°.

The unreacted liquid product that separated on dilution of the mother liquor was extracted with petroleum ether. The 1.7 g. of residue crystallized for the most part to the dimer III, which after recrystallization melted at 65–66°.

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

Steroid 17(α)-Acetates*

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RECEIVED JUNE 16, 1952

In contrast to statements in the literature, it has been found possible to acetylate a variety of 17(α)-hydroxy-20-ketosteroids under mild as well as vigorous conditions without invoking structural change.

The 17(α)-hydroxyl group of 20-ketosteroids has been generally acknowledged to be strongly hindered and not acetylatable.[1] In contrast thereto, the direct acetylation of steroid tertiary hydroxyl functions situated 17(β)[2] and 5(α)[3] has been successfully accomplished employing acetic anhydride in pyridine at 100° and refluxing acetic anhydride, respectively. The recently reported isolation of a 17(α)-lactone from the oxidation of sitosterol[4] as well as an earlier described diacetate derived from 3(β), 17(α)-dihydroxy-11-keto-etioallocholanic acid[5] indicated the possibility of esterification of steroid 17(α)-hydroxyl groups in general. It had been of interest to us, for some time, to investigate the reactivity of this functional group and attempt to define the conditions necessary for its participation in direct acetylation. It was anticipated that as the conditions of forced reaction were made more extreme, dehydration and/or rearrangement might intervene. In this latter regard, numerous 17-hydroxy steroids, including 17(α)-hydroxyprogesterone,[6] have been observed to be exceptionally prone to D-ring homoannulation under a variety of conditions.[7] Of particular significance with regard to the compounds of the type reported in the present work is the recent discovery by Mattox[8] that the 20-keto-17(α),21-dihydroxy cortical side chain is smoothly converted to a substituted glyoxal derivative in the presence of methanolic hydrogen chloride. In this connection, however, it is noteworthy that this rearrangement does not occur to any measurable extent with hydrogen chloride in acetic acid.[9]

Conditions found to be sufficient to acetylate steroid 17(β)-hydroxyl groups[2] (acetylation employing acetic anhydride in pyridine at 100°) were found in the present work to be essentially without

* We regret that through inadvertence on our part a Communication (THIS JOURNAL, **74**, 4220 (1952)) on the same subject was received and accepted after the definitive paper published here.—THE EDITORS.

(1) *See for example:* (a) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **30**, 205 (1947); (b) L. F. Fieser, *Experientia*, **6**, 312 (1950); (c) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 411; (d) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952).

(2) C. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 185 (1943).

(3) Pl. Plattner, Th. Petrzilka and W. Lang, *ibid.*, **27**, 513 (1944).

(4) A. J. Ryer and W. H. Gebert, THIS JOURNAL, **74**, 41 (1952).

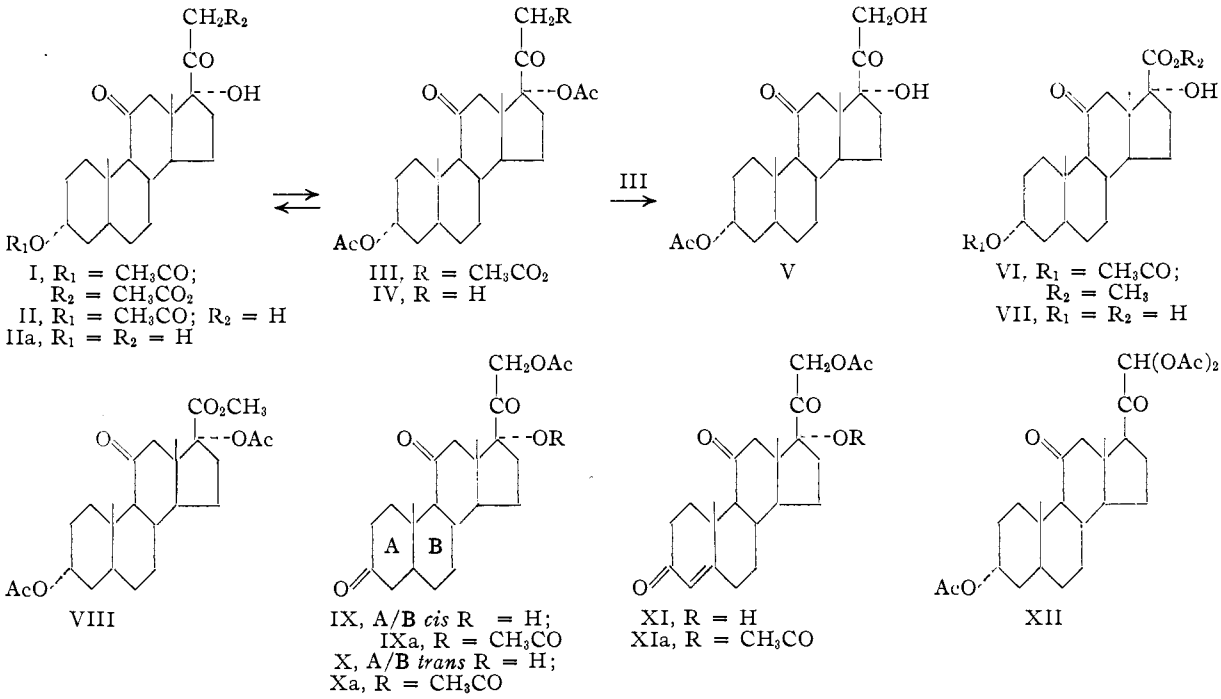
(5) H. L. Mason, W. M. Hoehn and E. C. Kendall, *J. Biol. Chem.*, **124**, 459 (1938).

(6) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

(7) Reference 1c, p. 377.

(8) V. R. Mattox, Abstracts of the Gordon Conferences on Steroids, New Hampton, N. H., Aug. 13–15 (1951).

(9) Observation by Dr. R. P. Graber of these laboratories.



effect on 17(α)-hydroxy steroids. On the other hand, when the diacetate (I), for example, was refluxed for 12 hours with freshly distilled acetic anhydride, the triacetate (III) could be easily isolated in 60% yield together with a small amount of unchanged I. This same triacetate (III), moreover, could also be prepared by room-temperature acetylation of I with acetic anhydride containing one equivalent of *p*-toluenesulfonic acid. The triacetate (III) exhibited no hydroxyl band in its infrared spectrum and was found to be totally different from XII prepared according to the procedure described by Fleisher and Kendall.[10] The latter comparison thereby ruled out the possibility of side chain rearrangement in the sense demonstrated by Mattox[8] (see above). Structure III for the triacetate was confirmed by hydrolysis followed by mild acetylation to give I and by partial hydrolysis with sodium methoxide in methanol to yield the 3-monoacetate (V). Attempts to effect partial hydrolysis of the C_{21}-acetate group of III, under conditions whereby I was converted to V, were unsuccessful. Thus treatment of III with one equivalent of sodium methoxide in methanol afforded an impure product; the latter on cleavage oxidation with periodic acid and subsequent esterification with diazomethane gave the same ester acetate (VI) in appreciable yield as was obtained from V directly. This demonstrates that the 17(α)-acetate group is hydrolyzed with a facility comparable with that observed for the 21-acetate function.

In a similar manner, pregnane-3(α),17(α)-diol-11,-20-dione-3-monoacetate (II), methyl 3(α)-acetoxy-17(α)-hydroxy-11-ketoetiocholanate (VI), pregnane-17(α),21-diol-3,11,20-trione-21-monoacetate (IX), allopregnane-17(α),21-diol-3,11,20,trione-21-monoacetate (X), and cortisone 21-monoacetate (XI) were converted to their respective 17(α)-acetate derivatives. In each case, the 17(α)-hydroxyl group could be regenerated by hydrolysis.

(10) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 573 (1951).

Experimental

Acetylations. (A) **Hot Method.**—The compound to be acetylated was refluxed with an excess of redistilled acetic anhydride for a period of 12 hours. At the end of this period, the reaction mixture was evaporated to dryness and the residue treated with water. If the product crystallized at this stage it was filtered; otherwise the residue was extracted with a suitable solvent, the organic layer washed with 5% aqueous bicarbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness. The latter residue was then either crystallized from a suitable solvent or chromatographed on acid-washed alumina as the need demanded.

(B) **Cold Method.**—The compound to be acetylated was suspended in an excess of acetic anhydride, treated with one equivalent of *p*-toluenesulfonic acid monohydrate and stirred at room temperature for 16–20 hours. At the end of this time the reaction mixture was chilled in an ice-bath and slowly treated with water. Stirring was continued for one hour in the cold and for three hours at room temperature. At the end of this period the acetylated product had usually crystallized and was filtered and recrystallized from a suitable solvent.

Hydrolyses. (A) **Total.**—A solution of the acetate derivative in methanol was treated with stirring in a nitrogen atmosphere with 10% aqueous sodium hyroxide at 20–35° for a period of 15 minutes to one-half hour. At the end of this period the excess alkali was neutralized with glacial acetic acid and the reaction mixture evaporated nearly to dryness at 40–50°. The residue was triturated with water, filtered and crystallized from a suitable solvent.

(B) **Partial.**—A solution of the acetate derivative in methanol was treated in a nitrogen atmosphere with one equivalent of sodium methoxide in methanol. The reaction mixture was allowed to stand at room temperature for three to five minutes and then treated with three equivalents of water and allowed to stand for an additional period of three minutes. At the end of this operation, the excess alkali was neutralized with glacial acetic acid and the colorless reaction solution evaporated to dryness. The residue was extracted with a suitable solvent (ethyl acetate), the extract washed with 5% aqueous bicarbonate solution and the organic layer evaporated to dryness, and the product crystallized from a suitable solvent.

Pregnane-3(α),17(α),21-triol-11,20-dione-3,17,21-triacetate (III). (A).—The diacetate (I), 6 g., was acetylated

by the hot method giving 6 g. of crude product. The latter was chromatographed on acid-washed alumina and eluted with benzene–petroleum ether to give 3.7 g. of III after recrystallization from 85% methanol, m.p. 147–149°. A sample was recrystallized for analysis; m.p. 150–152°, $[\alpha]^{26}D$ +40.9° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.80. Found: C, 66.04; H, 7.82.

(**B**).—Acetylation of I by the cold method afforded the triacetate (III) in somewhat lower yield than by the hot method, melting at 150–151° and undepressed on admixture with III obtained by the hot method.

A solution of 3 g. of III in 30 cc. of methanol was partially hydrolyzed at 20–22° with two equivalents of sodium methoxide in 25 cc. of methanol. The product was crystallized from ethyl acetate giving 2.37 g. of V, m.p. 209–212°, $[\alpha]^{22}D$ +80° (chloroform).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 67.94; H, 8.43. Found: C, 67.92; H, 8.34.

Acetylation of V in pyridine with acetic anhydride at room temperature provided I, m.p. 232–235°.

Methyl 3(α)-Acetoxy-17(α)-hydroxy-11-ketoetiocholanate (VI).—A solution of 1 g. of III was hydrolyzed in the same manner as above except that only one equivalent of sodium methoxide was employed. The crude hydrolysis product (0.8 g.) in 30 cc. of dioxane was oxidized at room temperature for 16 hours with 0.7 g. of periodic acid dissolved in 6 cc. of water. The reaction mixture was evaporated to dryness, extracted with ether and the washed ether solution treated with an excess of ethereal diazomethane. Evaporation of the solution after treatment with diazomethane gave 0.36 g. of the methyl ester VI, m.p. 144.3–145.5°, $[\alpha]^{22}D$ + 71.2° (chloroform).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43. Found: C, 67.82; H, 8.20.

Pregnane-3(α),17(α)-diol-11,20-dione-3,17-diacetate (IV).—IV was prepared from 3 g. of II by the hot acetylation procedure and crystallized from methanol; m.p. 203–204°, wt. 2.27 g., $[\alpha]^{23}D$ +46.7° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.54; H, 8.10.

Total hydrolysis of 0.4 g. of IV in 40 cc. of methanol with 6 cc. of 10% aqueous sodium hydroxide at 35° for 20 minutes afforded 0.33 g. of IIa from benzene, m.p. 203–204°, undepressed on admixture with authentic IIa. Acetylation of IIa with acetic anhydride in pyridine at room temperature gave the **3-monoacetate II**, m.p. 205.5–206.5°, showing no depression with authentic II.

Methyl-3(α),17(α)-diacetoxy-11-ketoetiocholanate (VIII).—Two-tenths of one gram of the acetate ester (VI) was acetylated by the hot method for five hours to give 0.19 g. of VIII as prisms from ether–petroleum ether; m.p. 195–197.2°. A sample recrystallized for analysis melted at 198–199°, $[\alpha]^{26}D$ +21.8° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.32; H, 8.09.

Total hydrolysis of 0.5 g. of VIII was effected in 50 cc. of 10% methanolic potassium hydroxide by refluxing for three hours to afford 0.35 g. of VII, m.p. 286–287°, $[\alpha]^{24}D$ +41.7° (dioxane).

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 69.07; H, 8.45.

Pregnane-17(α),21-diol-3,11,20-trione-17,21-diacetate (IXa).—A sample of IX, 2.5 g., was acetylated by the hot method and afforded, after crystallization from dilute methanol, 1.45 g. of IXa, m.p. 221–222°, $[\alpha]^{26}D$ +27.4° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67; CH_3CO, 19.28. Found: C, 67.43; H, 7.56; CH_3CO, 19.10.

Hydrolysis of IXa by the method described for III followed by acetylation at room temperature with acetic anhydride in pyridine gave IX from ethyl acetate, m.p. 230–233°, identical with authentic material.

Allopregnane-17(α),21-diol-3,11,20-trione-17,21-diacetate (Xa).—A sample of X, 2.4 g., was acetylated by the cold method employing 30 cc. of acetic anhydride and 1.4 g. of *p*-toluenesulfonic acid monohydrate. Crystallization of the product from methanol gave 2.13 g. of Xa, m.p. 167–70°, solidified and remelted at 177–182°, $[\alpha]^{23}D$ +43.9° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.07; CH_3CO, 19.3. Found: C, 67.20; H, 7.51; CH_3CO, 18.5.

Hydrolysis of Xa with sodium methoxide followed by reacetylation by the method described for the conversion of III to I gave X, m.p. 233–236°, identical with authentic material.

Cortisone-17,21-diacetate (XIa).—A 4.5-g. sample of cortisone 21-acetate (XI) was acetylated by the hot method for 12 hours to afford after crystallization from methanol 2.3 g. of XIa, m.p. 221–222°, $[\alpha]^{23}D$ +133° (chloroform), $\lambda_{max}^{CH_3OH}$ 238 mμ, log ε 4.2.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.79; H, 7.48.

Hydrolysis of XIa by the sodium methoxide procedure produced cortisone identical with authentic material, m.p. 218–224°.

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