from an acetamido group. This band is absent in the spectrum of 2-acetylsulfamyl-*N*-methylacetanilide. Moreover no bands are present in diacetylorthanilamide in the 3-μ region which are normally associated with the presence of an unsubstituted $-SO_2NH_2$ group. Confirmation of the fact that diacetylorthanilamide contains an acetylated sulfamyl group was obtained from a study of pK_a data since the pK_a value for this compound is 5.33, which may be compared with the figure 6.2 for 2-acetylsulfamyl-*N*-methylacetanilide. In comparison, *o*-sulfamylacetanilide is so weakly acidic that its alkali titration curve does not show a break. These facts are only consistent with the formulation of diacetylorthanilamide as 2-acetylsulfamylacetanilide (I. $R_1 = H$, $R_2 = R_3 = COCH_3$).

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Facile Preparation of 17β-Hydroxy-5β-androstan-3-one and Its 17α-Methyl Derivatives

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Investigation on correlation of steroid structure with androgenic activity required availability of 5β-androstane derivatives. Accordingly, we investigated the stereochemistry of catalytic hydrogenation of the carbon-carbon double bond of Δ^4-3-ketones under basic conditions. Addition of potassium hydroxide to the catalytic hydrogenation of Δ^4-3-ketones of the ergostane or spirostane series has been reported to lead to A/B *cis* (5β) products.[1-5]

To our knowledge, however, use of potassium hydroxide in the catalytic hydrogenation of Δ^4-3-ketones of the androstane series has not previously been described. We observed that 17α-methyltestosterone, or testosterone, in 2.5% ethanolic potassium hydroxide were easily hydrogenated, with palladium black as catalyst, to their 5β-dihydro derivatives. The product from the hydrogenation of 17α-methyltestosterone, 17β-hydroxy-17α-methyl-5β-androstan-3-one, seems not to have been described previously.

Infrared spectrophotometry was employed for the establishment of the absence of contaminating 5α-dihydro isomers. Both 17β-hydroxy-5α-androstan-3-one and its 17α-methyl derivative exhibit a characteristic peak at 11.38 μ, which is entirely absent for the 5β isomer. The presence of as little as 5% 5α contamination could be detected in 17β-hydroxy-17α-methyl-5β-androstan-3-one by this means, but in the case of 17β-hydroxy-5β-androstan-3-one 25%, but not 10% 5α contamination could be detected, perhaps because the 11.38 μ band is comparatively more intense for the 17α-methyl-5α-compound. Optical rotatory dispersion was found to be a better tool for analyzing quantitatively the presence of 5α impurities in the 5β compounds. It was found that the crude 17β-hydroxy-5β-androstan-3-one from the reduction of testosterone had approximately 15% 5α contamination.[6] Consequently, partition chromatography on alumina was found necessary for the purification of the testosterone reduction product, whereby the less polar 5β product was easily separated from its 5α isomer.

When either 17β-hydroxy-17α-methyl-5β-androstan-3-one or 17β-hydroxy-5β-androstan-3-one were assayed for androgenic activity, each possessed 1% of the activity of the testosterone reference standard. Both compounds were given subcutaneously, dissolved in oil. The assessment was based on stimulation of ventral prostate growth of castrated immature male rats.

EXPERIMENTAL

17β-Hydroxy-17α-methyl-5β-androstan-3-one. Fifty grams of 17β-hydroxy-17α-methylandrost-4-ene-3-one was partially dissolved in 500 ml. of absolute ethanol containing 500 mg. of palladium black and 12.5 g. of potassium hydroxide previously dissolved in 25 ml. of distilled water, and hydrogenated at an initial pressure of 45 lb. for 2 hr. Afterwards, the palladium catalyst was removed by filtration through kaolin under reduced pressure, the filtrate neutralized with a sufficient amount of glacial acetic acid, diluted with 1500 ml. of distilled water, and placed in the cold (4°) until the precipitated oil was completely crystallized, usually within 24 hr. The crude product was collected by filtration under reduced pressure, dried *in vacuo* over potassium hydroxide, and added to 2000 ml. of boiling petroleum ether (b.p. 60–110°), which facilitated separation of insoluble impurities from the soluble 5β-dihydro reduction product. Decantation of the supernatant into another Erlenmeyer flask, boiling down to 500 ml., and setting the flask aside to cool in the cold (4°) afforded 30 g. (60%) of pure 17β-hydroxy-17α-methyl-5β-androstan-3-one, colorless glistening plates, $[\alpha]_D^{25}$ +3° (chloroform), double m.p. 74–76° and 119–121° (Köfler stage). Careful crystallization from dilute ethanol yielded the higher melting point form as

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(3) M. Velasco, J. Rivera, G. Rosenkranz, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 18, 92 (1953).
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(6) We are greatly indebted to Dr. Fred Kincl of Syntex Laboratories for optical rotatory dispersion measurements.

colorless needles, m.p. 120–121°. The compound gave a correct analysis for $C_{20}H_{32}O_2$.[7]

17β-Hydroxy-5β-androstan-3-one. Twenty-nine grams of testosterone was dissolved in 290 ml. of absolute alcohol containing 290 mg. of palladium black and 7.25 g. of potassium hydroxide previously dissolved in 15 ml. of distilled water, and hydrogenated at an initial pressure of 45 lb. for 2 hr. The work-up of the hydrogenation mixture was the same as described above, except that purification of the dried crude product was accomplished by dissolving in 500 ml. of a solution of benzene and ether 2:1, passing the solution through a chromatographic column containing 150 g. of chromatographic grade alumina (Harshaw), and eluting with 3 l. of a solution of benzene–ether 2:1. Evaporation of the eluate to dryness and crystallization from 500 ml. of hot petroleum ether (b.p. 60–110°) afforded 17.3 g. (60%) of pure 17β-hydroxy-5β-androstan-3-one, colorless plates, m.p. 142–144° (Kofler stage), $[\alpha]_D^{21}$ +32° (ethanol). Its infrared spectra was identical with that for an authentic sample of 17β-hydroxy-5β-androstan-3-one, and the mixed m.p. showed no depression.

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(7) We are greatly indebted to the Cancer Preparations Laboratory of Merck Sharp and Dohme for determination of optical rotation and carbon-hydrogen analyses of the compound.

Reaction of Diosgenin Acetate with Hydrogen Chloride in Acetic Anhydride

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In 1956 Miner and Wallis described an interesting fission of the spiroketal ring juncture of diosgenin acetate (I) with anhydrous hydrogen chloride in refluxing acetic anhydride to give an acetoxy chloro derivative.[1] The chloro compound, which crystallizes remarkably well from the resinous reaction product in 10% yield, was tentatively considered by its discoverers to be 3β,27-diacetoxy-16α-chloro-25α-5-cholesten-22-one. An attempt to use the substance as starting material for synthesis of steroid pyrroline derivatives of a type recently prepared,[2] however, has established that it must possess the structure 3β,16β-diacetoxy-27-chloro-25α-5-cholesten-22-one (II).

(1) R. S. Miner, Jr., and E. S. Wallis, *J. Org. Chem.*, 21, 715 (1956).

(2) F. C. Uhle and F. Sallmann, *J. Am. Chem. Soc.*, 82, 1190 (1960).

Treatment of II with three equivalents of potassium phthalimide in dimethylformamide at 105° gave the phthalimido derivative III. Hydrolysis of III with 5% ethanolic potassium hydroxide, followed by phthalamidic acid ring closure with *N*-cyclohexyl-*N'*-[2-(4-morpholinyl)ethyl]carbodiimide metho-*p*-toluenesulfonate, afforded the hemiketal IV, an intermediate in the synthesis of solasodine (VII) from kryptogenin.[3] Hemiketal dehydration of IV with glacial acetic acid at 100° gave the phthalimido furostene V, an intermediate in the synthesis of solasodine (VII) from pseudodiosgenin.[3]

Hydrazinolysis of III afforded VI, a tetrahydropyridine derivative first prepared from solasodine (VII) with acetic anhydride in the presence of zinc chloride.[4] Subjection of the gross product from hydrazine treatment of III to acetate hydrolysis with aqueous ethanolic potassium hydroxide gave solasodine (VII), constituting a three-step synthesis of the alkaloid from the sapogenin.

EXPERIMENTAL[5]

3β,16β-Diacetoxy-27-chloro-25α-5-cholesten-22-one (II). The compound ($C_{31}H_{47}ClO_5$) (535.14) was prepared from diosgenin acetate with anhydrous hydrogen chloride and refluxing acetic anhydride according to the procedure of Miner and Wallis.[1]

3β,16β-Diacetoxy-27-phthalimido-25α-5-cholesten-22-one (III). A magnetically stirred solution of 267 mg. (0.0005 mole) of 3β,16β-diacetoxy-27-chloro-25α-5-cholesten-22-one (II) and 277 mg. (0.0015 mole) of potassium phthalimide in 2 ml. of anhydrous dimethylformamide was heated at 105° for 24 hr.[6] After the mixture had been diluted with 20 ml. of saturated aqueous potassium chloride, the precipitate was collected by filtration, washed with water and dried. Initial attempts to recrystallize the product from methanol were erratic, giving low melting material which did not improve and even appeared to deteriorate on repetition, suggesting an instability to prolonged heating in alcoholic solution. Recrystallization was accomplished by brief warming in isopropyl alcohol, followed by rapid chilling. Two such recrystallizations gave 200 mg. (62%) of very small plates, m.p. 160–180°. The analytical sample, from isopropyl alcohol, melted at 179–182°; $[\alpha]_D$ + 14° (chloroform); infrared spectrum (KBr): 5.80 (acetoxy), 5.65, 5.90, 13.8, 14.0 μ (phthalimido).

Anal. Calcd. for $C_{39}H_{51}NO_7$ (645.81): C, 72.43; H, 7.96; N, 2.17. Found: C, 72.25; H, 7.82; N, 2.43.

3β,22-Dihydroxy-27-phthalimido-25α-5-furostene ($C_{35}H_{47}NO_5$) (561.73) (IV). A solution of 129 mg. (0.0002 mole)

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(4) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, 22, 1496 (1957); Y. Sato and N. Ikekawa, *J. Org. Chem.*, 25, 786 (1960).

(5) Melting points were observed on a calibrated micro hot stage. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Rotations were measured by Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y. Infrared spectra were recorded with a Perkin-Elmer spectrophotometer, model 137. Only those functional bands of significance in interpretation are mentioned.

(6) The sparingly soluble 27-chloro compound was altogether unreactive with potassium phthalimide in dimethylformamide at 25° under conditions used with 27-iodo derivatives.[3]