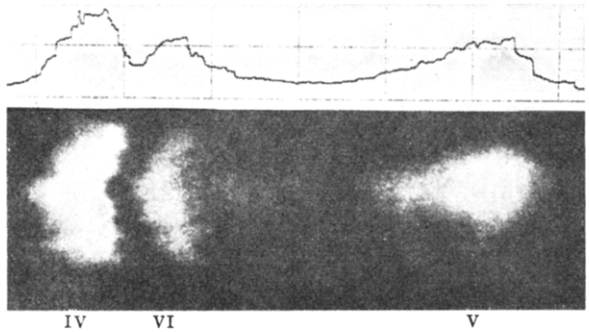
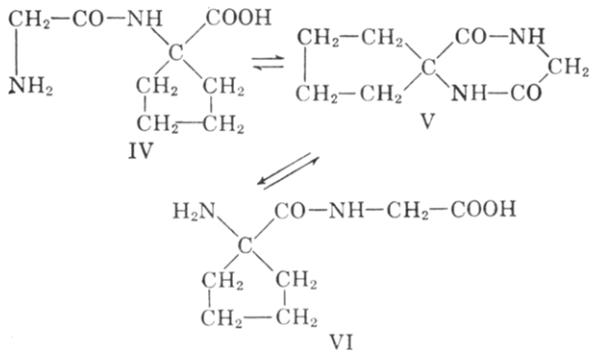


Fig. 1. Radiochromatogram after partial hydrolysis of V

in a little boiling water, the residue was purified with charcoal and crystallized out upon cooling. Yield: 0.63 g. (70%), m.p. 276°. Specific activity: 2.2×10^3 c.p.m./mg.

Anal. Calcd. for $C_8H_{12}N_2O_2$: N, 16.67. Found: 16.63.

Partial hydrolysis of 1,4-diazaspiro[4.5]decane-2,5-dione-5-C[14]. The piperazinedione (0.2 g.) was hydrolyzed by dissolving in 10 ml. of 1*N* hydrochloric acid and by boiling during 5–6 minutes. The solution was cooled and the volume was exactly completed to 10 ml. An aliquot of 0.1 ml. was submitted to paper chromatography in 2,4,6-trimethylpyridine (1 part), 2,4-lutidine (85%) (1 part), and water (2 parts), in order to separate the two peptides and the nonhydrolyzed piperazinedione.



Measure of the radioactivity (*a*) *By elution from the paper.* The paper band was sectioned and the radioactive spots of the two peptides and of the nonhydrolyzed piperazinedione were eluted with water. This water was collected on planchets which were dried under an infrared light. The radioactivity was determined using a Nuclear Chicago detector D 47. The mean actual counts for fifteen determinations were 59×10^3 c.p.m. for IV, 43×10^3 c.p.m. for VI, and 60×10^3 c.p.m. for the nonhydrolyzed V. This gave a proportion of 58% in favor of IV and 42% in favor of VI.

(*b*) *By direct measure on the paper.* The paper band was passed directly into a Nuclear Chicago Actigraph. The areas of the two first curves obtained (Fig. 1) were determined and found to be in a proportion of 58% for IV and 42% for VI.

The paper band was also placed on a Kodak X-Ray Royal Blue Film during seven days, after which time the film was developed (Fig. 1). Three spots were found and their relative intensities were of the same order as the ones found by the actigraph and the elution method.

Acknowledgment. The authors are indebted to the National and Medical Research Councils of Canada and to Dr. L. M. Babineau for the radioactivity determinations.

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Diacetylorthanilamide

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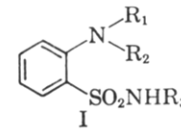
Received July 31, 1961

Ekbom[1] heated orthanilamide (I. $R_1 = R_2 = R_3 = H$) with acetic anhydride and obtained a product m.p. 191.5–192.5° to which he assigned the structure I ($R_1 = R_2 = COCH_3$, $R_3 = H$). Parke and



I

Williams[2] stated that acetic anhydride and orthanilamide gave mainly diacetylorthanilamide and that acetylation with pyridine and acetic anhydride yielded the same compound almost quantitatively. The latter authors reported a melting point of 190° and named this product in the Experimental section *o*-diacetylaminobenzenesulfonamide, thus assigning the same structure as Ekbom. Recently, Yale, Losee, and Bernstein[3] in referring to the work of Parke and Williams showed the structure of the acetylation product as I ($R_1 = R_2 = COCH_3$, $R_3 = H$).

We have prepared diacetylorthanilamide, m.p. 196°, using pyridine and acetic anhydride according to the procedure of Parke and Williams.[2] However, a consideration of infrared spectral[4] and pK_a[5] data shows that the compound is 2-acetylsulfamylacetanilide (I. $R_1 = H$, $R_2 = R_3 = COCH_3$). Two bands of medium to strong intensity attributable to —C=O vibrational modes are present in the infrared spectrum of diacetylorthanilamide at 5.78 μ and 6.00 μ. The band at 6.00 μ is also found in 2-sulfamylacetanilide[1] (I. $R_1 = R_3 = H$, $R_2 = COCH_3$) and clearly results from the presence of the acetamido substituent. The band at 5.78 μ corresponds well with the expected lower wave length absorption of $-C=O$ present in the group $-SO_2NHC(=O)-CH_3$ and correlates with the absorption at 5.80 μ shown by 2-acetylsulfamyl-*N*-methylacetanilide[6] (I. $R_1 = CH_3$, $R_2 = R_3 = COCH_3$). Further evidence is obtained by a consideration of absorptions due to N—H stretching vibrations. Diacetylorthanilamide has a sharp band in its infrared spectrum at 2.95 μ corresponding to the N–H absorption

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(2) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 1950.

(3) H. L. Yale, K. Losee, and J. Bernstein, *J. Am. Chem. Soc.*, **82**, 2042 (1960).

(4) The infrared spectra of the compounds were determined as Nujol mulls.

(5) Determined in 66% dimethylformamide solution.

(6) L. Raffa, *Farmaco Ed. Sci.*, **12**, 483 (1957).

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. $R_1 = H$, $R_2 = R_3 = COCH_3$).

Acknowledgment. The author is indebted to Mr. R. Wayne for discussions in connection with the interpretation of the infrared spectra and Mr. J. McGlotten for the acidity studies.

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

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Received July 31, 1961

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.