Phenacyl Kojate (VI).—Kojic acid, 2.12 g., was dissolved in 25 ml. of warm 95% ethanol. To this was added a solution of 0.6 g. of sodium hydroxide pellets in 2.5 ml. of water, and then 2.98 g. of phenacyl bromide. The solution was shaken by hand in a stoppered flask for fifteen minutes, then refluxed for thirty minutes. On chilling and concentrating, there was obtained 3.6 g. of material which was recrystallized thrice from absolute ethanol, m. p. 144.5–145°. The product (2.8 g. or 72%) appeared as white needles, giving no color test with ferric chloride. Drying in the oven at 110° resulted in partial decomposition, but a sample desiccated over sulfuric acid *in vacuo* for several hours showed no change in melting point.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.63; H, 4.65; mol. wt., 260. Found: C, 64.43; H, 4.84; mol. wt.,[8] 257.

Substitution of an equivalent amount of phenacyl chloride for the bromide in this reaction gave a 62% yield of the same product.

2-Acetoxymethyl-5-phenacyloxy-1,4-pyrone.—A mixture of 1.3 g. of VI, 6.5 ml. of acetic anhydride and 0.5 g. of dry sodium acetate was heated for two hours at 100°. After processing, the solid residue was recrystallized from methanol, giving 0.8 g. of white plates, m. p. 116–116.5° (53% theoretical). It was dried *in vacuo* over sulfuric acid with no change.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.53; H, 4.67; mol. wt., 302. Found: C, 63.40; H, 4.87; mol. wt.,[8] 299.

bis-(Phenacyl Kojate) Sodium Halide.—(a) To a solution of 2.0 g. of kojic acid in 20 ml. of dry methanol was added an equivalent amount of sodium methoxide in 10 ml. of dry methanol. This was refluxed for one hour with 2.81 g. of phenacyl bromide. Chilling and concentrating gave 2.67 g. of m. p. 197–197.5°. Recrystallization from 25 ml. of methanol gave no change. Qualitative tests showed the presence of sodium and active halogen. Washing with water resulted in a sharp drop in melting point to 145–146°. Mixed melting with VI then gave no depression.

Anal. Calcd. for $C_{28}H_{24}BrNaO_{10}$: C, 53.90; H, 3.86; Na, 3.70; Br, 12.84. Found: C, 53.35; H, 3.94; Na, 3.58; Br, 13.20.

(b).—When an equivalent amount of phenacyl chloride was substituted for the bromide, an eight-hour reflux period gave 2.45 g. of white needles, m. p. 158–158.5°. Qualitative tests showed the presence of sodium and active halogen, and washing with water left a residue identical with VI.

Anal. Calcd. for $C_{28}H_{24}ClNaO_{10}$: C, 58.10; H, 4.15; Na, 3.96; Cl, 6.14. Found: C, 56.10; H, 4.20; Na, 3.88; Cl, 6.15.

Phenylhydrazone, m. p. 140.5–141.5° (dec.), yield 85%, contains sodium and halogen, which was inert toward aqueous or alcoholic silver nitrate solutions. It was recrystallized from methanol.

Anal. Calcd. for $C_{40}H_{36}ClN_4NaO_8$: N, 7.39. Found: N, 7.52.

2,4-Dinitrophenylhydrazone, m. p. 235° (dec.), yield 91%, contains sodium and inactive halogen. It was recrystallized from ethanol.

Anal. Calcd. for $C_{40}H_{32}ClN_8NaO_{16}$: N, 11.93. Found: N, 11.48.

Acknowledgments.—The kojic acid was supplied by Dr. A. L. Elder of Corn Products Refining Company. Microanalyses for carbon and hydrogen were performed by Mrs. J. Gibbs and by Miss M. Hines. Those for nitrogen were done by Miss V. Hobbs.

Summary

Acetyl, caproyl, allyl and phenacyl derivatives of kojic acid are discussed.

(8) Smith and Young, *J. Biol. Chem.*, **75**, 289 (1927).

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

Preparation of Pregnane-17α,21-diol-3,11,20-trione Acetate

BY L. H. SARETT

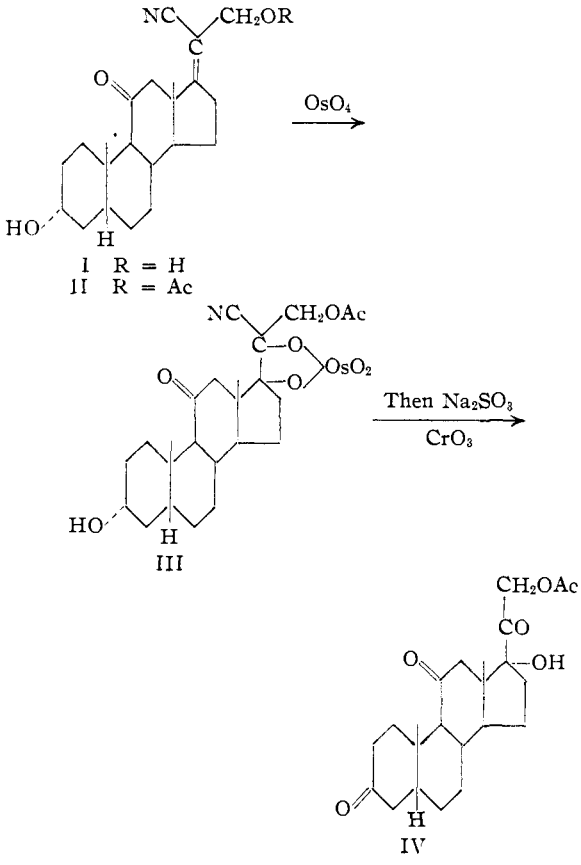
It was shown recently that pregnane-17α,21-diol-3,11,20-trione acetate (IV), a chemical precursor of Kendall's Compound E, could be prepared from pregnane-3α,21-diol-11,20-dione 21-acetate *via* the 20-cyanohydrin, the 3-keto-20-cyanohydrin, the 3-keto unsaturated nitrile and the 3-keto-20-cyano-17,20-osmate as successive intermediates.[1] Since the dehydration step went quite poorly because of the adverse influence of the 3-keto group, a revised scheme has now been tried. As starting material Δ[17]-20-cyanopregnene-3α,21-diol-11-one (I), which may be prepared from pregnane-3α,21-dione diacetate in excellent yield, was used. Partial acetylation gave the 21-monoacetate (II) and the latter with osmium tetroxide afforded the osmate ester (III). It has been found that the osmate bridge in this molecule is sufficiently stable toward chromic acid in acetic acid to permit oxidation of the C-3 hydroxyl group.[2] Neutralization of the acetic acid with potassium bicarbonate followed by hydrolysis of the 3-keto osmate yielded IV. It has been found that by the addition of a suitable volume of benzene to the aqueous sulfite hydrolysis solution, the saponification of the C-21 acetoxy group could be largely suppressed. The combined contributions to the efficiency of the process resulted in an over-all yield of IV from pregnane 3α,21-diol-11,20-dione acetate which is somewhat more than twice the previous value.

Experimental

Δ[17]-20-Cyanopregnene-3α,21-diol-11-one 21-Acetate (II).—A solution of 754 mg. of Δ[17]-20-cyanopregnene-3α,21-diol-11-one (I) in 2.75 cc. of pyridine containing 255 mg. of acetic anhydride (1.0 molecular equivalent) was left at room temperature overnight. The solution was then diluted with ether, washed successively with dilute hydrochloric acid, dilute potassium carbonate and water, then concentrated to dryness. Several crystallizations of the residue from dilute alcohol and finally from ben-

(1) Sarett, THIS JOURNAL, **70**, 1454 (1948).

(2) However this stability seems to rest upon the presence of the negative cyano group at C-20 since the 17,20-osmate of pregnane-3α,17α,20α-triol-11-one was converted by chromic acid and subsequent sulfite hydrolysis into a mixture from which no dioldione could be isolated.



zene gave 479 mg. of the monoacetate, m. p. 151–152° (cor.), $[\alpha]^{25}D$ + 16° (acetone). A solvated form which melted with decomposition at about 130–140° was obtained by crystallization from dilute alcohol. Saponification of the mother liquors gave a nearly quantitative yield of the free diol, m. p. 256–258°. For analysis a sample was heated at 120° *in vacuo* for two hours.

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.14; H, 8.33. Found: C, 71.77; H, 8.42.

Pregnane-17α,21-diol-3,11,20-trione Acetate (IV).—To a solution of 429 mg. of Δ^{20}-20-cyanopregnene-3α,21-diol-11-one 21-acetate in 4 cc. of benzene was added 600 mg. of osmium tetroxide followed by 0.30 cc. of pyridine. After sixteen hours the mixture was concentrated nearly to dryness *in vacuo* at 35°. To the residue was added 5 cc. of 90% acetic acid and 1.05 cc. of acetic acid containing 3.70 milliequivalents of sulfuric acid. The solution was cooled to 0° and treated dropwise with 4.4 cc. of a 90% acetic acid solution containing 200 mg. of chromic acid. The mixture was permitted to stand at 15° for forty-five minutes, then poured into 20 cc. of water containing 15 g. of potassium bicarbonate (partly in solution), the flask being rinsed with a little dilute methanol. The mixture was stirred until evolution of carbon dioxide ceased, and the remaining carbon dioxide was removed from solution *in vacuo* at 30°. Ten cc. of an aqueous solution containing 2.0 g. of sodium sulfite and 2.0 g. of potassium bicarbonate was added followed by 20 cc. of benzene and 20 cc. of methanol. The mixture was stirred overnight, filtered, acidified to *p*H 6 with acetic acid, concentrated *in vacuo* until the organic solvents were removed and the aqueous suspension then extracted with four 50-cc. portions of chloroform. The washed chloroform extracts were combined and concentrated to dryness giving 323 mg. of crystalline residue consisting mostly of the dioldione acetate (IV) but containing a small amount of the free dioldione. The latter was converted to the acetate by dissolving the residue in 2 cc. of a pyridine–acetic anhydride mixture and warming at 50° for five minutes. The addition of water precipitated the crystalline acetate; after recrystallization from alcohol it melted at 227–229°. A mixed melting point with pregnane-17α,21-diol-3,11,20-trione acetate (m. p. 229–231°) was 228–231°; yield, 200 mg.

Acknowledgment.—The author is indebted to Dr. Karl Folkers for various suggestions and to Miss Jean E. Andrews for assistance.

Summary

A more efficient method for the preparation of pregnane-17α,21-diol-3,11,20-trione acetate is described. The method is based upon the stability of the addition product of osmium tetroxide and Δ^{17}-20-cyanopregnenes toward chromic acid.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazoles. III. 1-Substituted Analogs of Histidine and Histamine

BY REUBEN G. JONES AND KEITH C. McLAUGHLIN

In the preceding paper of this series[1] there was described a convenient method for the synthesis of 4(or 5)-imidazolecarboxylic acid esters and 1-substituted-5-imidazolecarboxylic acid esters. It has been found that the ester group in these compounds can be converted readily to aldehyde and to hydroxymethyl. This has now made it possible to synthesize a series of analogs of histidine and histamine having substituents in the 1-position of the imidazole ring. Five such analogs of histidine and one analog of histamine have been prepared and are described at this time. This work constitutes part of a study concerned with possible relationships of chemical structure to biological activity of α-amino acids and amines.

The 5-imidazolecarboxylic acid esters (A) were smoothly reduced with lithium aluminum hydride in ether solution to the corresponding 5-hydroxymethyl compounds (B). The imidazole ring was not attacked by the reducing agent. The 1-substituted-5-imidazole aldehydes (D) were obtained in satisfactory yields through the benzenesulfonhydrazides (C) according to the procedure of McFadyen and Stevens.[2] The aldehydes were readily hydrogenated to the hydroxymethyl compounds.

(1) Jones, THIS JOURNAL, **71**, 644 (1949).

(2) McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).