diazomethane, 54 mg. (after chromatography) m.p. 71–72° undepressed upon admixture with an authentic sample of 3β-carbomethoxycholestane.

Attempted Lactonization of 3β-Carboxy-Δ⁵-cholestene.—A solution of 750 mg. of pure 3β-carboxy-Δ⁵-cholestene (Iβ) in 250 ml. of alcohol-free chloroform was saturated with hydrogen chloride at 20° and allowed to stand at *ca.* 25°. Three runs were made using reaction times of 30 minutes, 5 and 70 hours. The total mixture was isolated by removal of the solvent and hydrogen chloride under reduced pressure. The infrared spectra of these materials (in chloroform or nujol mull) showed no trace of carbonyl absorption at 5.0–5.8 μ indicating the complete absence of lactone. When a solution of the total reaction product in 200 ml. of ether was washed quickly with two 1-l. portions of 0.5 *N* sodium hydroxide solution (10°) and then evaporated only a few mg. of yellow oil could be obtained. Upon acidification and extraction with ether the basic wash solution afforded the starting acid Iβ in almost pure condition. After one recrystallization from benzene pure acid 610–630 mg. (two runs), m.p. 224–225.5, was obtained.

The same results were obtained in a run using *p*-toluenesulfonic acid in chloroform.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF KITASATO INSTITUTE]

Preparation of 3′,4′-Dihydroxy-6-carboxyflavonol

BY TOYOYUKI NAGANO AND KONOMU MATSUMURA

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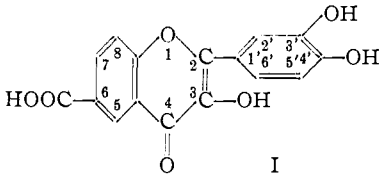
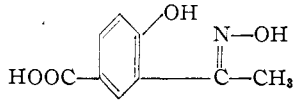
Using *p*-acetoxybenzoic acid as starting material, 3′,4′-dihydroxy-6-carboxy-flavonol was prepared, *via* 2-hydroxy-5-carboxyacetophenone, 3,4-methylenedioxy-2′-hydroxy-5′-carboxychalcone and 3′,4′-methylenedioxy-6-carboxyflavonol.

The preparation of certain derivatives of flavone and flavanone, which would contain a carboxy group in addition to the phenol groups present and which have not been found as yet in natural products, was undertaken with the thought that such compounds might possess "vitamin P"-like activity, as has been shown by rutin and hesperidin. Also of interest would be the expected increase in the solubility of these compounds in weak alkali. Details of the preparation of 3′,4′-dihydroxy-6-carboxyflavanol (I) are reported in this paper.



I



II

The Fries reaction with 4-acetoxybenzoic acid gave 2-hydroxy-5-carboxyacetophenone in 50% yield. The substituted chalcone was obtained on condensation of the latter compound with piperonal. By the reaction of the chalcone with hydrodrogen peroxide in methanolic sodium hydroxide, 3′,4′-methylenedioxy-6-carboxyflavonol was prepared. The removal of the methylene at the 3′,4′-position was effected by aluminum chloride in nitrobenzene.

The oxime II of 2-hydroxy-5-carboxyacetophenone, on Beckmann rearrangement with sulfuric acid, produced a mixture of 3-acetamino-4-hydroxybenzoic acid and 2-methyl-5-carboxybenzoxazole. Thus the configuration of the oxime is *cis* with respect to the methyl, assuming that spacial isomerization did not take place during the treatment.

Experimental

2-Hydroxy-5-carboxyacetophenone.—A solution of *p*-acetoxybenzoic acid (10 g., 0.056 mole) and aluminum chloride (15 g., 0.112 mole) in nitrobenzene (100 ml.) was heated gradually in an oil-bath.

After about one hour heating at 150°, the mixture turned to a gel and heating was continued for another three hours at that temperature. After the solution was cooled, ice-water was added, the nitrobenzene removed by steam distillation and the solution was filtered hot to remove a small amount of a resinous solid and acidified strongly with concentrated hydrochloric acid. The precipitated crystals were collected after standing overnight, yield 5.2 g., m.p. 233–234°. On crystallization from ethanol, colorless plates melting at 241–242° were formed; on further purification, the m.p. remained unchanged.

Chattaway and Calvet[1] reported the m.p. of this compound as 246–247° and that of its phenylhydrazone as 286°. It was almost insoluble in hot water, and an alcoholic solution gave a deep red color with ferric chloride.

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.44. Found: C, 60.01; H, 4.36.

The resinous solid (5 g.) which was deposited at the end of steam distillation yielded 1.2 g. of 2-hydroxy-5-carboxyacetophenone of inferior quality (m.p. 210–234°). The oxime, m.p. 273° dec., formed colorless prisms on crystallization from ethanol and gave a purple color with ferric chloride in ethanol.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 7.22.

The phenylhydrazone, m.p. 282° dec., was obtained as colorless prisms.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: N, 10.37. Found: N, 10.50.

3,4-Methylenedioxy-2′-hydroxy-5′-carboxychalcone.—A mixture of 2-hydroxy-5-carboxyacetophenone (1.8 g., 0.01 mole), piperonal (1.5 g., 0.01 mole), methanol (15 ml.) and aqueous sodium hydroxide (2 g., 0.05 mole, in 5 ml. of water) was refluxed gently for six hours. The cooled reaction fluid was acidified with dilute hydrochloric acid, and the precipitated yellow solid was filtered and washed with water and ethanol, yield 2.7 g. (86.5%), m.p. 250–253°.

Upon two recrystallizations from ethanol, it formed yellow needles, m.p. 261–263°, which were shown to be chromatographically pure and gave a reddish-brown color with ferric chloride in ethanol and were almost insoluble in ether or benzene; they were only very slightly soluble in hot water, but soluble in aqueous sodium carbonate which was neutral to phenolphthalein.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.85. Found: C, 65.37; H, 4.01.

3′,4′-Methylenedioxy-6-carboxyflavonol.—Oyamada's[2] method was used for this preparation. The chalcone (1 g.,

(1) F. D. Chattaway and F. Calvet, *J. Chem. Soc.*, 692 (1927).

(2) T. Oyamada, *J. Chem. Soc. Japan*, **55**, 1256 (1934).

0.003 mole) was added to a mixture of methanol (5 ml.) and 10% sodium hydroxide (3.5 ml., 0.009 mole). To the resulting solution, was added dropwise 15% hydrogen peroxide (4 ml., 0.009 mole) with stirring and ice cooling. Yellow needles gradually separated from the red solution which finally turned to a thick paste. After standing overnight in a refrigerator, it was filtered, and acidified with dilute hydrochloric acid to give a yellow crystalline product (0.6 g., 57.4%), m.p. > 320°.

Upon crystallization from glacial acetic acid, light yellow needles separated which gave a brown color with ferric chloride in ethanol and an orange-red color in concentrated sulfuric acid; they were difficultly soluble in hot ethanol or acetone.

Anal. Calcd. for $C_{17}H_{10}O_7$: C, 62.58; H, 3.07. Found: C, 62.49; H, 3.08.

3′,4′-Dihydroxy-6-carboxyflavonol.—Ozawa's[3] method was used in this preparation. To a solution of aluminum chloride (1 g., 0.007 mole) in nitrobenzene (20 ml.) was added 3′,4′-methylenedioxy-6-carboxyflavonol (1 g., 0.003 mole) in small portions with shaking at room temperature. After standing overnight (calcium chloride tube), the resulting dark orange viscous mass was decomposed by the addition of water (20 ml.) and concentrated hydrochloric acid (3 ml.). After removal of the nitrobenzene by steam distillation, a yellow solid (0.9 g.) was formed which was crystallized from ethanol to give yellow plates, m.p. > 320° with darkening around 310° and sintering at 316°. The compound gave a deep dark brown color with ferric chloride in ethanol and an orange red color in concentrated sulfuric acid, it was very slightly soluble in hot water but readily soluble in aqueous sodium carbonate. It was adsorbed upon silicic acid in ethanol with decomposition and the decomposed matter eluted by glacial acetic acid. On treatment with magnesium in ethanolic concentrated hydrochloric acid, it developed a red color and in ethanolic acetic acid, a greenish-yellow color.

Anal. Calcd. for $C_{16}H_{10}O_7$: C, 61.15; H, 3.18. Found: C, 61.02; H, 3.49.

Triacetyl Derivative.—The above flavonol (0.2 g.) was acetylated with acetic anhydride (0.5 ml.) in the presence of pyridine (1 ml.) by standing for 15 hours in a refrigerator. The product was crystallized from 80% acetic acid to give colorless prisms, m.p. 218–220° (dec. with foaming), which gave no color with ferric chloride.

Anal. Calcd. for $C_{22}H_{16}O_{10}$: C, 60.00; H, 3.64. Found: C, 60.25; H, 4.12.

(3) H. Ozawa, T. Okuda, M. Kawanishi and K. Fujii, *J. Pharm. Soc. Japan*, **71**, 1182 (1951).

Beckmann Rearrangement of the Oxime.—A solution of 0.4 g. of the oxime of 2-hydroxy-5-carboxyacetophenone in 4 ml. of concentrated sulfuric acid was heated at 100° for one-half hour, and the cooled solution was poured into ice-water. The resulting precipitate was collected, washed with water and dried.

The crude product A (0.36 g.) began to sinter at 140° and melted completely at 215°. A portion of A (0.20 g.) was repeatedly recrystallized from 50% acetic acid to yield colorless prisms (0.03 g.), which gave no color reaction with ferric chloride and which melted at 186–188° alone or on admixture with a sample of 2-methyl-5-carboxybenzoxazole.

Anal. Calcd. for $C_9H_7NO_3$: N, 7.91. Found: N, 7.95.

The filtrate from the recrystallizations was evaporated to dryness, and the residue was recrystallized repeatedly from 50% acetic acid to yield colorless prisms (0.09 g.) which gave a yellowish-brown color with ferric chloride and melted at 258° (dec. with foaming). A mixture with a sample of 3-acetamino-4-hydroxybenzoic acid showed no depression of melting point.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 7.19.

The remaining portion of the crude product was refluxed with 15% hydrochloric acid for one hour to give prismatic crystals melting at 275° dec. They were identified as the hydrochloride of 3-amino-4-hydroxybenzoic acid by the mixed m.p. method.

Anal. Calcd. for $C_7H_7NO_3 \cdot HCl$: N, 7.47. Found: N, 7.52.

The hydrochloride was made alkaline with sodium sulfide in water to give the free base, m.p. 205°, a mixture with a sample of 3-amino-4-hydroxybenzoic acid, m.p. 202°, showed no depression of the melting point.

Anal. Calcd. for $C_7H_7NO_3$: N, 9.15. Found: N, 9.26.

3-Acetamino-4-hydroxybenzoic Acid.—3-Amino-4-hydroxybenzoic acid (0.15 g.) was acetylated with acetic anhydride (0.2 ml.) in 50% acetic acid at room temperature. On crystallization from 50% acetic acid, colorless prisms, melting at 258° (dec. with foaming), were produced.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 7.29.

2-Methyl-5-carboxybenzoxazole.—A small portion of 3-acetamino-4-hydroxybenzoic acid was carefully distilled by heating in a free flame at atmospheric pressure, and the distillate was crystallized from benzene to give colorless prisms, m.p. 186–188°.

Anal. Calcd. for $C_9H_7NO_3$: N, 7.91. Found: N, 7.97.

TOKYO, JAPAN

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

6-Substituted Δ^6-Desoxymorphines

BY H. D. BROWN, I. M. RASMUSSEN, G. B. PAYNE AND KARL PFISTER, 3RD

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A series of pharmacologically interesting 6-substituted Δ^6-desoxymorphines (VII) has been synthesized. Although only small yields of the desired olefins were obtained by dehydration of the corresponding 6-substituted dihydromorphines and by demethylation of suitable Δ^6-desoxycodeines, the new analgetics were readily produced by acylation of the dihydromorphines (IV) followed by thionyl chloride dehydration and hydrolysis of the protecting groups.

In the morphine series of analgetics it is well known that "muzzling" or eliminating the 6-hydroxyl increases potency though frequently at the expense of other desirable properties such as duration of action, minimal respiratory depression and relative freedom from convulsant and emetic actions.[1] Thus O,O′-diacetylmorphine, dihydromorphinone and dihydrodesoxymorphine-D ("Desomorphine") are all considerably more potent analgetics than the parent alkaloid. No particular effect has been ascribed to unsaturation in the oxygen-free alicyclic ring, and in fact the pair "Desomorphine" and Δ^7-desoxymorphine show very similar activity,[2] while Δ^6-desoxymorphine (desoxymorphine-C) was reported to be less active.[3]

(1) N. B. Eddy, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 245 (1950); Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports, U. S. Gov't. Printing Office, Washington, 1938.

(2) (a) Personal communication from Dr. N. B. Eddy; (b) synthesis by H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 5485 (1951).

(3) N. B. Eddy and H. A. Howes, *J. Pharm. Expt. Ther.*, **55**, 257 (1935).