of diacetyl, methylacetylcarbinol, furan, furfuraldehyde, furfuryl alcohol, acetaldehyde, pyridine, and hydrogen sulfide is reported. The contributions of Staudinger and Reichstein and of Prescott and his associates are discussed and the relation of the volatile constituents to the staling of coffee is considered briefly. Coffee staling is probably concerned with changes in the volatile aroma and flavor substances and does not involve fat rancidity.

810 GRAND CONCOURSE
NEW YORK, N. Y.

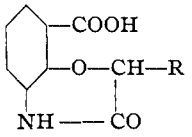
RECEIVED APRIL 12, 1938

[CONTRIBUTION FROM THE MELLON INSTITUTE OF INDUSTRIAL RESEARCH AND E. R. SQUIBB AND SONS]

The Preparation of 2-Methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine

BY HAROLD W. COLES[1] AND WALTER G. CHRISTIANSEN[2]

In the search for new analgesics without the chemical structures said to cause agranulocytosis[3] we have been interested in the possibilities of the benzoxazine ring system, and particularly in the 8 - carboxy - 3 - keto - 3,4 - dihydro - 1,4 - benzoxazines (I) since it is seen that these compounds



I

may be considered as derivatives of salicylic acid, and they also contain the skeleton of acetanilide. The carboxyl group not only acts in a detoxifying capacity, but also permits the preparation of a soluble sodium salt.

A number of carboxylated benzoxazines have been reported in the literature[4] but, so far as we know, were not tested pharmacologically. Therefore, 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine (I, R = CH_3) was synthesized and, being physiologically inactive, no further members of this series were prepared.

The authors wish to record their appreciation for the interest and advice of Dr. George D. Beal, Assistant Director of Mellon Institute, during the progress of this work.

Experimental Part

3-(α-Bromopropionylamino)-salicylic Acid.—The procedure, here described, is adapted from directions given by Sanna[5] for the non-carboxylated aminophenols. One mole equivalent (4.25 g.) of 3-aminosalicylic acid and slightly more than one mole equivalent (6.25 g.) of α-bromopropionyl bromide was added to 50 g. of dry benzene. The aminosalicylic acid remained suspended in the benzene since it is quite insoluble. The Erlenmeyer flask contents were refluxed on a water-bath for twelve to fourteen hours with the evolution of acid fumes. The flask contents were chilled and the grayish crystalline material was removed to a Büchner funnel and washed repeatedly with cold benzene. The crystals, after drying in the air, weighed 8 g. representing a practically theoretical yield. It was recrystallized from a minimum of boiling 50% alcohol, washing repeatedly on the filter with distilled water. It was dried in an 80° oven. The white solid has an irritating odor, and in a melting point tube it softened quite sharply at 178°, but the column did not break until 188° (U. S. P. corr.).

Anal. (Kjeldahl). Calcd. for $C_{10}H_{10}O_4BrN$: N, 4.86. Found: N, 4.64.

The crystals are easily soluble in acetone, alcohol and alkalies, but sparingly soluble in water and benzene.

2 - Methyl - 8 - carboxy - 3 - keto - 3,4 - dihydro - 1,4-benzoxazine (I, R = CH_3).—3-(α-Bromopropionylamino)-salicylic acid (3.3 g.) was dissolved in 25 cc. of 10% sodium hydroxide solution and warmed on the water-bath at 60° for one hour. The color darkened considerably. The solution was cooled, filtered and dilute (1:1) hydrochloric acid added until the dark solution was acid to congo red. A dark precipitate came out on standing, and was washed repeatedly with distilled water. Recrystallized from a minimum of boiling absolute alcohol, the product was secured as colorless crystals (yield 60%). The substance is sparingly soluble in the usual solvents. It is readily soluble in alkalies; m. p. 285° (U. S. P. corr.).

Anal. Calcd. for $C_{10}H_9O_4N$: N, 6.61. Found: N, 6.76.

Pharmacological Tests.[6]—6-Carboxy-3-keto-3,4-dihydro-1,4-benzoxazine[4a] and 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine, administered intravenously to mice, rats and rabbits, exhibited no antipyretic or hypnotic action in doses up to 2000 mg. per kg. The first compound shows some toxic effects above 500 mg. per kg., while the second is non-toxic at least up to a dosage of 1500 mg. per kg. The compounds were not tested as to possible local anesthetic properties. The effect of the introduction of the carboxyl group into the benzene ring is very marked

(1) Senior Industrial Fellow, E. R. Squibb and Sons Industrial Fellowship, Mellon Institute.

(2) E. R. Squibb and Sons, Brooklyn, N. Y.

(3) Council on Pharmacy and Chemistry, A. M. A., *J. Am. Med. Assoc.*, **102**, 2183 (1934).

(4) (a) Christiansen, THIS JOURNAL, **47**, 1158 (1925); **48**, 460 (1926); (b) Einhorn and Oppenheimer, *Ann.*, **311**, 154 (1900).

(5) Sanna and Vacca, *Gazz. chim. ital.*, **62**, 555 (1932); Puxeddu and Sanna, *ibid.*, **61**, 158 (1931).

(6) The authors are greatly indebted to the Biological Laboratories, E. R. Squibb & Sons, New Brunswick, N. J., for these tests.

in this series, as benzoxazines without the carboxyl group, or with other groups such as the methyl group, have been reported as being of considerable medicinal value.[7]

Summary

3-(α-Bromopropionylamino)-salicylic acid was synthesized and, from this by treatment with alkali, 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine. Both of these substances are new compounds.

Neither 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine nor 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine exerts either antipyretic or analgesic action in various test animals.

(7) F. Hoffman, La Roche & Co. A.-G., British patent 370,375 (Apr. 17, 1931); German patent, 557,111 (Apr. 18, 1931); Preiswerk and Mayer, U. S. patent 1,951,897 (Mar. 20, 1934).

PITTSBURGH, PENNA.
BROOKLYN, N. Y. RECEIVED FEBRUARY 28, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND]

A New Method for the Purification of the Alcoholate of the Trimer of Hydroxypyruvic Aldehyde

BY WILLIAM E. EVANS, JR., C. JELLEFF CARR AND JOHN C. KRANTZ, JR.

Hydroxypyruvic aldehyde is of interest owing to its relationship to the intermediate metabolites of glucose. This compound has been prepared by the oxidation of dihydroxyacetone[1-4] and by the photochemical decomposition of glyoxal.[5] Evans and Waring[1] treated dihydroxyacetone with an excess of cupric acetate and removed the excess of copper by precipitation as sulfide. Friedemann[2] employed the same method but did not separate the compound from solution. This process was objectionable on account of the formation of sulfur derivatives of hydroxymethyl glyoxal which are toxic. Küchlin and Böeseken[3] decomposed the sulfur compounds with an excess of silver acetate at 30° and subsequently removed the excess of silver as chloride. Hynd[4] found that the use of silver acetate caused the formation of a highly polymerized product. He avoided the use of hydrogen sulfide by precipitating the excess copper with barium hydroxide. The barium was then removed as sulfate. Norrish and Griffiths[5] prepared small amounts of glycerosone by the photochemical decomposition of glyoxal and isolated it as the trimer combined with one molecule of alcohol.

Experimental

Preparation of Hydroxypyruvic Aldehyde.—One mol of dihydroxyacetone was dissolved in 10 mols of water and treated at room temperature with 2.25 mols of finely divided crystallized cupric acetate. The mixture was shaken frequently in order to keep the solution saturated with copper acetate. The reaction was allowed to proceed until the calculated amount of cuprous oxide was precipitated. The usual period of time necessary was five to seven days. At this time a grayish-colored precipitate of cupric oxalate began to appear. The excess of Cu^{++} was then precipitated carefully by the addition of a calculated amount of a 10% solution of oxalic acid. After filtering the solution was reduced to a small volume by distilling at 17 mm. at 35°. Successive portions of alcohol were added and the product was reduced to dryness at 17 mm. The residue was then dissolved repeatedly in small amounts of absolute alcohol and precipitated by the addition of ether. The ether–alcohol solutions were worked up later, using the same procedure, to recover some of the product. Substances which were insoluble in water and in absolute alcohol were removed and the product was dried *in vacuo* at 70°. The yield of the product was 87%. After purification for biological use the yield was 64%. The product gave a negative test for Cu^{++} or oxalate. It was obtained as a pale yellow amorphous solid which melted between 155 and 160°. A 1% aqueous solution exhibited a *p*H of 3.12 at 25°. It reduced Fehling's solution and mercuric chloride solution rapidly in the cold. No immediate reaction was obtained when Schiff's reagent was added to the freshly prepared solution but the characteristic color appeared within several minutes.

Anal. Calcd. for $(C_3H_4O_3)_3 \cdot C_2H_5OH$: C, 42.47; H, 5.85; mol. wt., 310. Found: C, 42.57; H, 5.42; mol. wt., 306.

This is in agreement with the results obtained by Norrish and Griffiths.[5]

On account of the ease of depolymerization, molecular weight determinations had to be made with the greatest possible rapidity.

The aqueous solution was depolymerized by long standing or by heating for ten minutes in a water-bath at 60–70°.

Mol. wt. Calcd. for $3C_3H_4O_3 + 1C_2H_5OH$: 77.6. Calcd. for $2C_3H_4O_3 + C_3H_4O_3 \cdot C_2H_5OH$: 103. Found 99.3. These mol. wts. confirm those of Norrish and Griffiths.[5]

Quinoxaline derivative: m. p. 250–251°; reported[5] m. p. 165°.

(1) W. L. Evans and C. E. Waring, THIS JOURNAL, **48**, 2678 (1926).

(2) T. E. Friedemann, *J. Biol. Chem.*, **73**, 331 (1927).

(3) A. T. Küchlin and J. Böeseken, *Rec. trav. chim.*, **47**, 1011 (1928).

(4) A. Hynd, *Biochem. J.*, **25**, 10 (1931).

(5) R. G. W. Norrish and J. G. A. Griffiths, *J. Chem. Soc.*, 2829 (1928).