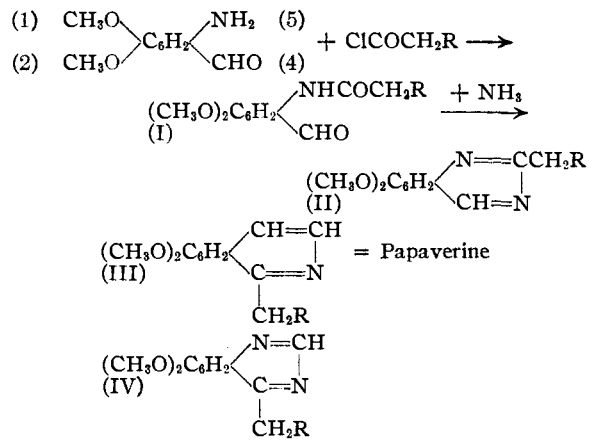
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Quinazolines. XL. Synthesis of a Quinazoline Derivative Structurally Related to Papaverine[1]

BY ELEANOR BEST MARR[2] AND MARSTON TAYLOR BOGERT

In a recent article,[3] we described the synthesis of quinazoline derivatives structurally analogous to the angostura alkaloids galiopine and galipine. The present paper records the synthesis of a quinazoline related structurally to papaverine. The steps involved were these, R being (3,4) $(CH_3O)_2C_6H_3$—



If the constitution of the product (II) be compared with that of papaverine (III), it will be seen immediately that the two are not strictly analogous, for in the papaverine molecule the veratryl group is attached to what corresponds to carbon No. 4 of the quinazoline nucleus, whereas in the new synthetic (II) it is in position 2. The synthesis of the true analog (IV) is now under way in our laboratories and the results will be reported later.

Experimental

6-Nitroveratraldehyde has been prepared by Pschorr and Sumuleanu,[4] and by Salway,[5] by nitration of veratraldehyde. Both methods of nitration were tried, but the following combination of the two was found preferable.

To 50 cc. of concentrated nitric acid (sp. gr. 1.42), cooled to 5°, there was added in small portions 5 g. of finely powdered veratraldehyde with vigorous stirring, allowing each portion to dissolve before the next one was added. After all the aldehyde had been added (about forty-five minutes), the solution was left for two hours at 0–5°, in the dark, for the nitro aldehyde is very sensitive to light.[6] The mixture was then poured into 600 cc. of ice water, the voluminous yellow precipitate collected, washed with water and crystallized from ethyl alcohol, giving yellow needles, m. p. 133.5–134.5° (corr.), in accordance with the literature; yield, 60%.

6-Aminoveratraldehyde.—Rilliet[7] obtained this, in yields of about 30%, by hydrolysis of 6-aminoveratrylidene anilines, but we have found that the nitroveratraldehyde can be reduced directly with ferrous sulfate and ammonium hydroxide solution with a yield of 90%. After removal of the ferric hydroxide, the filtrate was cooled and extracted with benzene. Slender flattened pale yellow needles, m. p. 84–85° (corr.), were secured by careful addition of ligroin to a cold (room temperature) saturated benzene solution. The *acetyl derivative* melted at 177–178° (corr.). These melting points agree with the literature.

Tröger and his co-workers[8] reduced the 2- and 6-nitromethoxybenzaldehydes to the corresponding amines, by the action of ferrous sulfate and ammonia upon their sodium bisulfite compounds; but, for the preparation of 6-aminoveratraldehyde, we found that method less satisfactory than the reduction of the nitro aldehyde itself.

6-Homoveratroylamino-veratraldehyde (I).—The azlactone of veratraldehyde and hippuric acid was prepared as described by Kropp and Decker.[9] Their process also was followed in hydrolyzing this to the 3,4-dimethoxyphenylpyruvic acid, except that we used the procedure of

(1) Based upon the Dissertation submitted by Eleanor B. Marr, December, 1934, for the degree of Ph.D., under the Faculty of Pure Science, Columbia University, New York, N. Y., to which Dissertation the reader is referred for further experimental details and literature citations. Presented in abstract before the Division of Organic Chemistry, at the New York Meeting of the American Chemical Society, April 22, 1935. M. T. B.

(2) Ferguson Fellow in Chemistry, Columbia University, 1933–1934.

(3) Marr and Bogert, THIS JOURNAL, **57**, 729 (1935).

(4) Pschorr and Sumuleanu, *Ber.*, **32**, 3412 (1899).

(5) Salway, *J. Chem. Soc.*, **95**, 1163 (1909).

(6) (a) Sumuleanu, *Ann. Sci. Univ. Jassy*, **2**, 139 (1903); (b) Bamberger and Elger, *Ann.*, **371**, 319 (1909); etc.

(7) Rilliet, *Helv. Chim. Acta*, **5**, 549 (1922).

(8) (a) Tröger and Dunker, *J. prakt. Chem.*, [2] **111**, 209 (1925); (b) Tröger and Cohaus, *ibid.*, **117**, 102 (1927).

(9) Kropp and Decker, *Ber.*, **42**, 1184 (1909).

Haworth, Perkin and Rankin[10] in separating the benzoic acid formed simultaneously. From this, homoveratric acid was produced by oxidation with hydrogen dioxide, as already recorded by Cain, Simonsen and Smith;[11] and this acid, when treated with thionyl chloride in chloroform solution, gave the acid chloride desired, as has been shown by Haworth, Perkin and Rankin.[10]

The preparation of homoveratroylamino-veratraldehyde from the acid chloride and 6-amino-veratraldehyde was accomplished in a well-cooled 50% acetic acid solution, in the presence of sodium acetate; yield of crude product (m. p. 138.5–139.5°), 50%. Recrystallized from alcohol and decolorized by norite, it formed colorless needles, m. p. 141.2–142.2° (corr.).

Anal. Calcd. for $C_{19}H_{21}O_6N$: C, 63.48; H, 5.86. Found: C, 63.85; H, 6.16.

The Schotten–Baumann method was also employed, but was not satisfactory. Free acids or free bases, of course, must be carefully avoided in this reaction, because of the ease with which *o*-aminobenzaldehydes form condensation products.

(10) Haworth, Perkin and Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).
(11) Cain, Simonsen and Smith, *ibid.*, **103**, 1036 (1913).

2-Veratryl-6,7-dimethoxyquinazoline (II).—A mixture of 1 g. of homoveratroylamino-veratraldehyde with 15 cc. of methanol saturated with ammonia was heated in a sealed tube for two hours at 100–120° and left in the furnace overnight, to cool to room temperature. From the tube contents, there was isolated 0.77 g. of crystals, which were recrystallized from ligroin until the melting point remained constant at 134–135° (corr.). The pure compound consisted of colorless needles, freely soluble in chloroform, carbon bisulfide, ethyl acetate, acetone or benzene, moderately soluble in water or methyl alcohol, very slightly in cold ligroin, and practically insoluble in petroleum ether.

Anal. Calcd. for $C_{19}H_{20}O_4N_2$: C, 67.02; H, 5.92; N, 8.24. Found: C, 67.47; H, 5.73; N, 8.00.

Summary

The synthesis of 2-veratryl-6,7-dimethoxyquinazoline is recorded, a compound structurally related to papaverine. Its pharmacological properties have not yet been studied.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

The Action of Alkali on Certain Acylated Ketoximes. I. The Effect of Structure and Configuration

BY R. P. BARNES AND A. H. BLATT

In an earlier communication[1] we reported that the acetate of α-benzoin oxime (I) on treatment with 5% aqueous sodium hydroxide was cleaved to benzaldehyde, benzonitrile and sodium acetate, while the stereoisomeric β-benzoin oxime acetate (II) under the same conditions was hydrolyzed without cleavage. Preparatory to a study of the mechanism of this cleavage process we thought it advisable to examine the behavior of a number of acylated ketoximes toward aqueous alkali. We chose first, in order to determine to what extent cleavage is conditioned by structure, a number of oxime acetates derived from structurally varied ketones. We chose next, in order to determine to what extent cleavage is conditioned by configuration, a series of acyl derivatives of α- and β-benzoin oximes. From our results, together with those already available in the literature, it is possible to define the limits of the cleavage reaction and, therefore, its usefulness. Since these features are quite independent of the mechanism proper we report on them briefly at this time.

(1) Blatt and Barnes, THIS JOURNAL, **56**, 1148 (1934).

$C_6H_5CHOHCC_6H_5$ (I: $NOCOCH_3$) $\qquad$ $C_6H_5CHOHCC_6H_5$ (II: CH_3CO_2N)

From our results (Table I) and those already published by other workers it follows that the structural factor in an acylated ketoxime[2] which determines the occurrence of cleavage is the presence α to the C=N linkage of an hydroxyl group, a carboxyl group[3] or a carbonyl group[4]—

(2) The type of cleavage which we are considering has long been known to occur with acylated aldoximes [Hantzsch, *Ber.*, **24**, 36 (1891)], but we are limiting the present discussion to ketoximes where a carbon–carbon linkage is broken in the cleavage process.
(3) Hantzsch, *ibid.*, **24**, 43 (1891).
(4) Meisenheimer, (a) *ibid.*, **54**, 3213 (1921); (b) *Ann.*, **446**, 228 (1926). See also Reference 1.