Thiachroman-S-dioxide (3,4-Dihydro-1,2-benzothiapyran-1,1-dioxide).—3-Phenylmercaptopropanoic acid,[14] prepared from thiophenol and 3-chloropropanoic acid, was converted by means of concentrated sulfuric acid to 4-thiachromanone[13] (67.7%); b.p. 112–114° (1.5 mm.), m.p. 29.0–29.5°, $n^{20}\mathrm{D}$ 1.6397. Semicarbazone: recrystallized from dilute alcohol melted at 215–216° (uncorrected). The reported m.p. is 219–220°.[13]

Fifty-nine grams (0.36 mole) of the ketone was reduced by the Clemmensen–Martin procedure[21] to thiachroman (32.1 g., 59.5%); b.p. 121–122° (11 mm.), $n^{20}\mathrm{D}$ 1.6148. The cyclic sulfide was then oxidized with 30% hydrogen peroxide to give thiachroman-S-dioxide; recrystallized from boiling water, m.p. 87.5–88.0°.

Homothiachroman-S-dioxide.—4-Phenylmercaptobutanenitrile[25] was prepared from 134.7 g. (0.91 mole) of 4-bromobutanenitrile,[26] 100 g. (0.91 mole) of thiophenol and 51.3 g. (0.95 mole) of sodium methoxide, b.p. 132–133° (1.5 mm.), $n^{20}\mathrm{D}$ 1.5667; yield 108.2 g., 67.3%.

One hundred and five grams (0.594 mole) of 4-phenylmercaptobutanenitrile, 89 g. (1.59 moles) of potassium hydroxide, 70 ml. of water and 340 ml. of absolute ethanol was refluxed for 18 hours. The ethanol was removed by distillation, water was added to the residue, and the solution was acidified with concentrated hydrochloric acid. 4-Phenylmercaptobutanoic acid was filtered off and dried; 107.3 g., 91.5%; m.p. 68.0–68.5°. Treatment of the acid with thionyl chloride gave a 96.5% yield of 4-phenylmercaptobutanoyl chloride, b.p. 129–130° (1.5 mm.), $n^{20}\mathrm{D}$ 1.5695. The amide melted at 96.0–96.5°.

A solution of 100 g. (0.467 mole) of 4-phenylmercaptobutanoyl chloride and 550 ml. of carbon disulfide was treated with 110 g. of aluminum chloride over a period of one-half hour. The temperature was maintained at 5° during the addition of the catalyst and then the reaction mixture was allowed to stand for three hours at room temperature. Distillation of the product gave 65.5 g. (79%) of 5-homothiachromanone, b.p. 119.5–120.0° (1.5 mm.), $n^{20}\mathrm{D}$ 1.6228. Semicarbazone: recrystallized from dilute alcohol melted at 222° (uncorrected). The reported[15] m.p. is 213°.

The ketone was converted by means of the Clemmensen–Martin reduction[21] to homothiachroman (55.5%), b.p. 103–104° (3 mm.).

Ten grams of homothiachroman was refluxed with 40 ml. of 30% hydrogen peroxide and 150 ml. of glacial acetic acid for four hours. The mixture was cooled, poured on ice, and the sulfone was filtered off and recrystallized from 60–70° petroleum ether, m.p. 77–78°; yield 8.1 g., 67.5%.

LAFAYETTE, INDIANA RECEIVED AUGUST 29, 1951

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[25] A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

[26] O. K. Behrens, *et al.*, *J. Biol. Chem.*, **175**, 789 (1948).

[CONTRIBUTION NO. 101 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

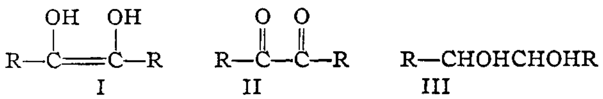
The Benzoin Condensation of 6-Methylquinaldehyde

BY C. A. BUEHLER AND S. PAUL EDWARDS

The benzoin condensation of 6-methylquinaldehyde produced 1,2-di-(6-methylquinolyl-2)-1,2-ethenediol, 1,2-di-(6-methylquinolyl-2)-1,2-ethanediol and 6-methylquinaldinic acid. A *trans* chelated formula has been assigned to the enediol on the basis of its physical and chemical properties.

In a recent publication[1] it was shown that quinaldehyde when subjected to the benzoin condensation does not give the benzoin, but instead the enediol and the reduced enediol or glycol. The enediol, in contrast to the proposal of Brown and Hammick,[2] was assigned a *trans* chelated structure from a study of its physical and chemical properties.

A similar study of 6-methylquinaldehyde produced parallel results. The enediol I is a brown-black solid, m.p. 258° (dec.), which decolorized sodium 2,6-dichlorobenzeneoneindophenol and reduced Tollens reagent in the cold. It formed a dibenzoate, m.p. 280° (dec.), and in bubbling air through a dioxane solution a yellow benzil (II), m.p. 278° (dec.), not in agreement with Brown and Hammick's value[2] of 250–251°, was obtained. The presence of the hydroxyl group in the enediol is not shown by infrared absorption.[3] All these properties of the enediol are best explained on the basis of the *trans* chelated form Ia.

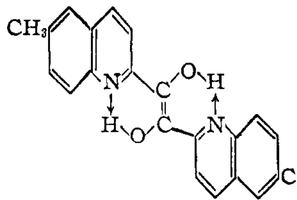


$$\mathrm{R{-}\overset{OH}{\overset{|}{C}}{=}\overset{OH}{\overset{|}{C}}{-}R} \qquad \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}R} \qquad \mathrm{R{-}CHOHCHOHR}$$

I II III

R = 6-methylquinolyl-2

A comparison of ultraviolet absorption spectrum of the enediol with that of *trans*-9,9′-diphenanthrylethylene[4] and that of the *trans*-enediol of 9,9′-phenanthroin[4] (Fig. 1) shows sufficient similarity to offer some support for the presence of the ethylenic double bond conjugated with condensed ring systems. The first maxima of the curves agree well, although the intermediate shoulder does not appear in the enediol and the second maximum of the enediol exhibits a pronounced hypsochromic effect over that shown by the reference compounds. Insufficient data are available to say whether this effect is due even in part to chelation, which might be expected to reduce the basic character of the ring nitrogens and thus decrease the contribution of the charge separation forms possible for the excited state. It is of interest to note, however, that Ewing and Steck[5] were unable to detect any chelation in 8-quinolinol by ultraviolet absorption.



Ia

As in the case of quinaldil, whose proposed structure also differed from that suggested by Brown and Hammick,[2] the benzil II appears to have the conventional structure in that it formed a

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[1] C. A. Buehler and J. O. Harris, THIS JOURNAL, **72**, 5015 (1950).

[2] B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 623 (1950).

[3] The hydroxyl group absorption failed to make its appearance even in a special experiment in which a saturated solution of the enediol in carbon tetrachloride using a cell thickness of 5 mm. was employed.

[4] Y. Hirschberg and F. Bergmann, THIS JOURNAL, **72**, 5118 (1950); R. N. Jones, *ibid.*, **67**, 1956 (1945).

[5] G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2182 (1946).

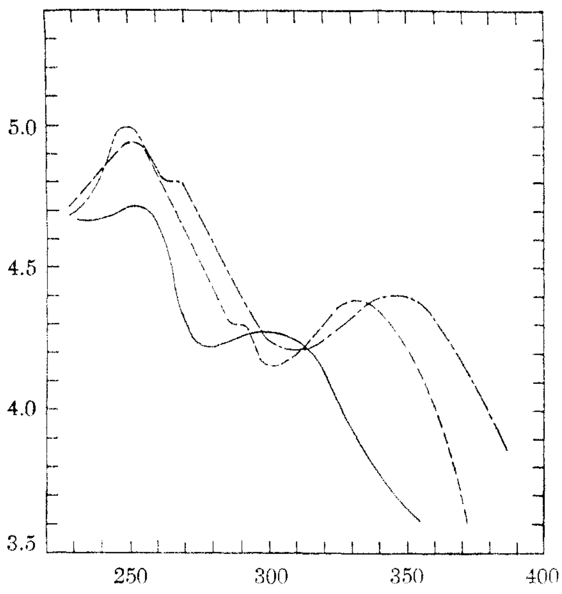

Fig. 1.—Ultraviolet absorption spectra of: 1,2-di-(6-methylquinolyl-2)-1,2-ethenediol, ——; *trans*-9,9′-phenanthroin enediol (Jones), — — — —; *trans*-9,9′-diphenanthrylethylene (Jones), - —— -.

p-nitrophenylhydrazone and a quinoxaline, and its infrared absorption spectrum gave maxima at 1651, 1682 and 1697 cm.$^{-1}$, all in the carbonyl region. The ultraviolet absorption spectrum as shown in Fig. 2 follows the pattern of other benzils and benzaldehydes, in that the wave lengths of the maxima are approximately the same and the extinction coefficients of the quinaldil maxima are roughly twice those of the quinaldehyde. Leonard, Rapala, Herzog and Blout[6] have interpreted such facts to mean that the benzil has the skew structure since each quinolyl unit acts more or less independently in absorption.

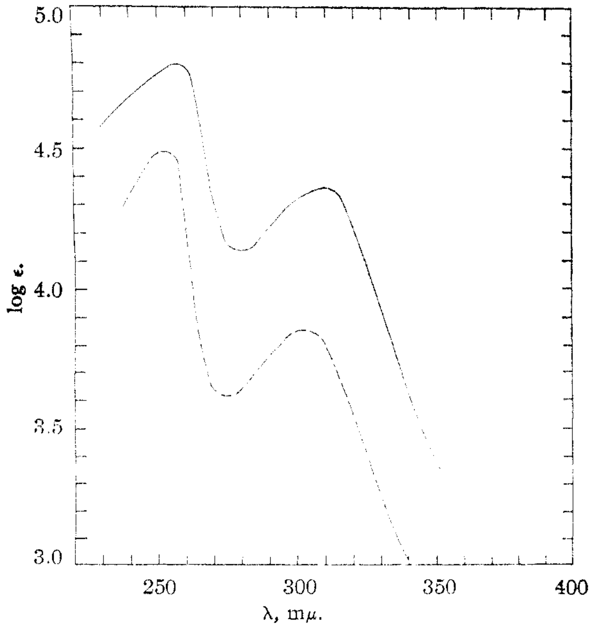

Fig. 2.—Ultraviolet absorption spectra of: 6,6′-dimethylquinaldil, ——; 6-methylquinaldehyde, — — — — —.

The glycol III was the second product of the condensation. A white crystalline compound, it turned yellow readily in solution. As with the glycol from quinaldehyde, it formed the desoxybenzoin in pyridine and hydrogen chloride and *p*-nitrophenylhydrazine gave the *p*-nitrophenylhydrazone of the original aldehyde. The infrared spectrum gave a broad maximum at 3158 cm.$^{-1}$ which appears to indicate chelated hydroxyl groups.

The explanation for glycol formation has now been indicated in that 6-methylquinaldinic acid has been isolated as a third product of the reaction. Thus it appears that a crossed Cannizzaro reaction occurs in which one molecule of the enediol is reduced while a molecule of the aldehyde is oxidized.

We are indebted to Dr. W. H. Fletcher of this Laboratory for the determination and interpretation of the infrared data.

Experimental[7]

6-Methylquinaldehyde.—This compound was prepared essentially by the method of Kaplan,[8] 5 g. of 2,6-dimethylquinoline giving 2.2 g. (40%) of buff-colored plates, m.p. 105–106° (Brown and Hammick[2] give 105–106°).

1,2-Di-(6-methylquinolyl-2)-1,2-ethenediol (I) (Operations in an atmosphere of nitrogen).—6-Methylquinaldehyde, 5 g., was dissolved with stirring and warming in 200 ml. of 95% ethanol. To the solution at 55° was added a solution of 0.4 g. of potassium cyanide in 6 ml. of water. The mixture immediately turned red and a brown solid separated. After refluxing for 30 minutes and cooling, the solid was filtered. It was then digested twice in such a quantity of boiling pyridine, about 150 ml., that on cooling to room temperature the brown-black enediol alone remained undissolved. One washing with ether gave 3.8 g. of product which on further digestion yielded 3.0 g. (60%) of dark brown, metallic needles, which melted at 258° (dec.).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30. Found: C, 77.07, 77.10; H, 5.31, 5.23.

In 30 minutes the enediol decolorized an intense blue, alcoholic solution of 2,6-dichlorobenzeneoneindophenol and produced a black finely divided solid in cold Tollens reagent.

The dibenzoate prepared in pyridine and crystallized from a mixture of monochloro- and *o*-dichlorobenzenes using Norite, was a white solid, melting at 280° (dec.).

Anal. Calcd. for $C_{36}H_{26}N_2O_4$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.65; H, 4.85; N, 5.13.

6,6′-Dimethylquinaldil (II).—This compound was prepared by the method previously described[1] for quinaldil. The enediol, 9.1 g., gave 7.5 g. (83%) of the yellow quinaldil, m.p. 278 (dec.) (Brown and Hammick[2] give 250–251°).

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.62; H, 4.74. Found: C, 77.56, 77.42; H, 4.54, 4.83.

The *p*-nitrophenylhydrazone prepared as described previously was an orange-red solid, m.p. 259° (dec.).

Anal. Calcd. for $C_{28}H_{21}N_5O_3$: N, 14.76. Found: N, 14.64.

The quinoxaline prepared by the method of Bost and Towell[9] consisted of tan plates, m.p. 202–203°.

Anal. Calcd. for $C_{28}H_{20}N_4$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.28; H, 4.96; N, 13.68.

1,2-Di-(6-methylquinolyl-2)-1,2-ethanediol (III) (Operations in an atmosphere of nitrogen).—6-Methylquinaldehyde 7.7 g., was dissolved in 300 ml. of 50% ethanol at 50° and a solution of 0.55 g. of potassium cyanide in 5 ml. of water was added. The brown solid which formed was separated and digested several times with boiling pyridine and

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[6] N. J. Leonard, R. T. Rapala, H. L. Herzog and E. R. Blout, This Journal, **71**, 2997 (1949).

[7] All melting and decomposition temperatures were measured, using an aluminum block.

[8] H. Kaplan, This Journal, **63**, 2654 (1941).

[9] R. W. Bost and E. E. Towell, *ibid.*, **70**, 904 (1948).

washed with ether to give 1.8 g.[10] of the enediol, m.p. 254° (dec.). The filtrates and washings after each digestion were diluted with an equal quantity of ether and cooled overnight. Filtration gave 12.7 g.[10] of an almost white solid,[11] which after crystallization from dioxane darkened over the range 165–195° and melted at 226° (dec.).

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N 8.13. Found: C, 76.79; H, 5.94; N, 8.03.

Cleavage led to the formation of the *p*-**nitrophenylhydrazone** of 6-methylquinaldehyde when 0.3 g. of the ethanediol, 0.45 g. of *p*-nitrophenylhydrazine and 70 ml. of absolute ethanol were refluxed for two hours. Concentration to approximately 20 ml., cooling and filtration gave 0.25 g. of mustard-colored crystals, m.p. 267° (dec.). There was no depression in melting point when mixed with the *p*-nitrophenylhydrazone prepared directly from 6-methylquinaldehyde.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61. Found: C, 66.46; H, 4.82.

6,6′-Dimethyldesoxyquinaldoin.—The glycol, 0.45 g., was refluxed for 30 minutes with 20 ml. of pyridine into which hydrogen chloride had been passed for a few seconds. Addition of the cooled solution to 150 ml. of 3 *N* ammonium hydroxide, filtration and drying gave 0.35 g. of the yellow hydrate, m.p. 224° (dec.). Two crystallizations from pyridine gave 0.20 g. (47%) of deep orange crystals, m.p. 235°.

Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56. Found: C, 80.91; H, 5.45.

6-Methylquinaldinic Acid.—To the aqueous ethanolic filtrate remaining after the filtration of the original brown condensation product as described under 1,2-di-(6-methylquinolyl-2)-1,2-ethanediol was added 0.6 g. of potassium carbonate. The solution was concentrated by boiling to approximately 40 ml., cooled, and acidified with glacial acetic acid to the isoelectric point (*p*H of 4 to 5). The white, flocculent solid which separated, after crystallization from ethanol, amounted to 0.8 g.[10] and melted at 204° with gas evolution. There was no depression when mixed with a sample of 6-methylquinaldinic acid prepared by the direct oxidation of 6-methylquinaldehyde with hydrogen peroxide in acetic acid.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.57; H, 4.85. Found: C, 70.49; H, 4.67.

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[10] The combined amounts of the three products account for 68% of the aldehyde used.

[11] The mother liquor was always yellow, perhaps because of the presence of some of the desoxyquinaldoin.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Some Transamination Reactions Involving Vitamin B_6[1]

BY DAVID E. METZLER[2] AND ESMOND E. SNELL[2]

Analytical methods have been devised or adapted for the measurement of pyridoxal, pyridoxal plus pyridoxamine, and keto acid concentrations in transamination reaction mixtures. Reversible transamination reactions at 100° between pyridoxal and most amino acids are catalyzed by copper, iron and aluminum salts. With equimolar reactant concentrations, equilibrium lies in most cases at about 50% conversion to products. Reaction rates decrease in the order: most amino acids > phenylalanine and tyrosine > isoleucine > valine > threonine > glycine. The *p*H optimum of the reaction of pyridoxal with glutamate is about 4.5. Transamination between pyridoxal phosphate and glutamate is rapid and goes nearly to completion, probably because pyridoxal phosphate cannot exist as a cyclic hemiacetal. The reaction is catalyzed by copper sulfate and probably by other metal salts. The *p*H optimum is about 4.5.

The reactions (1), (2) occur upon autoclaving neutral aqueous solutions of the reactants; similar

$$\text{pyridoxal} + \text{glutamate} \underset{(2)}{\overset{(1)}{\rightleftarrows}} \text{pyridoxamine} + \alpha\text{-ketoglutarate}$$

reactions occur with other amino acids.[3] In view of the function of pyridoxal phosphate as a coenzyme in biological transamination, it seemed desirable to study non-enzymatic transamination reactions of this type more fully.

Experimental

Chemicals.—Pyridoxal hydrochloride, pyridoxamine dihydrochloride and the calcium salts of pyridoxal and pyridoxamine phosphates were generously supplied by Merck and Company, Inc., Rahway, N. J. Commercially available amino acids were used. Sodium pyruvate was prepared from freshly distilled pyruvic acid[4] and recrystallized once from 80% ethanol. The sodium content by flame photometry was 97 ± 2% of theoretical. The other keto acids used have been described elsewhere.[5] Sodium ethylenediamine tetraacetate was obtained as a *ca.* 0.9 *M* solution from the Bersworth Chemical Company, Framingham, Massachusetts.

Unless otherwise stated, a purity of 100% was assumed for the above compounds.

Stock Solutions.—Pyridoxal, pyridoxamine and keto and amino acids, when solubility permitted, were kept as 0.05 *M* solutions in redistilled water and stored in a refrigerator. Pyridoxal and pyridoxamine phosphates were kept as 0.004 *M* solutions in 0.02 *N* sodium hydroxide. The solutions were filtered to remove a small amount of insoluble matter. All solutions were used within a few days except for those of pyridoxal, pyridoxamine, glutamic acid and α-ketoglutaric acid which gave no evidence of decomposition, and were used over one to two month periods.

"50%" Ethanolamine.—Equal volumes of good quality ethanolamine and water were mixed.

Phosphate Buffer, *p*H 6.7.—Equal volumes of 0.5 *M* solutions of reagent grade potassium dihydrogen phosphate and disodium hydrogen phosphate were mixed.

2,4-Dinitrophenylhydrazine Reagent.—0.1 g. of 2,4-dinitrophenylhydrazine was dissolved in 100 ml. of 2.00 *N* hydrochloric acid and filtered after 24 hours.

Sodium Hydroxide–Buffer Solution.—One hundred ml. of 2.00 *N* sodium hydroxide, 40 ml. of 0.5 *M* potassium dihydrogen phosphate and 60 ml. of 0.5 *M* disodium hydrogen phosphate were mixed and diluted to 500 ml.

Photometric Measurements.—The Beckman model DU spectrophotometer and the Evelyn photoelectric colorimeter were employed. One cm. cells were used with the spectrophotometer. Results are expressed in terms of molar extinction coefficients.

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[1] Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Presented in part at the 119th Meeting of the American Chemical Society at Cleveland, Ohio, April, 1951. Part of this work was taken from the M.S. thesis of D. E. Metzler.

[2] Department of Chemistry, University of Texas, Austin, Texas.

[3] E. E. Snell, THIS JOURNAL, **67**, 194 (1945).

[4] W. W. Umbreit, R. H. Burris and J. F. Stauffer, "Manometric Techniques," Burgess Publishing Company, Minneapolis, Minn., 1948, p. 185.

[5] J. T. Holden, R. B. Wildman and E. E. Snell, *J. Biol. Chem.*, **191**, 559 (1951).