Action of One Mole of Phenylmagnesium Bromide on Triketoindane (Inverse Grignard Reaction).—An ethereal solution of phenylmagnesium bromide containing 0.4 g. of magnesium was added gradually with continual stirring to a suspension of triketoindane (5.3 g.) in 50 cc. of dry benzene. The mixture was then refluxed for 2 hours on the boiling water-bath and decomposed with an ammoniacal ammonium chloride solution. The ethereal solution, separated, washed and dried, yielded yellow crystalline 2-phenyl-2-hydroxy-1,3-diketoindane (2.2 g.) which after recrystallization from ligroin (60–80°) melts at 192°, undepressed with authentic sample.

Action of Diazomethane on 2-Phenyl-2-hydroxy-1,3-diketoindane.—2-Phenyl-2-hydroxy-1,3-diketoindane (0.1 g.) was treated with an excess of freshly prepared ethereal solution of diazomethane. A vigorous reaction immediately took place with evolution of nitrogen. The mixture was left overnight and then evaporated in vacuum. The colorless residue (0.07 g.) was recrystallized from methyl alcohol to yield colorless needles of 2-methoxy-2-phenyl-1,3-diketoindane, m.p. 114°, undepressed with authentic sample.

Action of Excess Grignard Reagent on Triketoindane.—Triketoindane (I) (1 g.) was added to an ethereal solution of phenylmagnesium bromide (prepared from 1 g. of magnesium and 10 g. of bromobenzene in 50 cc. of ether), a vigorous reaction took place. Benzene (50 cc.) was then added and the mixture was refluxed for half an hour, left overnight, then treated with dilute hydrochloric acid and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, evaporated up to dryness, and the residue (2 g.) was crystallized from benzene–petroleum ether (1:3 by volume) to give 1,2,3-triphenyl-1,2,3-trihydroxyindane, colorless needles, m.p. 124–130°. *Anal.* Calcd. for: $C_{27}H_{22}O_3 \cdot C_6H_6$: C, 83.8; H, 5.9. Found: C, 83.6; H, 6.0.

When this substance is left for a few days at room temperature or dried in vacuum, benzene of crystallization is lost giving colorless crystals, m.p. 178°. *Anal.* Calcd. for: $C_{27}H_{22}O_3$: C, 82.2; H, 5.6. Found: C, 82.3; H, 5.8. It is soluble in benzene and ethyl alcohol, insoluble in sodium hydroxide, and gives a yellow orange color with concentrated sulfuric acid.

CAIRO, EGYPT RECEIVED MAY 23, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

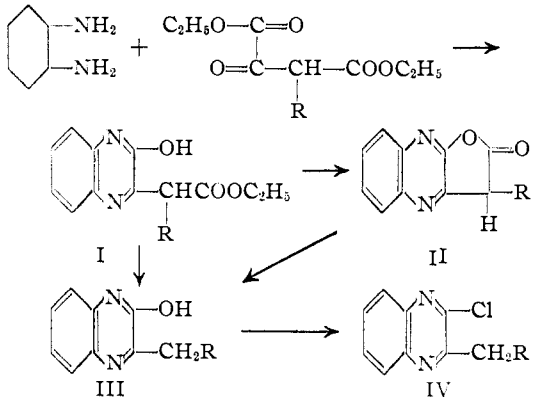
2-Hydroxy-3-alkylquinoxalines

BY YVON J. L'ITALIEN AND C. K. BANKS[1]

It was desired to prepare several 1,10-phenanthrolines and so the reactions of *o*-phenylenediamine with ethyl ethoxymethylenemalonate, ethyl oxalacetate and ethyl oxalpropionate were studied. It was found, however, that the products of the reaction were quinoxalines rather than phenanthrolines. Hydrolysis and decarboxylation of the quinoxalines led to 2-hydroxy-3-alkylquinoxalines which could be converted to the corresponding 2-chloro compounds. In contrast with *o*-phenylenediamine, *p*-phenylenediamine gave 4,7-phenanthrolines when reacting with the same ring closure compounds.

The development of methods for the syntheses of quinolines utilizing primary arylamines and ethyl ethoxymethylenemalonate,[2] ethyl oxalacetate and ethyl oxalpropionate[3] suggests that these same reactions may be utilized for the production of phenanthrolines. Snyder and Freier[4] have condensed *o*-phenylenediamine with ethyl ethoxymethylenemalonate to yield a 1,10-phenanthroline. When the phenylenediamines were treated with ethyl oxalacetate and ethyl oxalpropionate, the *o*-phenylenediamine gave a quinoxaline (I) rather than a phenanthroline. Such behavior is not unexpected since Gowenlock, *et al.*,[5] found that ethyl glyoxylate reacted with *o*-phenylenediamine to yield 2-hydroxyquinoxaline.

The reaction between the oxal esters and the diamine was very rapid, being essentially completed in ten minutes at steam-bath temperatures. A further condensation occurred when the reactants were cyclized in boiling diphenyl ether or when the quinoxaline (I, R = CH_3) was heated in diphenyl ether. This product proved to be 3-methyl-2-furo[2,3-b]quinoxalone (II, R = CH_3). The corresponding oxalacetate (I, R = H) failed to yield an isolatable furoquinoxalone (II, R = H), only starting material and gums being obtained. Both I and II, when hydrolyzed with alkali and then acidified, lost carbon dioxide rapidly to yield the 2-hydroxy-3-alkylquinoxalines (III). I and III (R = H) have been prepared by Ruhemann and Stapleton[6] from *o*-phenylenediamine and ethyl acetylenedicarboxylate. The hydroxyquinoxalines were converted to the corresponding chloroquinoxalines (IV) by phosphorus oxychloride. The chlorine atom of the 2-chloroquinoxalines was sufficiently active to react with arylamines.



In contrast to the behavior of *o*-phenylenediamine, even in excess of oxal esters, *p*-phenylenediamine reacted with two equivalents of ethyl oxalpropionate to give a bis-anil which cyclized to a 4,7-phenanthroline.

Experimental[7]

Ethyl 2-Hydroxy-3-quinoxalylacetate.—*o*-Phenylenediamine (0.1 mole) was dissolved in hot 95% ethanol, the solution treated with Darco G-60 and filtered. A concd.

(1) Metal and Thermit Corporation, Rahway, N. J.
(2) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).
(3) Surrey and Hammer, *ibid.*, **68**, 113 (1946).
(4) Snyder and Freier, *ibid.*, **68**, 1320 (1946).
(5) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945).
(6) Ruhemann and Stapleton, *ibid.*, **77**, 248 (1900).
(7) The microanalytical data were obtained by our Microanalytical Department under the direction of C. E. Childs.

aqueous solution of sodium ethyl oxalacetate (0.11 mole) and 7 ml. of acetic acid was added and the mixture heated on the steam-bath for ten minutes. After cooling and allowing to stand for two hours, a yellow solid separated which was filtered off, recrystallized from Butyl Cellosolve and dried *in vacuo*. The yield was 75–85% of a yellow crystalline product, m.p. 210°. *Anal.* Calcd.: C, 62.05; H, 5.21; N, 12.06. Found: C, 61.93; H, 5.02; N, 12.49.

Ethyl α-(2-Hydroxy-3-quinoxalyl)-propionate.—The reaction was carried out as above with sodium ethyl oxalpropionate. The product, which was extremely soluble in ethanol and acetone, was obtained in nearly quantitative yields, m.p. 160–162°.

Anal. Calcd.: C, 63.40; H, 5.72; N, 11.37. Found: C, 62.95; H, 6.13; N, 11.72.

3-Methyl-2-furo[2,3-b]quinoxalone.—Diphenyl ether (500 ml.) was heated to reflux and ethyl α-(2-hydroxy-3-quinoxalyl)-propionate (10 g.) added portionwise over a period of one-half hour. After the final addition had boiled out ethanol, the solution was cooled, diluted with ligroin and the solid separating collected, washed with ether and recrystallized from Methyl Cellosolve. The yield was 60% of the theoretical, m.p. 310°.

Anal. Calcd. C, 65.99; H, 4.02; N, 13.99. Found: C, 65.90; H, 4.01; N, 13.67.

2-Hydroxy-3-ethylquinoxaline Hydrate.—Ethyl α-(2-hydroxy-3-quinoxalyl)-propionate (12.3 g.) was suspended in a small volume of water containing 3 g. of potassium hydroxide and boiled for one-half hour. Concd. hydrochloric acid was added dropwise until the solution was acidic. Carbon dioxide was evolved and the product separated. After recrystallization from hot water, the yield was 75% of the product, m.p. 198°.

Anal. Calcd.: C, 62.48; H, 6.29; N, 14.58. Found: C, 63.25; H, 6.22; N, 14.84.

2-Hydroxy-3-methylquinoxaline.—This product was obtained from ethyl 2-hydroxy-3-quinoxalylacetate and from 3-methyl-2-furo[2,3-b]quinoxalone by the same procedure as used for the 3-ethyl compound. The product was recrystallized from hot water, yield 72%, m.p. 250°.[8]

(8) Hinsberg, *Ann.*, **292**, 249 (1896), gives the m.p. as 245°.

Anal. Calcd.: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.00; H, 5.06; N, 17.80.

2-Chloro-3-ethylquinoxaline.—2-Hydroxy-3-ethylquinoxaline (0.1 mole) was refluxed in 150 ml. of phosphorus oxychloride. After removing the excess oxychloride, the residue was triturated with ice and water, the solution neutralized with ammonia. A low-melting solid separated and was recrystallized from acetone and water, m.p. 38–40°.

Anal. Calcd.: C, 62.34; H, 4.70; N, 14.59. Found: C, 62.16; H, 4.52; N, 14.72.

The 2-chloro-3-methyl isomer, m.p. 79–81° was prepared similarly.

Anal. Calcd.: C, 60.51; H, 3.95; N, 15.68. Found: C, 60.72; H, 4.10; N, 15.12.

2-*o*-Chloroanilino-3-methylquinoxaline.—Equimolar amounts of 2-chloro-3-methylquinoxaline and *o*-chloroaniline reacted in slightly acid aqueous suspension at the reflux temperature for three days. The product was recrystallized from water, m.p. 114–115°.

Anal. Calcd.: C, 66.78; H, 4.48; N, 15.57. Found: C, 66.70; H, 4.71; N, 15.36.

Tetraethyl α,α′-(*p*-Phenylenedinitrilo)-bis-(β-methylsuccinate).—*p*-Phenylenediamine reacted with two equivalents (⅔ mole) of ethyl oxalpropionate on a steam-bath in the same manner as for the *o*-phenylenediamine. The product precipitated and was recrystallized from methanol, yield 75%, m.p. 105–106°.

Anal. Calcd.: C, 60.48; H, 6.76; N, 5.88. Found: C, 60.94; H, 6.98; N, 6.02.

3,8-Dicarbethoxy-1,10-dihydroxy-2,9-dimethyl-4,7-phenanthroline.—The previous bis-anil was heated in boiling diphenyl ether until no more ethanol was evolved. The diphenyl ether was cooled and diluted with ligroin to obtain a solid which was recrystallized from Methyl Cellosolve, yield 88%, m.p. 285–290° dec.

Anal. Calcd.: C, 62.48; H, 5.24; N, 7.28. Found: C, 62.48; H, 5.15; N, 7.16.

DETROIT 32, MICH. RECEIVED NOVEMBER 8, 1950

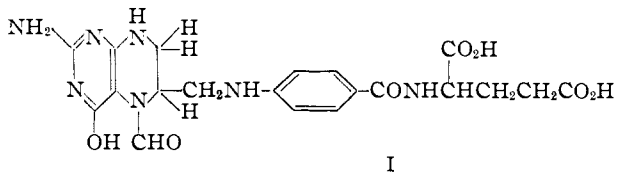
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES AND FROM THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH]

A Proposed Structure for Folinic Acid-SF, a Growth Factor Derived from Pteroylglutamic Acid

BY ALBERT POHLAND, EDWIN H. FLYNN, REUBEN G. JONES AND WILLIAM SHIVE

The structure 5-formyl-5,6,7,8-tetrahydropteroylglutamic acid is proposed for folinic acid-SF, a synthetic growth factor derived from pteroylglutamic acid.

A new group of factors, the folinic acid group, has recently been reported to be more effective than pteroylglutamic acid in preventing the toxicity of *x*-methylfolic acid for *Lactobacillus casei*[1] and to be essential for the growth of *Leuconostoc citrovorum*.[2,3] A recent communication has described the preparation from pteroylglutamic acid of a reaction mixture which has the biological activities of folinic acid derived from purified liver extracts.[4] A synthetic factor, folinic acid-SF, has been obtained in crystalline form.[5,6] The synthetic factor is effective in promoting the growth of chicks,[6] and in preventing the toxicity of aminopterin for the mouse.[6] More recently folinic acid-SF has been reported to be an effective antianemic substance for the human.[7] It is the purpose of this paper to propose as a tentative structure, 5-formyl-5,6,7,8-tetrahydropteroylglutamic acid (I), for folinic acid-SF.



I

The proposed structure is based on evidence ob-

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(2) H. E. Sauberlich and C. A. Baumann, *J. Biol. Chem.*, **176**, 165 (1948).

(3) T. J. Bardos, T. J. Bond, J. Humphries and W. Shive, THIS JOURNAL, **71**, 3852 (1949).

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(5) E. H. Flynn, T. J. Bond, T. J. Bardos and W. Shive, *ibid.*, **73**, 1979 (1951).

(6) J. A. Brockman, B. Roth, H. P. Broquist, M. E. Hultquist, J. M. Smith, M. J. Fahrenbach, D. B. Consulich, R. P. Parker, E. L. R. Stokstad and T. H. Jukes, *ibid.*, **72**, 4326 (1950), have reported a crystalline substance which may be the same as folinic acid-SF.

(7) T. D. Spies, G. G. Lopez, F. Milanes, R. L. Toca, A. Reboredo and R. E. Stone, *Southern Med. J.*, **43**, 1076 (1950).