in a small metal bomb was added 22.5 g. (0.5 mole) of anhydrous ethylamine. The bomb was closed and heated to 100–105° for twenty hours. It was then cooled, opened and the contents filtered. The solid consisted of ethylamine hydrochloride (16.1 g.). The yellow filtrate was concentrated *in vacuo*. The cooled residue was mixed with 2.7 g. (0.1 mole) of liquid hydrogen cyanide. The solution became warm. It was cooled and mixed with 500 ml. of cold, dilute hydrochloric acid. Treatment with 8.9 g. (0.11 mole) of potassium cyanate and purification of the product as previously described in the preparation of 1-methyl-5-methyl-5-phenylhydantoin yielded a crystalline product.

1-β-Hydroxyethyl-5-phenylhydantoin.—Fifty-three grams (0.5 mole) of benzaldehyde and 14.9 g. (0.55 mole) of liquid hydrogen cyanide were mixed together in a small pressure bottle (ice-bath) and allowed to stand at 25° for two hours. The product was cooled and 30.5 g. (0.5 mole) of ethanolamine was added. Heat was evolved. The resulting mixture was cooled and added to a cold solution of 50 ml. of concentrated hydrochloric acid and 200 ml. of water. After the solution had cooled to 0°, 44.6 g. (0.55 mole) of potassium cyanate was added. Within a few minutes a yellow, semi-solid material precipitated. The mixture was left in the ice-bath for an hour before being heated on the steam-bath with an additional 100 ml. of concentrated hydrochloric acid. After the mixture was thoroughly chilled, it was filtered. The yellow solid was purified by dissolving in 800 ml. of boiling water, charcoaling and cooling to reprecipitate the product.

1-β-Bromoethyl-5-phenylhydantoin.—Twenty-two grams (0.1 mole) of 1-β-hydroxyethyl-5-phenylhydantoin was mixed with 50 ml. of dry chloroform and cooled in an ice-bath. Ten grams of phosphorus tribromide in 50 ml. of chloroform was added with stirring. After one-half hour the mixture was placed on a steam-bath and warmed for an hour. The resulting solution was poured with stirring into an excess of chipped ice. The solid product was filtered off and recrystallized from ethanol and water.

Summary

A series of 1-R-5-R′-5-phenylhydantoins, most of which are new compounds, has been prepared and tested for anticonvulsant activity.

Maximum activity is exhibited by those derivatives having a lower hydrocarbon group in the 1-position and only a phenyl group in the 5-position.

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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of Some Substituted Quinoxalines

BY R. W. BOST AND E. E. TOWELL[1,2]

The reaction between aromatic ortho-diamines and alpha-diketones to form quinoxalines has been utilized to prepare a series of 2,3-disubstituted quinoxalines and 2,3-disubstituted-6-methoxyquinoxalines, with the purpose of studying their pharmacological properties.

The two diamines used were *o*-phenylenediamine and 3,4-diaminoanisole in the form of its hydrochloride, which was prepared in the laboratory from 4-amino-3-nitroanisole. The 4-amino-3-nitroanisole was prepared from commercial *p*-anisidine by the method of Reverdin,[3] with minor modifications. The diacetyl was obtained from the Forest Products Company. 3,5-Dicarboethoxycyclopentanedione-1,2 was prepared by the condensation of ethyl oxalate and ethyl glutarate in the presence of sodium ethoxide.[4] The following benzoins were prepared from the corresponding aldehydes by the "benzoin" condensation in the presence of alcoholic potassium cyanide: 4,4′-dimethoxybenzoin, *p*-dimethylaminobenzoin, 3,3′,4,4′-bis-(methylenedioxy)-benzoin, 2,2′,3,3′-tetramethoxybenzoin, 4-methoxy-3′,4′-methylenedioxybenzoin, and *p*-diethylaminobenzoin. *alpha*-Furoin and benzil were available in the laboratory.

The following diketones were prepared by oxidation of the corresponding hydroxyketone with copper sulfate in pyridine[5]: 4,4′-dimethoxybenzil, *p*-dimethylaminobenzil, 3,3′,4,4′-bis-(methylenedioxy)-benzil, 2,2′,3,3′-tetramethoxybenzil[6]; 4-methoxy-3′,4′-methylenedioxybenzil, alpha-furil, and *p*-diethylaminobenzil (not obtained in crystalline form; alcoholic solution used to prepare the quinoxaline).

Attempts to prepare the quinoxaline from 2,3,2′-3′-tetramethoxybenzil and *o*-phenylenediamine were unsuccessful. An explanation of this anomalous behavior of an alpha-diketone toward an aromatic ortho-diamine has been offered by Schönberg and co-workers.[7]

Bennett and Willis[8] have shown that the methyl groups in 2,3-dimethylquinoxaline react with certain aromatic aldehydes in an excess of boiling acetic anhydride to form mono- and di-styrylquinoxalines. Attempts were made by us to bring about a similar reaction between 2,3-dimethylquinoxaline and formaldehyde, acetaldehyde and *n*-butyraldehyde, respectively, using the method of Bennett and Willis. Since no identifiable products could be isolated from the reaction mixtures, the experimental details are not given in this paper. An unsuccessful attempt was made to carry out a

(1) This paper is a portion of a dissertation presented by E. E. Towell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of North Carolina, June, 1944.

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(3) Reverdin, *Ber.*, **29**, 2595 ff. (1896).

(4) Adams, *et al.*, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 284.

(5) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 87; Kinney, THIS JOURNAL, **51**, 1595 (1929); Hartmann and Dickey, *ibid.*, **55**, 1228 (1933).

(6) Hartwell and Kornberg, *ibid.*, **67**, 1607 (1945).

(7) Schönberg and co-workers, *Ber.*, **55B**, 1174 ff., 3746 ff., 3755 (1922).

(8) Bennett and Willis, *J. Chem. Soc.*, 1960 (1928); 256 (1929).

Mannich[9] type reaction using 2,3-dimethylquinoxaline, methylamine hydrochloride and formaldehyde.

Experimental

3,4-Diaminoanisole.—This compound has been reported by Meldola and Eyre,[10] and has been prepared in the pure state by Bergeim,[11] *et al.*, by the reduction of 4-amino-3-nitroanisole with stannous chloride and hydrochloric acid. The free base has also been prepared by the reduction of 4-amino-3-nitroanisole with hydrogen and Raney nickel catalyst.[12] The authors prepared and used the compound in the form of its crude hydrochloride, since in this form it was less susceptible to oxidation by the air. In a typical run, 4-amino-3-nitroanisole (50.4 g., 0.30 mole) and fluid Raney nickel catalyst (8–9 cc.) were added to anhydrous ether (150 cc.) and reduced catalytically under pressure in the presence of hydrogen in the usual manner at an initial pressure of 1500 p. s. i. and an initial temperature of 30°. The reduction was complete within thirty to forty minutes. As soon as possible after opening the bomb, the straw-colored ether solution was poured rapidly through a glass-wool filter into chilled, anhydrous ether (1000 cc.), previously saturated with dry hydrogen chloride gas, and contained in a three-liter, three-necked, round-bottomed flask fitted with stirrer and gas trap. The diamine hydrochloride, pale purple in color, formed immediately, and the product from each run was allowed to remain in the flask until several runs had been made. The product was then filtered, washed with anhydrous ether, dried in air for two hours, and stored in the dark. One series of five runs gave 276 g. of the crude hydrochloride (87%). The product was used to prepare quinoxaline without further purification. A small sample reacted with benzoyl chloride in 20% sodium hydroxide solution to form the dibenzoyl derivative which, after recrystallization from glacial acetic acid, melted at 248–249°. Reported m. p. 251–252°.[10]

Benzoins.—The usual methods[13] of preparing benzoins, both simple and mixed, were employed, with certain modifications as to proportions of reagents used, time of reflux and standing, and method of isolating and purifying the product. In general, it was found that yields were improved by filtering off the first batch of product, returning the filtrate to the reaction vessel, adding a fresh portion of potassium cyanide solution and refluxing again. In some instances, this process was repeated more than once. The yields ranged from 25% for 4-methoxy-3′,4′-methylenedioxybenzoin to 74% for 3,3′,4,4′-bis-(methylenedioxy)-benzoin.

***p*-Diethylaminobenzoin.**—*p*-Diethylaminobenzaldehyde (53.1 g., 0.30 mole), freshly distilled benzaldehyde (41.8 g., 0.30 mole) and 150 cc. of 95% ethanol were warmed on the steam-bath until solution was complete. Potassium cyanide solution (5 g. in 100 cc. of water) was added, the whole refluxed for two hours, then allowed to stand overnight. A second portion of potassium cyanide solution (8 g. in 50 cc. of water) was added, the whole refluxed for three hours, and allowed to stand overnight. Chilling failed to produce crystallization, the reaction mixture persisting as two layers, the lower being dark orange-red in color. The mixture was steam-distilled until about five liters of distillate had come over. The residue was allowed to stand overnight, after which the aqueous layer was decanted, and the viscous orange-red lower layer taken up in 50 cc. of 95% ethanol. The solution was diluted with water (150 cc.), the resulting suspension warmed on the steam-bath, and 95% ethanol added gradually until the solution just became clear. The solution was boiled with Norite, filtered, and allowed to stand at room temperature for six hours whereupon 30.8 g. of lustrous golden-yellow flakes were obtained. After recrystallization twice from 95% ethanol, lustrous white flakes, m. p. 105–106°, were obtained.

Anal. Calcd. for $C_{18}H_{21}O_2N$: N, 4.94. Found: N, 4.97.

Benzils.—The oxidation of the benzoins to the corresponding benzils by copper sulfate in pyridine was found to give good yields (better than 60%) in nearly every case. The products were easily isolated and purified. An exception was the product from the oxidation of *p*-diethylaminobenzoin, which could be obtained only as a sticky yellow gum adhering to the walls of the vessel. This material was taken up in 95% ethanol, in which it was readily soluble, and the solution used to prepare the corresponding quinoxaline by reaction with *o*-phenylenediamine.

2,3,2′,3′-Tetramethoxybenzil.—This compound was obtained in an 84% yield when 2,3,2′,3′-tetramethoxybenzoin was oxidized by the above procedure. It consists of white needles, m. p. 140–142°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.05: H, 5.29.

The 2,4-dinitrophenylhydrazone of this compound was prepared according to the method of Allen,[14] being obtained as brilliant orange crystals, m. p. 169–171° (uncor.), after three recrystallizations from a chloroform–methanol mixture.

Anal. Calcd. for $C_{24}H_{22}O_9N_4$: N, 10.99. Found: N, 11.11.

Quinoxalines.—The general procedure for preparing the 2,3-disubstituted quinoxalines was as follows[15]; equimolar portions (approx. 0.10 mole) of *o*-phenylenediamine and the benzil were refluxed for two to three hours in boiling glacial acetic acid (200–400 cc.), the reaction mixture allowed to cool, then poured, with vigorous stirring, into cold water (1000–2000 cc.). The resulting suspensions in most cases yielded precipitates on standing, or were broken with 20% sodium hydroxide solution. The products were recrystallized from ethanol, after treatment with Norite. The yields ranged from 85 to 99%. The 2,3-disubstituted-6-methoxyquinoxalines were prepared generally by the same procedure, except that the crude diamine hydrochloride was used instead of the free base. The yields ranged from 41 to 81%, it being found that the sooner the diamine hydrochloride was used after its preparation, the higher was the yield. The 2,3-dimethylquinoxalines were prepared in 10% acetic acid medium as given below.

2,3-Dimethyl-6-methoxyquinoxaline.—Crude 3,4-diaminoanisole hydrochloride (42.2 g., approx. 0.20 mole) was taken up in 10% acetic acid (300 cc.). Diacetyl (20 g., 0.23 mole) in 50 cc. of 10% acetic acid was added dropwise, with stirring, the mixture being heated on the steam-bath throughout the addition and for thirty minutes afterward. The dark-green mixture was allowed to cool to room temperature, diluted with water (750 cc.) and made alkaline to litmus with 20% sodium hydroxide solution. The brownish-black precipitate which formed was filtered, washed with water, taken up in dilute ethanol (1:1, 1000 cc.), boiled with Norite, then filtered. This operation was repeated four times, until the filtrate became pale straw-colored. Upon chilling, cream-colored crystals formed. Repeated recrystallization from dilute ethanol gave cream-colored crystals of constant m. p. 99–100° (uncor.).

Anal. Calcd. for $C_{11}H_{12}ON_2$: N, 14.89. Found: N, 14.81.

2,3-Dimethylquinoxaline Sulfate.—2,3-Dimethylquinoxaline (15.8 g., 0.10 mole), prepared according to the procedure given above, was taken up in anhydrous ether

(9) Adams, *et al.*, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303 ff.

(10) Meldola and Eyre, *J. Chem. Soc.*, **81** [2], 990 (1902).

(11) Bergeim, Losee and Lott, THIS JOURNAL, **69**, 586 (1947).

(12) Cavagnol and Wiselogle, *ibid.*, **69**, 796 (1947).

(13) Buck and Ide, *ibid.*, **52**, 223 (1930); **52**, 4107 (1930); **53**, 2352 (1931); **54**, 3305 (1932); Jenkins and co-workers, *ibid.*, **52**, 4496 (1930); **52**, 5201 (1930); **54**, 1159 (1932); Wöhler and Liebig, *Ann.*, **3**, 276 (1832); Perkin, *J. Chem. Soc.*, **59**, 164 (1891); Staudinger, *Ber.*, **46**, 3537 (1913); Tiffeneau and Levy, *Bull. soc. chim.*, [4] **49**, 725 (1931).

(14) Allen, THIS JOURNAL, **52**, 2957 (1930).

(15) Fuson, Emerson and Gray, *ibid.*, **61**, 482 (1939), prepared quinoxalines by the reaction of arylglyoxals and *o*-phenylenediamine in boiling glacial acetic acid.

TABLE I

2,3-DISUBSTITUTED QUINOXALINES

Substituents	Yield, %	M. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Found
2,3-Dimethyl	90	104–106	$C_{10}H_{10}N_2$	17.72	17.66
2,3-Diphenyl	87	124	.....	...	...
2,3-Di-*p*-anisyl	85	145.5–146	$C_{22}H_{18}O_2N_2$	8.18	8.06
2,3-Di-α-furyl	92	131–132	$C_{16}H_{10}O_2N_2$	10.68	10.58
2,3-Piperonyl	99	199–200	.....	...	...
2,3-Di-(3′,5′-dicarboethoxy)-cyclopentane	94	202–203	$C_{17}H_{18}O_4N_2$	8.91	8.92
[a]2-Phenyl-3-(*p*-dimethylamino)-phenyl	88	120–121	$C_{22}H_{19}N_3$	12.91	12.70
[a]2-Phenyl-3-(*p*-diethylamino)-phenyl	..	126–127	$C_{24}H_{23}N_3$	11.89	10.22
2,3-DISUBSTITUTED-6-METHOXYQUINOXALINES					
[a]2,3-Dimethyl[b]	49	99–100	$C_{11}H_{12}ON_2$	14.89	14.81
2,3-Diphenyl	77	154.5–155	.....	...	...
[a]2,3-Di-*p*-anisyl[b]	81	131–132	$C_{23}H_{20}O_3N_2$	7.52	7.43
[a]2,3-Di-α-furyl	42	109–110	$C_{17}H_{12}O_3N_2$	9.58	9.35
[a]2,3-Dipiperonyl[c]	55	171–172	$C_{23}H_{16}O_6N_2$	6.99	7.29

[a] These compounds have not hitherto been reported. [b] Specific preparation given. [c] A sample of this quinoxaline with an authentic sample of piperil, m. p. 171.5°, gave a mixed m. p. 145–155°.

(400 cc.). Ten cubic centimeters of concentrated sulfuric acid (sp. gr. 1.84, 96–98% H_2SO_4) was added dropwise, with vigorous stirring. A voluminous pale yellow solid formed, and as the mass became too thick for efficient stirring, 100-cc. portions of dry ether were added at three successive intervals. The yellow solid was filtered and washed with dry ether. Two recrystallizations from absolute ethanol (300 cc.) gave 20 g. (78%) of pale green flakes, m. p. 151–152° (d.). The salt is readily soluble in water.

Anal. Calcd. for $C_{10}H_{10}N_2 \cdot H_2SO_4$: neutral equivalent, 256.27. Found: neutral equivalent, 256.01.

2,3-bis-(*p*-Methoxyphenyl)-6-methoxyquinoxaline.—4,4′-Dimethoxybenzil (10 g., 0.04 mole) and crude 3,4-diaminosanisole hydrochloride (20 g., approx. 0.10 mole) were taken up in glacial acetic acid (300 cc.). The mixture was refluxed for two hours, allowed to stand overnight at room temperature, then refluxed again for two hours. After cooling, the mixture was poured, with vigorous stirring, into cold water (2500 cc.). The resulting light tan suspension was diluted with water (2500 cc.) and broken by the addition of 20% sodium hydroxide solution. The flocculent solid was filtered, washed with water, and recrystallized from 95% ethanol (300 cc.), after treatment with Norite. The cream-colored crystals weighed 7.6 g. after drying in air. A second crop (3.5 g.) was obtained by diluting the mother liquor to a volume of one liter with water and allowing to stand several hours. The combined yield of 11.1 g. was 81% of the theoretical, based on the 4,4′-dimethoxybenzil. Repeated recrystallization from 95% ethanol gave a product of constant m. p. 131–132° (uncor.).

Anal. Calcd. for $C_{23}H_{20}O_3N_2$: N, 7.52. Found: N, 7.43.

The 2,4-dinitrophenylhydrazone of 2,3-dimethoxybenzaldehyde was prepared, being obtained as brilliant red crystals, m. p. 218–219° (uncor.), after two recrystallizations from chloroform.

Anal. Calcd. for $C_{15}H_{14}O_6N_4$: N, 16.22. Found: N, 16.07.

Pharmacological Properties.—The pharmacological studies on these quinoxalines were carried out by the Wm. S. Merrell Co. of Cincinnati, Ohio, through the courtesy of Dr. Robert S. Shelton, to whom the authors are deeply grateful. The results will be reported elsewhere.

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Summary

1. A series of 2,3-disubstituted quinoxalines and 2,3-disubstituted-6-methoxyquinoxalines have been prepared.

2. A method for the preparation of 3,4-diaminoanisole hydrochloride in sizeable quantities has been developed.

3. The 2,4-dinitrophenylhydrazones of 2,3-dimethoxybenzaldehyde and 2,3,2′,3′-tetramethoxybenzil have been prepared.

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