Anal. Calcd. for $C_{10}H_{19}N \cdot C_6H_3O_7N_3$: C, 50.26; H, 5.7. Found: C, 50.57; H, 5.75.

Bz-Tetrahydroisoquinoline. A. By Partial Dehydrogenation with Palladium Black.—The picrate fractions 6–9 (Table I) were combined (270 mg.) and freed from the much less soluble isoquinoline picrate by sufficient recrystallizations from acetone. The pure product finally crystallized in golden-yellow needles of uniform appearance, m. p. 144°.

Anal. Calcd. for $C_9H_{11}N \cdot C_6H_3O_7N_3$: C, 49.73; H, 3.87. Found: C, 50.25; H, 3.87.

In another experiment, starting with the same amount (1 g.) of decahydro bases, dehydrogenation was stopped after the evolution of 310 cc. of hydrogen (calcd. for 5 moles of hydrogen, 781 cc.). In this case the medium fractions yielded 690 mg. of picrate, corresponding to about 25% yield of Bz-tetrahydroisoquinoline.

Picrolonate.—The free base, prepared from the above picrate, had a smell reminiscent of substituted pyridines (*e. g.*, collidine). Aqueous picrolonic acid precipitated from the solution of the hydrochloride the picrolonate which, recrystallized from methanol, melted at 214°.

Anal. Calcd. for $C_{19}H_{19}O_5N_5$: C, 57.43; H, 4.78. Found: C, 57.94; H, 5.03.

B. By **Partial Dehydrogenation with Selenium in Tetralin.**—*cis*-Decahydroisoquinoline (0.8 g.) was boiled under reflux in 15 cc. of freshly distilled tetralin with 0.5 g. of black selenium dust for forty-eight hours. The reaction mixture was filtered from the selenium, diluted with ether and extracted with 2-cc. portions of 0.1 *N* hydrochloric acid. The fractions were converted into the picrates, which had the properties: 1-3, *cis*-decahydroisoquinoline picrate (0.19 g.), m. p. 150°; 4, mixture, not crystallized, sticky; 5, Bz-tetrahydroisoquinoline picrate, m. p. (after removal of little accompanying isoquinoline picrate) 144°; 6, isoquinoline picrate, m. p. 223°. After evaporation of the ether and tetralin a small amount of naphthalene was obtained.

Summary

Catalytic hydrogenation of isoquinoline in glacial acetic acid with sulfuric acid leads to a mixture containing 70–80% *cis*- and at least 10% *trans*-isomer. The *cis*-isomer is more readily dehydrogenated with Pd than the *trans* isomer. By controlled dehydrogenation of the *cis*-isomer bz-tetrahydroisoquinoline was obtained.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Basically Substituted Quinoxalines

BY HENRY GILMAN AND H. SMITH BROADBENT

Of the many thousands of compounds synthesized and tested for antimalarial activity, those which have shown by far the greater promise, in general, are the derivatives of nitrogen-containing heterocycles bearing basic side chains, in particular the derivatives of quinoline. At the inception of this investigation very few basically substituted quinoxalines had been described in the chemical literature and even fewer had been tested for *antimalarial* activity.[1] Since quinoxaline differs from quinoline only in having a tertiary nitrogen substituted for the carbon in the 4-position of the ring, derivatives of quinoxaline appeared to have some interest as antimalarials.

In order to explore this possibility, a series of substituted aminoquinoxalines and their 2,5-dimethyl-1-pyrryl derivatives was prepared and subjected to pharmacological testing. In addition the rather high tuberculocidal activity of some related types of compounds prompted the synthesis of 2,3-bis-(*p*-aminophenyl)-quinoxaline, 2,3-bis-(*p*-hydroxyphenyl)-quinoxaline and 2,3-bis-(*p*-hydroxyphenyl)-6-aminoquinoxaline.

(1) While this investigation was in progress and since its completion three years ago, several papers have appeared dealing with the synthesis of quinoxaline derivatives for pharmacological purposes, *viz.*, (a) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945); (b) Hall and Turner, *ibid.*, 699 (1945); (c) King and Beer, *ibid.*, 792 (1945); (d) Gawron and Spoerri, THIS JOURNAL, **67**, 514 (1945); (e) Mizzoni and Spoerri, *ibid.*, **67**, 1652 (1945); (f) Cavagnol and Wiselogle, *ibid.*, **69**, 795 (1947); (g) Stevens, Pfister and Wolf, *ibid.*, **68**, 1035 (1946); (h) Weijlard, Tishler and Erickson, *ibid.*, **66**, 1957 (1944); (i) Linsker and Evans, *ibid.*, **68**, 874 (1946); and (j) Wiedling, *Acta Path. Microbiol. Scand.*, **22**, 379 (1945), as well as a few notes.

The quinoxaline nuclei of the compounds synthesized in the course of this work were prepared by condensing appropriately substituted α-diketones with either *o*-phenylenediamine or 1,2,4-triaminobenzene dihydrochloride in acetic acid or aqueous ethanol solutions, respectively. In all cases the yields were satisfactory, although in the latter case, the removal of resinous by-products was troublesome.

The 1,2,4-triaminobenzene required was prepared and used in the form of its dihydrochloride. The original method of Hinsberg[2] for its preparation did not prove to be satisfactory. The complex formed between the amine and chlorostannous(ic) acids was often difficult to decompose completely and a tin-containing product was secured only difficultly purified by recrystallization. In addition, the frequent exposure to the air entailed in this process was deleterious to the very easily oxidized polyamine. In order to circumvent these difficulties, it was found that the catalytic reduction of 2,4-dinitroaniline in ethanol over Raney nickel was more rapid, convenient, and less expensive than the former method, and it yielded the product desired in greater yields of at least equal purity.

In the preparation of substituted benzoins, the experimental conditions necessary in order to get good yields of crystalline products are often quite rigid.[3] Rather than isolate the intermediate benzoins, anisoin and *o,o'*-dichlorobenzoin, in the prep-

(2) Hinsberg, *Ber.*, **19**, 1253 (1886).

(3) Dewar and Read, *J. Soc. Chem. Ind.*, **55T**, 347T (1936).

aration of the corresponding benzils, it was found that the crude nitrogenous mixtures containing less than 50% of the benzoin obtained from the potassium cyanide–aldehyde reaction could be oxidized directly with copper sulfate in pyridine.[4] This method converted the contained benzoin to the pure crystalline benzil in nearly quantitative yields.

The reported preparation of 4,4′-dihydroxybenzil by the demethylation of anisil[5] requires hydrobromic acid of 1.78 density, which is not conveniently available. Neither aqueous hydrobromic acid (d. 1.48, 48%) nor 33% hydrogen bromide in acetic acid was found to be efficacious alone; however, the use of equal parts of the two acid solutions was found to cleave smoothly the methyl groups from anisil resulting in a good yield of pure 4,4′-dihydroxybenzil.

The preparation of 2,3-bis-(*p*-aminophenyl)-quinoxaline was conveniently effected by Raney nickel reduction of the corresponding nitro compound (*cf.* ref. 1d and 1f) without reduction of the heterocyclic nucleus.[6]

The 2,5-dimethyl-1-pyrrylquinoxalines were synthesized from the corresponding amines by condensation with 2,5-hexanedione. In the case of 2-aminoquinoxaline we were not able to isolate any pure product other than starting material.

Solutions of 2,3-bis-(*p*-hydroxyphenyl)-6-aminoquinoxaline in strong acids are a bright, cherry-red color and in bases a brilliant yellow. On adding small amounts of the indicator dissolved in a dilute sodium hydroxide solution to a series of Clark and Lubs buffers, the transition point was found to lie between *p*H 3.4 and 3.6 indicating an approximate pK_{In} of 3.5 assuming the color intensities of the acidic and basic forms to be equal.

The 6-aminoquinoxalines and their pyrryl derivatives all have an intense yellowish-green fluorescence observable even in extremely dilute solutions, being red by transmitted light. An interesting observation on the effect of molecular structure on solubility is afforded by the 2,3-diphenyl-, 2,3 bis-(*p*-methoxyphenyl)-, and 2,3-bis-(*o*-chlorophenyl)-6-aminoquinoxalines and their pyrryl derivatives. The amino compounds are very soluble in ethanol and only moderately soluble in benzene whereas the corresponding pyrryl compounds are almost completely insoluble in hot ethanol and exceedingly soluble in hot benzene.

The results of the pharmacological tests on these compounds will be published elsewhere, and the authors are grateful to Parke, Davis and Company for arranging for the tests.

Experimental

1,2,4-Triaminobenzene Dihydrochloride.—(A) Tin and Hydrochloric Acid Method.—Following the general procedure of Hinsberg,[2] 0.5 mole of 2,4-dinitroaniline yielded 40 g. (41%) of 1,2,4-triaminobenzene dihydrochloride. A second 0.25-mole run gave a 35-g. (71.5%) yield.

(B) **Catalytic Reduction Method.**—In 300 ml. of absolute ethanol 61 g. (0.33 mole) of 2,4-dinitroaniline and 4–5 g. of "wet" Raney nickel catalyst were suspended and shaken under 1–3 atm. of hydrogen until the required amount for complete reduction of the nitro groups had been absorbed (*ca.* twelve hours). The violet solution was filtered free of catalyst and treated with an excess of concentrated hydrochloric acid with cooling in an ice-bath. A fine, purple, crystalline solid separated, which was filtered off, washed with ethanol and ethyl acetate, and finally dried *in vacuo*. The yields of dry, purplish solid in six successive runs were 81, 86, 93, 86, 98 and 85%, respectively, of a purity superior to that obtained by the Hinsberg procedure.

Anisil.—Anisoin was prepared from purified anisaldehyde according to the directions of Dewar and Read[3] in yields of 40% and 43% (m. p. 113°). A run made according to the procedure of Boesler[7] gave only a 22% yield.

Eleven grams (0.0405 mole) of anisoin, 45 g. (0.18 mole) of copper sulfate, 20 ml. of water, and 60 g. of pyridine were heated on a steam-bath with stirring for four hours. On filtering and washing with water, 10.5 g. (96%), of fine, pale yellow crystals melting sharply at 131–132° was obtained without crystallization (reported,[7] 133° by another technique). Two successive runs gave yields of 96% and 100%.

2,2′-Dichlorobenzil.—2,2′-Dichlorobenzoin was prepared from 100 g. (0.712 mole) of *o*-chlorobenzaldehyde following the procedure of Hodgson and Rosenberg[8]; however, the product was an oil which would not crystallize (reported,[8] m. p. 56–57° in 40% yield).

The crude mixture consisting of approximately 40% aryloin from the above reaction was stirred and heated at 100° for four hours with 180 g. copper sulfate, 80 ml. water, and 240 ml. pyridine. This crude product obtained on diluting with water was crystallized from benzene as beautiful, yellow needles melting at 128–129° (reported,[8] 128° by another method). The over-all yield was 38.5 g. (39%), nearly 100% based upon the contained aryloin.

4,4′-Dihydroxybenzil.—Ten grams (0.037 mole) of anisil, 50 ml. of aqueous hydrobromic acid (d. 1.48), and 50 ml. of 33% hydrogen bromide in glacial acetic acid were refluxed with vigorous stirring for six hours while a slow current of dry carbon dioxide was passed over the mixture. The solution was poured into water precipitating a fine gray powder, which was dissolved in a small volume of 15% sodium hydroxide, filtered, and then precipitated with hydrochloric acid. A light, gray powder melting at 245–247° was obtained. The melting point was unchanged on crystallizing from a large volume of boiling water. The yield was 8 g. (89%) (reported,[5] m. p. 235°).

6-Amino-2,3-bis-(*p*-methoxyphenyl)-quinoxaline: Procedure A.—A suspension of 10 g. (0.037 mole) of anisil and 7.5 g. (0.038 mole) of 1,2,4-triaminobenzene dihydrochloride in 100 ml. of ethanol and water (1:1) was refluxed with stirring for four hours on the steam-bath. Sodium hydroxide solution was added in slight excess, and the mixture was cooled. The hard cake of crude product was pulverized, taken up in hot ethanol, charcoaled and cooled. The dark purplish crystals separating out were then recrystallized to constant melting point from benzene giving a yield of 8.1 g. (61%) of light brown crystals melting at 194–196°.

2,3-bis-(*p*-Aminophenyl)-quinoxaline: Procedure B.—4,4′-Dinitrobenzil was prepared by the nitration of 4,5-diphenylglyoxalone according to the method of Chattaway and Coulson.[9] The yield of 2,3-bis-(*p*-nitrophenyl)-

(4) Clarke and Dreger, "Organic Syntheses," Coll. Vol. I, 1941, p. 87.

(5) Schönberg and Kraemer, *Ber.*, **55**, 1188 (1922).

(6) Since the work was completed, a similar reduction has been reported (see ref. 1b).

(7) Boesler, *Ber.*, **14**, 327 (1881).

(8) Hodgson and Rosenberg, *J. Chem. Soc.*, 16 (1930).

(9) Chattaway and Coulson, *J. Chem. Soc.*, 1361 (1928).

TABLE I

QUINOXALINES

Quinoxaline derivative	Procedure[a]	M. p., °C.[b]	Yield, %	Recrystallized from	Formula	N Analyses, % Calcd.	Found
6-Amino-2,3-dimethyl	A	186–187	100	Benzene–ethanol	$C_{10}H_{11}N_3$	24.2	23.9
6-Amino-2,3-diphenyl[c]	A	172–173	57	Benzene	$C_{20}H_{15}N_3$	...	...
6-Amino-2,3-bis-(*p*-methoxyphenyl)	A	194–196	61.5	Benzene	$C_{22}H_{19}O_2N_3$	11.76	11.71
6-Amino-2,3-bis-(*o*-chlorophenyl)	A	178–179	54	Benzene–ligroin	$C_{20}H_{13}N_3Cl_2$	11.47	11.48
6-Amino-2,3-bis-(*p*-hydroxyphenyl)	A	338–340	...	Ethanol–water	$C_{20}H_{15}O_2N_3$	12.77	12.84
2,3-bis-(*p*-Aminophenyl)[e]	B	260–262	18	Acetone–ethanol	$C_{20}H_{16}N_4$	17.94	17.95
2,3-bis-(*p*-Nitrophenyl)[d]	B	203–204	100	Acetic acid	$C_{20}H_{12}O_4N_4$	...	...
2,3-bis-(*p*-Hydroxyphenyl)	C	326–328	94	Ethanol	$C_{20}H_{14}O_2N_2$	8.91	9.02
6-(2,5-Dimethyl-1-pyrryl)-2,3-dimethyl	D	161–163	74	Ethanol	$C_{16}H_{17}N_3$	16.72	16.75
6-(2,5-Dimethyl-1-pyrryl)-2,3-diphenyl	D	151–153	44	Benzene–ethanol	$C_{26}H_{21}N_3$	11.19	11.12
6-(2,5-Dimethyl-1-pyrryl)-2,3-bis-(*p*-methoxyphenyl)	D	189–190	59	Benzene–ethanol	$C_{28}H_{25}O_2N_3$	9.65	9.70
6-(2,5-Dimethyl-1-pyrryl)-2,3-bis-(*o*-chlorophenyl)	D	211–212	29	Benzene-ethanol	$C_{26}H_{19}N_3Cl_2$	9.46	9.67

[a] An example representative of each procedure is described in the experimental part. The others were prepared in analogous fashion. [b] All melting points are uncorrected. The two above 300° were taken with a Berl–Kuhlmann type block, the others by capillary or hot-stage methods. [c] This compound has been prepared by Hinsberg, *Ann.*, **292**, 254 (1896), and Bertels, *Ber.*, **37**, 2277 (1904), m. p. 175°. [d] See ref. 11. [e] See ref. 12.

quinoxaline, obtained from the benzil and *o*-phenylenediamine, on recrystallization from acetic acid was 2.45 g. (100%) of large, tan crystals melting at 203–204° (reported,[7] 201°).

Two and three-tenths grams (0.0062 mole) of the nitrophenylquinoxaline was suspended in 60 ml. of absolute ethanol with 1–2 g. Raney nickel and shaken under 3 atm. pressure of hydrogen until the required amount was absorbed. The insoluble deposit was dissolved in methyl cellosolve, and the solution filtered free of catalyst. On evaporation of most of the solvent and diluting with water, brownish-yellow crystals melting at 255–258° were obtained. The product was recrystallized successively from acetone and water, and then acetone and ethanol until the melting point was raised to 260–262°.[10] The final yield of shining yellow plates of product was 0.350 g. (18%).

2,3-bis-(*p*-Hydroxyphenyl)-quinoxaline: Procedure C.—In 75 ml. of glacial acetic acid, 1.1 g. (0.01 mole) of *o*-phenylenediamine and 2.4 g. (0.01 mole) of 4,4′-dihydroxybenzil were refluxed for three hours. On cooling, glistening, yellow crystals of product separated. They were recrystallized from ethanol to a melting point of 326–328°. The yield was 2.9 g. (94%). The compound is easily soluble in sodium hydroxide, but very difficultly soluble in hydrochloric acid.

2,3-Dimethyl-6-(2,5-dimethyl-1-pyrryl)-quinoxaline: Procedure D.—Three grams (0.017 mole) of 2,3-dimethyl-6-aminoquinoxaline in 12 ml. of absolute ethanol was refluxed for four hours with 2.18 g. (0.0191 mole) of 2,5-hexanedione and 1 ml. of glacial acetic acid. The mixture was poured with rapid stirring into 50 ml. of water, cooled and filtered. The granular product after treatment with Norit was crystallized from ethanol as long, straw-colored needles melting at 161–163°. The yield was 3.2 g. (74%).

Attempted Preparation of 2-(2,5-Dimethyl-1-pyrryl)-quinoxaline.—2-Aminoquinoxaline was prepared from alloxazine in 67% over-all yield.[11] From 3.5 g. (0.0242 mole) of 2-aminoquinoxaline refluxed for two hours in 15 ml. of absolute ethanol with 3 ml. of 2,5-hexanedione, and 1 ml. of glacial acetic acid, a dark brown gum, and 2 g. of crystalline material was isolated on drowning in water. The gum could not be readily purified. The crystalline portion after several recrystallizations from ethanol–water (1:3) followed by sublimation melted at 156–157°. It was shown by mixed melting point to be recovered 2-aminoquinoxaline.

On a second attempt only a dark unmanageable gum was obtained.

Summary

Several quinoxaline derivatives have been synthesized for testing for antimalarial activity and some of them, as noted, for tuberculostatic activity also.

They are strongly fluorescent in benzene solution and one of them, 6-amino-2,3-bis-(*p*-hydroxyphenyl)-quinoxaline has the properties of an acid-base indicator at *p*H 3 to 4.

The results of the pharmacological tests will be published elsewhere.

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(10) Previously prepared by another method by Kuhn, Moller and Wendt, *Ber.*, **76**, 412 (1943), who give its melting point as 267–268°.

(11) Weijlard, Tishler and Erickson, THIS JOURNAL, **66**, 1957 (1944).