[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

1-Alkyl-1,2,3,4-tetrahydroquinoxalines[1]

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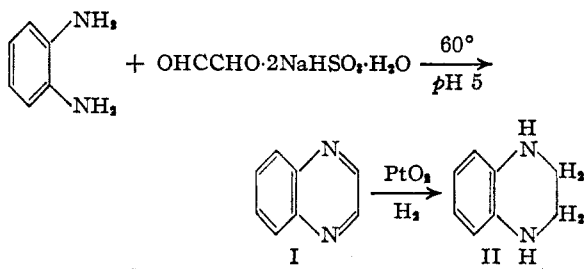
The intense, wartime search for new chemical series which might show antimalarial activity has led us to make exploratory studies in the field of 1,2,3,4-tetrahydroquinoxalines. In particular, we were interested in the preparation of 1-alkyl derivatives, and our primary objective was to devise and develop a satisfactory route for the preparation and proof of structure of these 1-alkyl derivatives.

When this research was started there were no satisfactory systematic routes to the preparation of 1-alkyl-1,2,3,4-tetrahydroquinoxalines and, indeed, the descriptions of quinoxalines[4,5,6] and their tetrahydro derivatives[7,8,9,10] left much to be desired. It was not until the latter part of this research that publications[11,12] appeared with detailed procedures for the preparation of several quinoxalines.

Merz and Ris[7] first prepared 1,2,3,4-tetrahydroquinoxaline in a one-step process from catechol and ethylenediamine. A repetition of their work revealed that the yields reported were attainable with difficulty and the final product was invariably impure. Furthermore, the necessity of carrying out sealed tube reactions at elevated temperatures was neither warranted nor desirable in view of the excellent results obtained by an alternate synthesis. The availability of sodium glyoxal bisulfite made possible the preparation of quinoxaline (I) from *o*-phenylenediamine. The hydrogenation of quinoxaline, using platinum oxide (Adams) catalyst, gave the desired tetrahydro derivative (II) in good yields. By using similar techniques we have prepared the 6-methyl-, 6-methoxy- and 6-chloro-derivatives, although the latter was isolated in small yields.



The monoalkylation of symmetrical diamines[13,14] is complicated by the competition of reactant and product for the alkylating agent. Indeed, a direct alkylation is usually not practical and, accordingly, it is necessary to block temporarily one of the reactive centers. We made many attempts to monoalkylate or monoacylate 1,2,3,4-tetrahydroquinoxaline with a number of alkyl halides, alkyl *p*-toluenesulfonates, acetic anhydride, acetyl chloride, ketene, acetamide and benzoyl chloride. The temperatures ranged from −70 to +300° and the solvents employed varied widely in polarity. In every case either the starting material or the disubstituted compound, or both, was formed, but no trace of the desired monosubstituted product could be isolated.

Moore, Boyle and Thorn[13] prepared monoalkylpiperazines and -ethylenediamines by monocarbethoxylation of the amine with ethyl chlorocarbonate at controlled *p*H, followed by alkylation and hydrolysis. Attempts to repeat this procedure with 1,2,3,4-tetrahydroquinoxaline at a *p*H of 2.5 failed. Doubtless the proximity of the dissociation constants[15] of the doubly charged and singly charged cations precluded a high ratio of singly charged cations to free base. This ratio may be increased by decreasing the *p*H, but acid hydrolysis of ethyl chlorocarbonate then seriously competes with the amine. The only products isolated were the dicarbethoxy derivative and starting material.

Meisenheimer and Wieger[9] were unsuccessful in their attempts to monoacetylate or monobenzoylate 1,2,3,4-tetrahydroquinoxaline, and reported only disubstitution products. We were able to obtain monoalkyl derivatives of 1,2,3,4-tetrahydroquinoxaline by low temperature acylation with benzenesulfonyl chloride to give the

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(5) Gabriel and Sönn, *ibid.*, **40**, 4850–4860 (1907).

(6) Bergstrom and Ogg, THIS JOURNAL, **53**, 245–251, 1846–1853 (1931).

(7) Merz and Ris, *Ber.*, **20**, 1190 (1887).

(8) (a) Hinsberg, *Ann.*, **237**, 333–339 (1887); (b) Hinsberg and Strupler, *ibid.*, **287**, 223–226 (1895).

(9) Meisenheimer and Wieger, *J. prakt. Chem.*, [2] **102**, 49 (1921).

(10) Kränzlein, Eckert and Besler, German Patent 495,101; *Frdl.*, **16**, 665 (1927).

(11) Gawron and Spoerri, THIS JOURNAL, **67**, 514–516 (1945).

(12) Mizzoni and Spoerri, *ibid.*, **67**, 1652–1654 (1945).

(13) Moore, Boyle and Thorn, *J. Chem. Soc.*, 39–51 (1929).

(14) King and McMillan, THIS JOURNAL, **68**, 1774 (1946), quote a literature review by Aspinall, *ibid.*, **63**, 852 (1941), on monoalkylethylenediamines but neither mentioned the successful work of Moore, Boyle and Thorn, ref. 13.

(15) Potentiometric titration of the acid in a nitrogen atmosphere yielded two inflection points, one at a *p*H of 3.38, and the other at a *p*H of 8.55 (Fig. 1). The observed *pK*'s were 2.10 and 4.97, respectively. When the corrections for activity coefficients were applied according to Bjerrum, *Z. Elektrochem.*, **24**, 321–328 (1918), and Kühn and Zümstein, *Ber.*, **59**, 488 (1926), the *pK*'s became 1.17 and 4.84, respectively. The corresponding thermodynamic dissociation constants are $K_1 = 6.8 \times 10^{-3}$ and $K_2 = 1.4 \times 10^{-5}$.

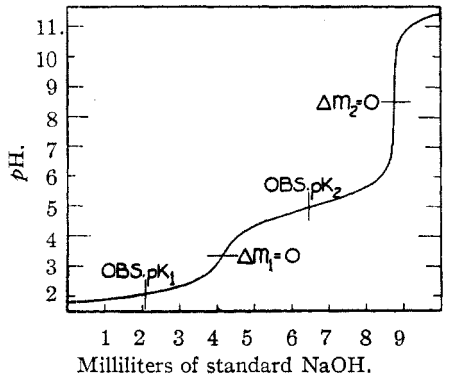
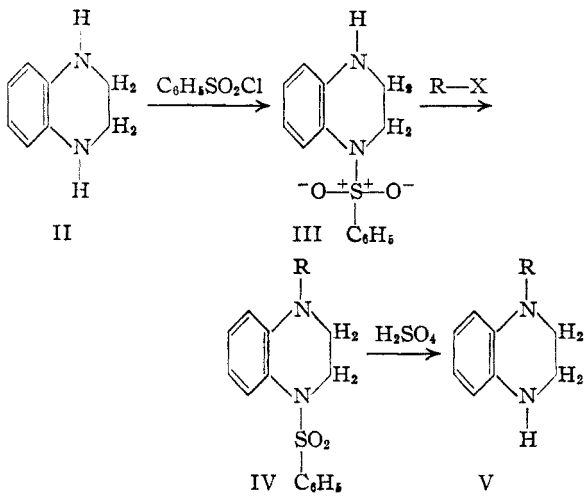


Fig. 1.—Potentiometric titration of 1,2,3,4-tetrahydroquinoxaline dihydrochloride.

1,2,3,4-tetrahydro-1-phenylsulfonylquinoxaline (III), alkylating the monophenylsulfonyl derivative to 1-alkyl-1,2,3,4-tetrahydro-4-phenylsulfonylquinoxaline (IV), followed by hydrolysis which yielded 1-alkyl-1,2,3,4-tetrahydroquinoxaline (V).



Examination of the 1,2,3,4-tetrahydro-1-phenylsulfonylquinoxaline molecule (III) reveals the fact that the sulfur atom, containing essentially a double positive charge, is capable of attracting electrons strongly, and this attraction is transmitted through the heterocyclic ring to the unsubstituted nitrogen. The decrease in electron density around this nitrogen reduces the basicity to such an extent that it is neutral, as illustrated by its insolubility in 25% hydrochloric acid. This effect is limited only to the extent that if the necessary activation energy is supplied by a temperature rise, the molecule is capable of reacting again to form the 1,4-bis-phenylsulfonyl compound.[19] Furthermore, the unreactivity of the monosubstituted compound is evidenced by the presence of a large (200%) excess of acylating agent during its formation, as well as the slow rate of reaction with low-molecular-weight alkyl iodides. Thus it may be inferred that the presence of powerful electron-attracting groups on one nitrogen atom permits the substitution of 1,2,3,4-tetrahydroquinoxaline to be effectively controlled.

Experimental

o-**Phenylenediamines.**—*o*-Phenylenediamine and 3,4-diaminochlorobenzene were obtained from Eastman Kodak Co.

3,4-Toluenediamine was conveniently prepared by hydrogenating a mixture of 152.1 g. (1.00 mole) of 4-amino-3-nitrotoluene (E. K. Co.), 10 cc. of moist Raney nickel catalyst, and 1500 cc. of purified benzene under 50–80 pounds pressure for four hours. The suspension was transferred to a suitable flask, and the solvent was removed under reduced pressure at 40–50°. Care was taken to exclude air in order to minimize undue oxidation. Distillation of the dried product under reduced pressure gave a colorless oil which solidified immediately. The yield of material, b. p. 92° (1 mm.), m. p. 89–89.5°, was 105.8 g. (86.5%).

The preparation of 3,4-diaminoanisole from 4-amino-3-nitroanisole[16] was effected in a parallel manner. From 168.2 g. (1.00 mole) of the nitroamine there was obtained 118.5 g. (86%) of a pale yellow oil boiling at 158° (7 mm.).

Quinoxaline (I).—To a solution of 108.1 g. (1.00 mole) of *o*-phenylenediamine in 500 cc. of 2 *M* acetic acid was added 250 cc. of 4 *M* sodium acetate solution. The mixture was heated to 60° and poured rapidly into a solution of 298.4 g. (1.05 moles) of sodium glyoxal bisulfite[17] in 1500 cc. of water previously heated to 60°. The resulting dark solution was stirred for one hour. It was then cooled in an ice-bath until the temperature had dropped below 10°, stirred, and neutralized with 120 g. of sodium hydroxide pellets. After the sodium hydroxide had dissolved, 500 g. of U. S. P. potassium carbonate was added. During the addition of alkali, the solution turned red and a black oil separated out. Most of the oily amine was removed by extraction with one 500-cc. portion of benzene. The clear red aqueous solution was transferred to a liquid–liquid extractor and extracted continuously with 300 cc. of benzene for eight hours. The organic solutions were combined, evaporated to one-half the volume on the steam-bath, and treated with 3 g. of Norit and 10 g. of anhydrous magnesium sulfate. The remainder of the benzene was removed on the steam-bath under slightly reduced pressure. The dark oily residue was vacuum distilled, yielding a colorless distillate that solidified in the receiving flask to form long, colorless to pale-yellow needles.

The 6-methyl-, 6-methoxy- and 6-chloroquinoxalines were prepared in the same manner from the corresponding

TABLE I

QUINOXALINES PREPARED FROM *o*-DIAMINES AND GLYOXAL BISULFITE

Substituent	Yield, %	M. p., °C.	B. p., °C.	p (mm.)
Unsubstituted[a]	85	30.5–31.5	44–45	1
			92–93	8
			96	10
			102.5	12.5
			104	15
			124	31
			225	760
6-Chloro-[b]	79	63.8–64.3	117–119	10
6-Methyl-[3a]	86	Below 0	86	1
			141.5	29
6-Methoxy-[c]	88	60	128	7

[a] McIlwain, *J. Chem. Soc.*, 322 (1943). [b] Chattaway and Humphrey, *ibid.*, 645 (1929). [c] Meister, Lucius and Brüning, German Patent, 38,322; *Frdl.*, 1, 220–221 (1885).

(16) "Organic Syntheses," **25**, 78 (1945).

(17) Carbide and Carbon Chemicals Corp.

TABLE II

1,2,3,4-TETRAHYDROQUINOXALINES OBTAINED BY REDUCTION OF QUINOXALINES

Substituent	Yield, %	Formula	M. p., °C.	Analyses, % Calcd.	Found
Unsubstituted[7,8]	92	$C_8H_{10}N_2$	98.5–99.0	C 71.61 H 7.51	C 71.43 H 7.56
6-Chloro-	..	$C_8H_9N_2Cl$	113–114	N 17.02	N 16.98
6-Methyl-[10]	92	$C_9H_{12}N_2$	104.5–105.5		
6-Methoxy-	95	$C_9H_{12}ON_2$	80.5–81.0	N 17.06	N 17.21

diamines. The properties and average yields of the four quinoxalines are listed in Table I.

1,2,3,4-Tetrahydroquinoxaline (II).—A solution of 130.1 g. (1.00 moles) of quinoxaline in 1200 cc. of C. P. benzene was shaken with 10 cc. of moist Raney nickel catalyst to remove catalyst poisons. The solution was filtered directly into a hydrogenation bottle and 1.5 g. of Adams catalyst (PtO_2) was added. The mixture was hydrogenated at 50–80 pounds pressure until absorption had ceased, and then for an additional three hours. The suspension was warmed on the steam-bath to dissolve the crystals, then filtered under suction to remove the catalyst. The clear straw-yellow solution was now heated to reflux on the steam-bath and an equal volume of purified petroleum ether (30–60°) added at the boiling point. After cooling overnight in ice, the white shining plates were filtered, washed with petroleum ether, and dried in an evacuated desiccator over paraffin chips. Additional material could be obtained from the mother liquor.

The **monohydrochloride** was prepared by dissolving equimolar amounts of the amine and 5 *N* hydrochloric acid in absolute methanol while stirring in a nitrogen atmosphere. The solution was cooled to 0° and 500 cc. of ice-cold anhydrous ether added. The white crystalline hydrochloride, after filtering, washing with cold ether, and drying *in vacuo*, melted at 167–169°.

Anal. Calcd. for $C_8H_{10}N_2 \cdot HCl$: neut. equiv., 170.7. Found: neut. equiv., 171.0.

The 6-chloro-, 6-methyl- and 6-methoxytetrahydroquinoxalines were prepared similarly, except that great difficulty[18] was experienced in the hydrogenation of 6-chloroquinoxaline. Only a very small amount of the tetrahydro compound was isolated in the pure state. In Table II are listed the average yields and physical properties of the 6-substituted-1,2,3,4-tetrahydroquinoxalines.

1,2,3,4-Tetrahydro-1-phenylsulfonylquinoxaline (III).—In a three-liter, three-neck flask fitted with an efficient stirrer, a thermometer and a 200-cc. dropping funnel was placed 40.3 g. (0.30 mole) of finely powdered 1,2,3,4-tetrahydroquinoxaline and 350 cc. of 20% sodium hydroxide solution. The flask was immersed to the neck in a bucket of running water kept below 20°. Benzenesulfonyl chloride, 115 cc. (0.90 mole), was added dropwise at a maximum rate of 60 drops per minute while the suspension was kept vigorously stirred[19]; the addition taking between two and one-half and three hours. After stirring for an additional hour, the suspension was diluted with one liter of water and filtered by suction. The precipitate was suspended in one liter of water, filtered and dried. It was transferred to a one-liter flask, dissolved in 600 cc. of boiling ethanol (95%), treated with 5 cc. of concentrated ammonia water and 5 g. of Norit, filtered by suction through a steam-jacketed funnel, and allowed to cool to room temperature. The crystalline mass was filtered, washed with 100 cc. of ethanol, and dried in an evacuated desiccator over calcium chloride for forty-eight hours. The yield of yellow product melting at 138–139° was 87% (Table III).

(18) Baltzly and Phillips, THIS JOURNAL, **68**, 261 (1946).

(19) Experimentally it has been found that with efficient stirring, disubstitution is non-existent below 30°, appreciable between 40 and 70°, and takes place exclusively above 80°. Without this precaution the product is contaminated with bis-(phenylsulfonyl)-tetrahydroquinoxaline, even at 0°. Apparently the local concentrations of acid chloride give rise to excessive heating which leads to disubstitution.

The phenylsulfonation may be run in pyridine instead of sodium hydroxide, using only a 10% excess of acid chloride. However, the solution was scarlet in color and the product retained a red tinge in spite of several recrystallizations.

1,2,3,4-Tetrahydro-1-alkyl-4-phenylsulfonylquinoxalines (IV).—A mixture of 0.10 mole of 1,2,3,4-tetrahydro-1-phenylsulfonylquinoxaline, 0.40 mole of alkyl halide (ethyl-, *n*-propyl-, *n*-butyl iodide or benzyl chloride), 0.20 mole of anhydrous sodium carbonate, and 100 cc. of 95% ethanol was placed in a 250-cc. round-bottom flask fitted with a reflux condenser. The top of the condenser was arranged to permit alternate evacuating and filling with nitrogen. The system was then filled with nitrogen and finally maintained under a positive pressure of about 10 cm. of mercury. The contents of the flask were refluxed gently for forty-eight hours. At the end of this time the supernatant liquid was decanted from the inorganic salts and the latter extracted with three 50-cc. portions of boiling ethanol. The alcoholic solutions were combined, evaporated to 100 cc., decolorized with 2 cc. of ammonia water and 1 g. of Norit, filtered hot under suction, and cooled in ice. The colorless needles were filtered, washed with a little cold ethanol, and dried in an evacuated desiccator over calcium chloride, yield 88–92%.

To prepare the corresponding methyl compound, a two-fold excess of methyl iodide was used and the mixture was allowed to reflux for five hours. In this case the alcohol was removed and the solid material extracted with six 25-cc. portions of benzene. The benzene solution was evaporated to dryness and the colorless methyl derivative obtained in 65% yield by crystallization from ethanol. The residue from the benzene extraction was treated with just enough 10% hydrochloric acid to decompose the residual sodium carbonate and dissolve inorganic salts. After cooling, the quaternary salt was filtered and recrystallized from a large volume of ethanol. The yield of methiodide, deposited as fine white needles, was 25%.

The *i*-propyl derivative was prepared by refluxing a mixture of 1 mole of 1,2,3,4-tetrahydro-1-phenylsulfonylquinoxaline, ten moles of *i*-propyl iodide, 20 cc. of *i*-propyl alcohol, and 1 mole of anhydrous sodium carbonate for five to six days. When the solution was treated as above, an 85% yield of colorless needles was obtained.

The physical properties of the 1,2,3,4-tetrahydro-1-substituted-4-phenylsulfonylquinoxalines are recorded in Table III.

TABLE III

PROPERTIES OF 1-SUBSTITUTED-1,2,3,4-TETRAHYDRO-4-PHENYLSULFONYLQUINOXALINES

Substituent	M. p., °C.	Formula	Analyses, % N Calcd.	N Found
Unsubstituted	138–139	$C_{14}H_{14}O_2N_2S$	10.21[a]	10.25
Methyl	88–89	$C_{15}H_{16}O_2N_2S$	9.72	9.67
Methyl[b]	168–169	$C_{15}H_{16}O_2N_2S \cdot CH_3I$	6.51	6.33
Ethyl	118.5–119.5	$C_{16}H_{18}O_2N_2S$	9.27	9.30
n-Propyl	119.5–120.0	$C_{17}H_{20}O_2N_2S$	8.86	8.78
i-Propyl	142.5–143.5	$C_{17}H_{20}O_2N_2S$	8.86	8.71
n-Butyl	95.0–95.5	$C_{18}H_{22}O_2B_2S$	8.48	8.51
Benzyl	134–135	$C_{21}H_{20}O_2N_2S$	7.69	7.70
Acetyl	111.5–112.0	$C_{16}H_{16}O_3N_2S$	8.86	8.93
Phenylsulfonyl	180–181[c]			

[a] Calcd.: C, 61.29; H, 5.14. Found: C, 61.22; H, 5.10. [b] Methiodide. [c] Hinsberg and Strupler[8b] report the melting point as 180°.

TABLE IV

THE 1-ALKYL-1,2,3,4-TETRAHYDROQUINOXALINES

Substituent	B. p., °C.	p (mm.)	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl	108.5	2	76	$C_9H_{12}N_2$	72.93	8.16	73.10	8.08
Ethyl[a]	88–90	1	59	$C_{10}H_{14}N_2$	74.03	8.70	74.16	8.69
n-Propyl	113.5	1.5	66	$C_{11}H_{16}N_2$	74.95	9.15	74.72	8.98
i-Propyl[b]	107.5	1.5	68	$C_{11}H_{16}N_2$	74.95	9.15	74.56	9.35
n-Butyl[c]	107.5	1	81	$C_{12}H_{18}N_2$	75.74	9.54	75.75	9.56
Benzyl[d]	178–179	1.5	66	$C_{15}H_{16}N_2$	80.32	7.19	80.23	7.22

[a] The *oxalate* melted at 130–131°. *Anal.* Calcd. for $C_{12}H_{16}O_4N_2$: N, 11.11. Found: N, 10.70. [b] Hygroscopic. [c] The *oxalate* melted at 142.5–143.5°. *Anal.* Calcd. for $C_{14}H_{20}O_4N_2$: C, 59.98; H, 7.19. Found: C, 59.81; H, 7.15. [d] M. p. 50.5–52.5°. N calcd.: 12.49; N found: 12.37.

TABLE V

DERIVATIVES OF 1,2,3,4-TETRAHYDROQUINOXALINE

Substituent	M. p., °C.	Formula	Analyses, % N Calcd.	N Found
1-Benzoyl-4-methyl	109–110	$C_{16}H_{16}ON_2$	11.11	11.00
1-Benzoyl-4-ethyl	123–124	$C_{17}H_{18}ON_2$	10.52	10.55
1-Benzoyl-4-*n*-propyl	88–89	$C_{18}H_{20}ON_2$	9.99	9.79
1-Benzoyl-4-*i*-propyl	114–115	$C_{18}H_{20}ON_2$	9.99	9.81
1-Benzoyl-4-*n*-butyl	87–88	$C_{19}H_{22}ON_2$	9.52[a]	9.43
1-Benzoyl-4-benzyl	123.3–123.8	$C_{22}H_{20}ON_2$	8.53	8.50
1,4-Dibenzoyl	206–207[b]			
1,4-Dibenzoyl-6-methyl	141.5–142.0	$C_{23}H_{20}O_2N_2$	7.86	7.80
1,4-Dibenzoyl-6-methoxy	138.5–138.8	$C_{23}H_{20}O_3N_2$	[c]	
1,4-Dibenzoyl-6-chloro	168.5–169.0	$C_{22}H_{17}O_2N_2Cl$	7.44	7.27
1,4-Diacetyl	147.0–147.5[d]			
1,4-Diacetyl-6-methyl	105.2–106.2	$C_{13}H_{16}O_2N_2$	12.06	12.00
1,4-Dicarbethoxy	42–44	$C_{14}H_{18}O_4N_2$	10.06	9.78
1,4-Dicarbethoxy trihydrate	Oil	$C_{14}H_{18}O_4N_2 \cdot 3H_2O$	[e]	
1,4-bis-(Phenylsulfonyl)-6-methyl	124–125	$C_{21}H_{20}O_4N_2S_2$	6.54	6.40

[a] Calcd.: C, 77.52; H, 7.53. Found: C, 77.45; H, 7.57. [b] Meisenheimer and Wieger[9] report a m. p. of 201–202°. [c] Calcd.: C, 74.17; H, 5.41. Found: C, 74.19; H, 5.39. [d] Ris[20] reports a m. p. of 144°. [e] Calcd.: C, 50.59; H, 7.28. Found: C, 50.62; H, 7.28.

1-Alkyl-1,2,3,4-tetrahydroquinoxalines (V).—The hydrolysis of 1-alkyl-1,2,3,4-tetrahydro-4-phenylsulfonylquinoxaline with concentrated sulfuric acid was carried out according to the procedure of Gawron and Spoerri,[11] with the following modifications: After the strongly acid solution had been made alkaline, enough water was added at 40° to dissolve precipitated salts. The mixture was transferred to a liquid–liquid extractor and extracted with 100 cc. of benzene for eighteen hours. The benzene extract was treated with Norit and the solvent removed on the steam-bath. The residual dark oil was distilled at reduced pressure and after a small forerun the 1-alkyl-1,2,3,4-tetrahydroquinoxaline distilled as a pale-yellow, non-viscous oil. It was moderately sensitive to air at room temperature.

In Table IV are listed the yields and physical constants of these 1-alkyl-1,2,3,4-tetrahydroquinoxalines. The 1-alkyl-1,2,3,4-tetrahydroquinoxalines were treated with benzenesulfonyl chloride and alkali in the usual manner to yield crystalline products identical in m. p. and mixed m. p. with those made by alkylation of the 1,2,3,4-tetrahydro-1-phenylsulfonylquinoxaline.

Derivatives.—The **benzoyl** derivatives were made by shaking a well cooled mixture of 2 g. of the amine with a three-fold excess of benzoyl chloride in 100 cc. of 10% sodium hydroxide solution. It was warmed on the steam-bath to hydrolyze unreacted acid chloride and cooled to room temperature. The solid material was decolorized with Norit and crystallized twice from ethanol.

The **oxalates**, made by adding equivalent quantities of the amine and anhydrous oxalic acid to absolute ethanol, were very unstable salts and turned dark red within a few days.

The **picrates** were prepared by adding the amine to an excess of a saturated solution of picric acid in alcohol. They were recrystallized twice from ethanol and formed large yellow to orange needles.

The **acetyl** derivatives were made by heating the amine with a large excess of acetic anhydride on the steam-bath for fifteen minutes. The solution was cooled, made alkaline, and extracted with ether; the ether extract now

TABLE VI

1,2,3,4-TETRAHYDROQUINOXALINE PICRATES

Substituent	M. p., °C.[a]	Formula	Analyses, % N Calcd.	N Found
Unsubstituted	128.5–129.5[b]			
1-Methyl	123.0–126.5	$C_{15}H_{15}O_7N_5$	18.56	18.45
1-Ethyl	111.5–112.0	$C_{22}H_{20}O_{14}N_8$[c]	18.06	18.19
1-*n*-Propyl	135–136	$C_{17}H_{19}O_7N_5$	17.28[d]	17.31
1-*i*-Propyl	131–132	$C_{17}H_{19}O_7N_5$	17.28	17.28
1-*n*-Butyl	130.0–131.5	$C_{18}H_{21}O_7N_5$	16.70[e]	16.68
1-Benzyl	150.0–151.5	$C_{21}H_{19}O_7N_5$	15.45	15.59
6-Methoxy	134–135	$C_{15}H_{15}O_8N_5$	17.81	17.68
6-Methyl	148.0–148.5	$C_{15}H_{15}O_7N_5$	18.56	18.59

[a] All melt with decomposition. [b] Merz and Ris[7] report a triamine dipicrate melting at >120°. [c] Dipicrate. [d] Calcd.: C, 50.37; H, 4.72. Found: C, 50.38; H, 4.60. [e] Calcd.: C, 51.55; H, 5.04. Found: C, 51.43; H, 5.12.

(20) Ris, *Ber.*, **21**, 381 (1888).

evaporated to dryness, and the acetyl derivative was crystallized twice from ethanol.

Summary

1. A practical procedure has been developed for the monoalkylation of 1,2,3,4-tetrahydroquinoxaline. This involves blocking one nitrogen with benzenesulfonyl chloride and alkylating at the other nitrogen followed by hydrolytic removal of benzenesulfonic acid. Simple monoalkyl derivatives may thereby be obtained in over-all yields of 42–58% from the parent quinoxaline.

2. Several series, comprising thirty compounds not previously described, have been prepared.

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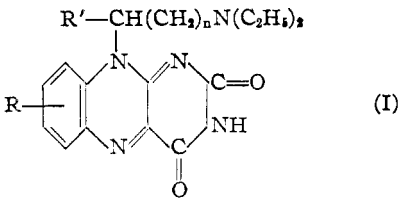
[FROM THE RESEARCH LABORATORIES OF ENDO PRODUCTS, INC., AND THE POLYTECHNIC INSTITUTE OF BROOKLYN]

9-(Dialkylaminoalkyl)-isoalloxazines

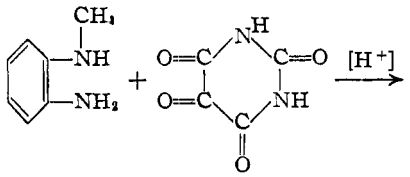
BY FRANK KIPNIS,[1] NATHAN WEINER AND PAUL E. SPOERRI

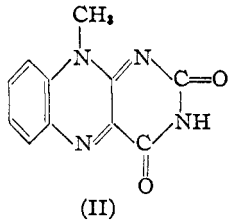
To determine whether appropriately substituted isoalloxazines



(I)

would show significant pharmacological properties a series of these compounds was prepared, where R = H, OCH_3, di-CH_3, Cl, R′ = H or CH_3, n = 2 or 3. 9-Substituted isoalloxazines have been synthesized by Kühling[2] by condensing N-alkyl-*o*-phenylenediamines with alloxan in aqueous or alcoholic-acid medium, according to the scheme





(II)

Later studies by Kuhn[3,4] indicated that much better yields could be achieved by performing the reaction in acetic acid, using boric acid as catalyst.

In the present work, both techniques were studied; the later method gave much more acceptable results, in regard to yield and ease of purification of final products. When aqueous hydrochloric acid was used in the attempt to prepare the series of compounds carrying a 9-(4′-diethylamino-1′-methylbutyl) substituent, extremely high-melting (above 350°), non-flavin materials were isolated; these were not further characterized. However, flavins resulted when Kuhn's method was applied.

These new compounds are yellow to orange-yellow in color, the intensity depending upon the particle size. Like riboflavin, they are quite light-sensitive, especially in solution; similar to the natural pigment, also, these flavins give yellow aqueous solutions with an intense green fluorescence which is quenched by acid or alkali; unlike riboflavin, however, the 9-(dialkylaminoalkyl)-isoalloxazines are extremely soluble in water and most organic solvents, a property which seriously complicates their isolation and purification.

Concentrated hydrochloric acid dissolves the new flavins without production of a red color, indicating that uncyclized material is absent.[5] Addition of a few zinc granules to this acid solution causes the development of a deep-red color, which seems to be a rather highly specific test for isoalloxazines.[6] Shaking the red solution with air regenerates the yellow flavin; if the reduction of the red intermediate[7] is carried to completion by the addition of more zinc, a yellow solution results, presumably by formation of a polyhydroflavin.

The N-(dialkylamino alkyl)-*o*-phenylenediamines required for the flavin synthesis were prepared by reduction of the corresponding *o*-nitranilines previously described.[8] Catalytic hydrogenation in the presence of Raney nickel was used mainly to characterize the new amines (Table I). For routine preparative purposes, the nitranilines were reduced with zinc powder in glacial acetic acid, and after removal of the excess zinc by filtration, immediately brought into reaction with alloxan.

(1) Abstracted from a thesis submitted by Frank Kipnis in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn, June, 1944. Present address: American Home Foods, Morris Plains, New Jersey.

(2) Kühling, *Ber.*, **24**, 2363 (1891).

(3) Kuhn and Weygand, *Ber.*, **68**, 1282 (1932).

(4) Kuhn, *Angew. Chem.*, **49**, 6 (1936).

(5) Tishler and Weilman, U. S. Patent 2,261,608, Nov. 4, 1941.

(6) Kuhn and Wagner-Jauregg, *Ber.*, **67**, 361 (1934).

(7) The intermediate red coloration may be indicative of a semiquinone.

(8) Kipnis, Weiner and Spoerri, THIS JOURNAL, **66**, 1446 (1944).