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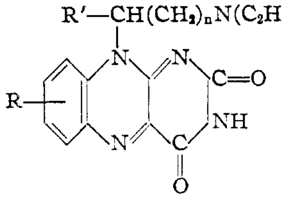
[FROM THE RESEARCH LABORATORIES OF ENDO PRODUCTS, INC., AND THE POLYTECHNIC INSTITUTE OF BROOKLYN]

9-(Dialkylaminoalkyl)-isoalloxazines

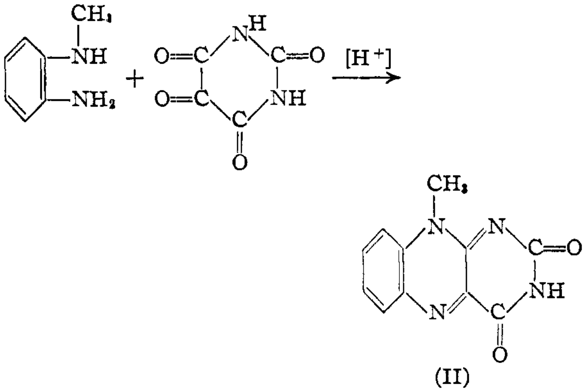
BY FRANK KIPNIS,[1] NATHAN WEINER AND PAUL E. SPOERRI

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.

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(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 Wellman, U. S. Patent 2,261,608, Nov. 4, 1941.

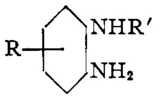
(6) Kuhn and Wagner-Jauregg, *Ber.*, **67**, 361 (1934).

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

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

TABLE I

SUBSTITUTED *o*-PHENYLENEDIAMINES



R	$R' = -(CH_2)_3N(C_2H_5)_2$			$R' = -(\overset{CH_3}{\overset{\vert}{C}}H_2)_3N(C_2H_5)_2$		
	B. p., °C.	mm.	Yield, %	B. p., °C.	mm.	Yield, %
H	168–170	3	86	162–165	2	96
6-Methyl	172	2.5	81	172–175	2.5	67
5-Methyl	170	3	84	168–172	2.5	85
4,6-Dimethyl	178–180	2	64	190–195	2.5	68
4,5-Dimethyl	...	...	..	190–192	3	80
5-Methoxy	198	4	83	...	...	..
5-Chloro	187–189	2.5	80	195	2.5	84

Experimental

N-(Dialkylaminoalkyl)-*o*-phenylenediamines

(a) **Reduction by Hydrogen with Raney Nickel.**—Five-hundredths of a mole of the *o*-(dialkylaminoalkyl)-aminonitrobenzene was dissolved in 100 ml. of absolute ethanol in the pressure bottle of a Parr hydrogenation apparatus, and 10 g. of Raney nickel catalyst[9] was added. The assembly was warmed until the internal temperature rose to 70°, at which point heating was discontinued and hydrogenation was initiated at 65 p. s. i. (gage). When the calculated volume of hydrogen was absorbed, the catalyst was removed by suction filtration through a thin bed of dicalite, and the solvent removed from the filtrate by distillation at reduced pressure under nitrogen. The solvent-free residue was fractionated *in vacuo* under nitrogen from an all-glass apparatus. The substituted *o*-phenylenediamines were colorless oils which discolored rapidly on exposure to air.

(b) **Reduction with Zinc in Glacial Acetic Acid.**—Five-hundredths of a mole of the nitroaniline was dissolved in 250 ml. of glacial acetic acid; 15 g. of zinc dust was added in small portions to the vigorously stirred solution, the temperature being kept below 35°, until it turned colorless. It was then filtered rapidly by suction through a layer of dicalite, the residue washed thoroughly with 250 ml. of glacial acetic acid, the filtrate and washings combined, and used immediately in the following operation.

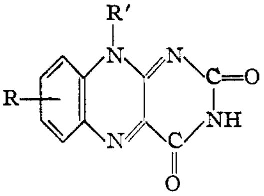
9-(Dialkylaminoalkyl)-isoalloxazines

To the acetic acid solution of the substituted *o*-phenylenediamine was added 15 g. of powdered boric acid and 0.055 mole of alloxan monohydrate. The mixture was stirred vigorously and heated on the steam-bath for three hours.[10] The acetic acid then was removed by distillation from the steam-bath under reduced pressure. Two hundred ml. of water was added to the residue with shaking. After solution was complete, cold 28% ammonia water was added until the mixture was distinctly alkaline. The mixture was transferred to a separatory funnel and extracted 15 times with 100-ml. portions of chloroform.[11] The solvent was distilled from the steam-bath, the last traces being removed under reduced pressure. To the cooled residue was added 300 ml. of anhydrous diethyl ether. Upon scratching the inside of the flask with a glass rod, the oil solidified, and the resulting powder was filtered by suction. The precipitate was washed thoroughly with anhydrous ether, dried and weighed (as crude product).

The 9-(3′-diethylaminopropyl)-isoalloxazines were most advantageously recrystallized from chlorobenzene; those with a 4′-diethylamino-1′-methylbutyl substituent were crystallized from *n*-dibutyl ether. The properties of these isoalloxazines are summarized in Table II.

TABLE II

ISOALLOXAZINES



R	M. p., °C.[a]	Crude yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
				$R' = -CH_2-CH_2-CH_2-N(C_2H_5)_2$					
H	229–230	77	$C_{17}H_{21}N_5O_2$	62.35	6.47	21.41	61.66	6.28	21.10
8-CH_3	218–219	62	$C_{18}H_{23}N_5O_2$	63.32	6.79	20.52	62.56	6.79	20.07
7-CH_3	219	42	$C_{18}H_{23}N_5O_2$	63.32	6.79	20.52	62.60	6.45	20.35
6,8-diCH_3	199–201	50	$C_{19}H_{25}N_5O_2$	64.20	7.09	19.71	64.52	7.52	18.98
7-Cl	253	40	$C_{17}H_{20}ClN_5O_2$	56.41	5.57	19.37	55.92	5.40	18.15
				$R' = -\overset{CH_3}{\overset{\vert}{C}}H-(CH_2)_3N(C_2H_5)_2$					
7-CH_3	182–183	82	$C_{20}H_{29}N_5O_3$[b]	61.99	7.55	18.05	62.00	7.65	18.93
6,8-diCH_3	158–163	20	$C_{21}H_{31}N_5O_3$[b]	62.82	7.78	17.44	62.22	7.29	17.31
6,7-diCH_3	185–186	68	$C_{21}H_{31}N_5O_3$[b]	62.82	7.78	17.44	63.96	7.59	17.79
7-OCH_3	165–166	40	$C_{20}H_{29}N_5O_4$[b]	59.53	7.25	17.36	59.42	7.05	17.39
7-Cl	235	50	$C_{19}H_{24}ClN_5O_2$	58.53	6.20	17.94	57.08	5.85	17.37

[a] All m. p.'s corrected. All compounds decompose on melting. [b] Hydrated (or uncyclized).

Summary

1. Twelve new N-(dialkylaminoalkyl)-*o*-phenylenediamines have been prepared by reduction of the corresponding *o*-nitranilines.

2. From these triamines, by condensation with alloxan in acid medium, ten 9-(dialkylaminoalkyl)-isoalloxazines were synthesized.

RECEIVED[12] JUNE 3, 1946

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[9] Mozingo, "Organic Synthesis," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

(10) Protection from light is desirable during this and subsequent operations.

(11) It is impossible to extract riboflavin from an alkaline solution into organic solvents. Apparently the increased basicity of the new flavins increases their solubility in organic solvents.

(12) Original manuscript received September 21, 1944.