[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Preparation of Some 9-Diethylaminoalkylphenazines[1]

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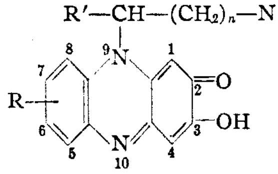
Among the compounds prepared in this Laboratory and tested for activity against malaria parasites were a number of phenazine derivatives bearing diethylaminoalkyl side-chains in the nine position. A study of the compounds of this type seemed appropriate not only because of their structural resemblance to known antimalarials but also because of the physiological importance of other related phenazine derivatives.[2]

Six members of the 2-keto-3-hydroxy-6 or 7-substituted-9-diethylaminoalkylphenazine series, Table I, were obtained in eighty to ninety per cent. yields by the condensation of 2,5-dihydroxyquinone[3] with the appropriate *o*-amino-N-diethylaminoalkylanilines in dilute hydrochloric acid solution.[4] The products were isolated either as the dihydrochlorides, which were buff to orange-red crystalline powders soluble in water, or as the free bases soluble in both water and organic solvents.

TABLE I

2-KETO-3-HYDROXY-9-DIETHYLAMINOALKYLPHENAZINES,



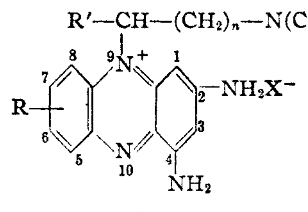
$R'-CH-(CH_2)_n-N(C_2H_5)_2$

R	R'	n	Derivative isolated	M. p., °C.	Nitrogen analyses, % Calcd.	Found
H	CH_3	3	$\cdot 2HCl\cdot H_2O$	210–211 (dec.)	9.47	9.35
			Free base	96–98		
6-Cl	CH_3	3	Free base	75	10.83	10.84
6-Cl	H	2	$\cdot 2HCl$	259–260 (dec.)	9.72	10.00
6-CH_3	H	2	$\cdot 2HCl$	253–254 (dec.)	10.20	10.16
6-OCH_3	H	2	$\cdot 2HCl$	262–263 (dec.)	9.80	9.85
7-OCH_3	H	2	$\cdot 2HCl\cdot H_2O$	206–208 (dec.)	9.42	9.38

Four compounds of the type shown in Table II were prepared by the condensation of 3,5-diamino-*o*-benzoquinone[5] with the *o*-amino-N-diethylaminoalkylanilines in glacial acetic acid solution. Yields ranged from twenty to forty per cent. The phenazonium hydroxides were ruby-red crystalline solids. The chlorides were dark green solids.

TABLE II

2,4-DIAMINO-9-DIETHYLAMINOALKYLPHENAZINES,



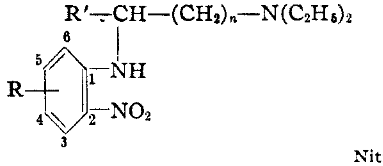
$R'-CH-(CH_2)_n-N(C_2H_5)_2$

R	R'	n	Derivative isolated (X^-)	M. p., °C.	Nitrogen analyses, % Calcd.	Found
H	CH_3	3	Cl^- $\cdot 2HCl$	171–173	15.20	15.45
6-Cl	CH_3	3	Cl^- $\cdot 2HCl$	206–208	14.15	13.94
6-OCH_3	H	2	OH^-	133–135	18.88	18.95
6-CH_3	H	2	OH^-	148–150	19.70	19.63

Of the six *o*-amino-N-diethylaminoalkylanilines used in this study only one, 2-amino-4-methoxy-N-(3-diethylaminopropyl)-aniline, appears to have been previously described.[6] The synthesis of these compounds involved two steps. Fifty to ninety per cent. yields of the *o*-nitroanilines, Table III, resulted upon heating the *o*-halogenated nitrobenzenes with 3-diethylaminopropylamine[7] or 4-diethylamino-1-methylbutylamine. Hydrogenation of the nitro compounds over Adams platinum catalyst gave the desired diamines, Table IV, which were isolated by distillation and obtained as light colored viscous liquids. Like other *o*-phenylenediamines they quickly darkened upon exposure to the air.

TABLE III

o-NITRO-N-DIETHYLAMINOALKYLANILINES,



$R'-CH-(CH_2)_n-N(C_2H_5)_2$

R	R'	n	Yield, %	B. p., °C.	Nitrogen analyses, % Calcd.	Found
H	CH_3	3[a]	79	....	...	...
4-Cl	CH_3	3	58	195–200 (2 mm.)	13.39	13.42
4-Cl	H	2	53	188–192 (2 mm.)	14.71	14.98
4-CH_3	H	2	69	180–185 (2 mm.)	15.84	16.00
4-OCH_3	H	2[b]	..	....	...	...
5-OCH_3	H	2[a,c]	93	....	...	...

[a] These compounds, prepared by a different method, have been previously described; see reference (8). [b] Previously described; see reference (6). [c] Isolated as the hydrochloride, difficultly soluble in water; m. p. 200–200.5°. *Anal.* Calcd. for $C_{14}H_{23}O_3N_3$: Cl, 11.16. Found: Cl, 11.10.

Experimental

o-Nitro- and o-Amino-N-diethylaminoalkylanilines (Tables III and IV).—The following example will illustrate the method. A mixture of 32 g. (0.2 mole) of *o*-chloronitrobenzene and 125 g. (0.8 mole) of 1-diethylamino-

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[1] Presented at the 109th meeting of the American Chemical Society, Division of Medicinal Chemistry, April 10, 1946.

[2] See Dickens, *Biochem. J.*, **30**, 1233 (1936); Kogl and Tonnis, *Ann.*, **497**, 265 (1932); Schoenthal, *Brit. J. Exptl. Path.*, **22**, 137 (1941); McIlwain, *J. Chem. Soc.*, 322 (1943).

[3] Jones and Shonle, THIS JOURNAL, **67**, 1034 (1945).

[4] For similar condensations see Kehrmann, *Ann.*, **290**, 301 (1896).

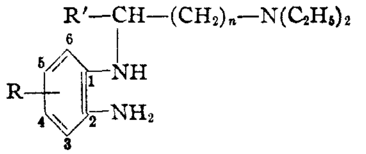
[5] Kehrmann and Poehl, *Helv. Chim. Acta*, **9**, 485 (1926).

[6] Izmail'skii and Simonvo, *J. Gen. Chem.*, *U. S. S. R.*, **10**, 1580 (1940); [*C. A.*, **35**, 2871 (1941)].

[7] Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

TABLE IV

o-AMINO-N-DIETHYLAMINOALKYLANILINES,



R	R'	n	B. p., °C.	Nitrogen analyses, % Calcd.	Found
H	CH_3	3	180–181 (6 mm.)	16.85	16.98
4-Cl	CH_3	3	189–191 (1 mm.)	14.80	14.58
4-Cl	H	2	168–169 (2 mm.)	16.43	16.31
4-CH_3	H	2	175–176 (4 mm.)	17.86	17.61
4-OCH_3	H	2[a]	....	...	...
5-OCH_3	H	2[b]	170–172 (1 mm.)	16.65	16.61

[a] Previously reported; see reference (6). [b] Prepared by reducing the nitro compound with tin and hydrochloric acid.

4-aminopentane was heated at 140° for fifteen hours. Excess 1-diethylamino-4-aminopentane was removed by distillation at 2 mm. The residue was taken up in 300 cc. of 1 *N* hydrochloric acid, washed with ether, made basic with sodium hydroxide and extracted with three 50-cc. portions of ether. The combined ether extracts were washed with water, dried over potassium carbonate, the ether removed, and the residue distilled in vacuum to yield *o*-nitro-N-(4-diethylamino-1-methylbutyl)-aniline.[8]

The nitro-compound (44 g. or 0.158 mole) was hydrogenated in alcohol over Adams catalyst to yield 37.5 g. (95%) of *o*-amino-N-(4-diethylamino-1-methylbutyl)-aniline, b. p. 180° (6 mm.).

2-Keto-3-hydroxy-9-diethylaminoalkylphenazines (Table I).—The method is illustrated in the following example: To a solution of 10 g. (0.04 mole) of 2-amino-N-(4-diethylamino-1-methylbutyl)-aniline in 60 cc. of water containing 13 cc. of concentrated hydrochloric acid was added 5.6 g. (0.04 mole) of 2,5-dihydroxyquinone. The flask was stoppered and the mixture was shaken, then allowed to stand at room temperature. The quinone gradually dissolved with the formation of a dark brown solution. After twenty-four hours the mixture had set to a crystalline mass. The product was collected, washed by suspension in two 150-cc. portions of acetone, and then dried at 90°. The yield was 13.8 g. (80%) of orange-yellow powder, m. p. 210–211° (dec.). The sample for analysis was dried in vacuum at 100° for one hour.

In a similar experiment the crystalline reaction mass was dissolved in water, made basic with ammonium hydroxide, and extracted with five 100-cc. portions of chloroform. The dark brown chloroform solution was evaporated to small volume and diluted with ether to furnish a 75% yield of dark red-brown crystalline base; m. p. 96–98°.

2,4-Diamino-9-diethylaminoalkylphenazonium Hydroxides and Chlorides (Table II).—The method is illustrated in the following example: A solution of 6.9 g. (0.05 mole) of 3,5-diamino-*o*-benzoquinone[5] and 12.5 g. (0.05 mole) of *o*-amino-N-(4-diethylamino-1-methylbutyl)-aniline in 125 cc. of glacial acetic acid was allowed to stand at room temperature for twenty-four hours. The resulting dark green solution was diluted with 1 liter of water and 200 cc. of concentrated ammonium hydroxide and filtered. The filtrate was washed with ether (about five 150-cc. portions) until the washings were no longer colored, and the ether was discarded. To the aqueous solution was added 600 cc. of 36% sodium hydroxide, and the mixture was extracted with eight 500-cc. portions of ether. The dark blood-red ether solution was dried over potassium hydroxide pellets. Upon evaporation of the ether solution, the phenazonium hydroxide was obtained as a red crystalline solid.

When the red ether solution was saturated with dry hydrogen chloride at first a green precipitate was formed, but in the presence of excess hydrogen chloride it turned purple. After decanting the ether, the purple precipitate was taken up in absolute ethanol forming a dark green solution. This was filtered, evaporated to dryness, taken up again in ethanol, filtered and again evaporated to dryness. The product was dissolved in 50 cc. of methanol, heated to boiling, diluted with 200 cc. of ethyl acetate and evaporated to about 100 cc. The dark green product which had crystallized weighed 9.0 g. (40% yield), m. p. 171–173°. It was highly soluble in water or alcohol forming dark green solutions.

Summary

Two series of phenazine compounds have been prepared carrying diethylamino alkyl side-chains in the nine position.

These compounds have been tested against malaria parasites in ducklings and in chicks and found to possess only low orders of activity.

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