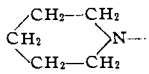
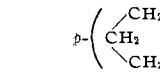
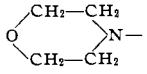
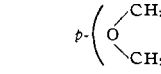
TABLE II

ALICYCLIC DIAMINES X—CH(CH$_2$—CH$_2$)CH—NH$_2$ (CH$_2$—CH$_2$)

X	Prepared from	Catalyst[a]	Yield, %	Boiling point, °C.	Mm.	n^{25}D	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$(CH_3)_2N$—	*p*-$(CH_3)_2NC_6H_4NH_2$[b]	Co-on-Al_2O_3	27	69–70	4	1.4758	$C_8H_{18}N_2$	67.5	12.8	67.4	13.0
$(C_2H_5)_2N$—	*p*-$(C_2H_5)_2NC_6H_4NH_2$[b]	RuO_2	74	81–85	3	1.4749	$C_{10}H_{22}N_2$	70.5	13.0	70.8	13.0
		Co-on-Al_2O_3	70	83–85	4	1.4720					
	p-$(C_2H_5)_2NC_6H_4NO_2$	Co-on-Al_2O_3	55	92–98	6						
		RuO_2	74	96–101	8						
	p-$(C_2H_5)_2NC_6H_4NO$	Co-on-Al_2O_3	37	88–95	5						
		RuO_2	63	94–95	7						
C_2H_5NH—	*p*-$C_2H_5NHC_6H_4NO_2$	RuO_2	63	86–87	11	1.4767	$C_8H_{18}N_2$	67.5	12.8	67.5	13.0
$(CH_3)_2CHNH$—	*p*-$(CH_3)_2CHNHC_6H_4NO_2$	RuO_2	43	90–92	10	1.4726	$C_9H_{20}N_2$	69.2	12.9	69.4	12.9
$C_6H_{11}NH$—[c]	*p*-$C_6H_{11}NHC_6H_4NH_2$	RuO_2	59	139–140	7		$C_{12}H_{24}N_2$	73.5	12.3	73.4	12.6
$(n\text{-}C_4H_9)_2N$—	*p*-$(n\text{-}C_4H_9)_2NC_6H_4NH_2$	RuO_2	15	92–95	0.5	1.4712	$C_{14}H_{30}N_2$	74.3	13.4	74.3	13.4
	*p*-  $C_6H_4NO_2$	RuO_2	44	108.5–109	4	1.5003	$C_{11}H_{22}N_2$	72.5	12.1	72.5	12.4
	*p*-  $C_6H_4NO_2$	RuO_2	39	116–117.5	3	1.5038	$C_{10}H_{20}N_2O$	65.4	10.9	66.0	11.1

[a] 10% by weight Co-on-Al_2O_3 or 5% by weight of RuO_2 was used. [b] No solvent was used in these reductions. All other reductions were made in dioxane. [c] This compound was partially solid below 56°.

N,N-diethyl-1,4-cyclohexanediamine boiling at 83–85° at 4 mm.

N-Isopropyl-1,4-cyclohexanediamine.—4-Nitroisopropylaniline (120 g., 0.67 mole) in 75 ml. of dioxane was reduced in the presence of 5 g. of ruthenium dioxide. Hydrogen was absorbed at 80° and 500 to 1500 lb. sq. in. hydrogen pressure to reduce the nitro group; the temperature was then raised to 100° and the hydrogen pressure increased to 2000–2500 lb. sq. in. to reduce the ring. The catalyst was removed by filtration. Distillation of the product yielded 45 g. (43% yield) of N-isopropyl-1,4-cyclohexanediamine boiling at 90–92° at 10 mm.

1-Piperazinepropylamine and 1,4-Piperazinebispropylamine.[7]—Acrylonitrile (90 g., 1.7 mole) was added dropwise with stirring over a period of 1.5 hours to 291 g. (1.5 mole) of piperazine hexahydrate maintained at 50° in a water-bath. After all the acrylonitrile had been added, the mixture was stirred for 0.5 hour at 40–50°. The reaction mixture was divided into three portions, and to each portion were added 75 ml. of methanol, 35 g. of liquid ammonia and 10 g. of Raney nickel. The mixtures were reduced at 90° and 2000 to 2500 lb. sq. in. hydrogen pressure. The material from these reductions was combined, and the catalyst removed by filtration. Distillation of the filtrate yielded 71 g. of 1-piperazinepropylamine boiling at 73.5 to 76° at 3 mm. (n^{25}D 1.4974) and 46 g. of 1,4-piperazinebispropylamine boiling at 123° to 123.5° at 1.5 mm. (n^{25}D 1.5005). *Anal.* Calcd. for $C_7H_{17}N_3$: C, 58.7; H, 11.9; N, 29.4. Found: C, 58.7; H, 11.7; N, 29.8. Calcd. for $C_{10}H_{24}N_4$: N, 28.0. Found: N, 28.0.

(7) Roh and Wolff, German Patent 641,597, describe the addition of acrylonitrile to piperazine and disclose the reduction of the product to the amine.

Acknowledgment.—The authors wish to thank Drs. E. W. Bousquet, B. W. Howk, R. S. Schreiber, J. C. Thomas and G. M. Whitman for their advice and assistance in this work.

Summary

The preparation of eight new nitrogen-substituted cyclohexanediamines and two piperazinepropylamines for use in the synthesis of antimalarial drugs is described.

WILMINGTON, DELAWARE RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY]

The Preparation of Some α-Dialkylamino-ω-methylaminoalkanes[1]

BY ROBERT MUNCH, GERTRUDE T. THANNHAUSER AND D. L. COTTLE[2]

In connection with the exploration of a program of varying the side chains in certain antimalarials, 1-di-*n*-butylamino-2-methylaminoethane, 1-diethylamino-3-methylaminopropane and 1-di-*n*-butylamino-3-methylaminopropane have been prepared by the classical method[3] involving alkylation of methylaniline by an appropriate amino halide, preparation of the *p*-nitroso derivative of the resulting methylaminoalkylaniline and hydrolysis of the nitroso compound. Of particular interest is the hydrolysis of the *p*-nitroso derivatives by the sodium bisulfite method[3,4] instead of the better known but, in this case, less successful sodium hydroxide method.

(1) This work was done on a volunteer basis in connection with the antimalarial program sponsored by the Committee on Medical Research and in cooperation with the group working at Columbia University.

(2) Present address: Standard Oil Development Company, Chemical Division, Elizabeth, New Jersey.

(3) Braun, Heider and Muller, *Ber.*, **51**, 737 (1918).

Experimental

3-Diethylamino-1-propanol and 3-Di-*n*-butylamino-1-propanol.—Trimethylene chlorohydrin,[5] prepared from

(4) Friedländer, Vol. III, p. 975 (1890–1894).

(5) Marvel and Calvery, "Organic Syntheses," Coll. Vol. I, J. Wiley and Sons, Inc., New York, N. Y., 1941, 2nd ed., p. 533.

trimethylene glycol,[6] was converted to the dialkylaminopropanols by a modification of the method used by Campbell and Campbell[7] for the same substances. One mole of chlorohydrin, 3 moles of amine and 1.5 moles of sodium bicarbonate were refluxed in 500 ml. of 50% alcohol for thirteen hours. The diethylamine was removed with the alcohol from the reaction mixture by distillation and, after evaluation by titration, used in subsequent runs. The alcohol and amine from the di-*n*-butylamine reaction were fractionated directly from the reaction mixture by means of a 6-bulb Snyder column. In both cases the remaining organic layer was separated, the salts dissolved in water, treated with 0.2 mole of sodium hydroxide and the water solution extracted with benzene. The combined portions were dried by refluxing. Fractionation through a 3-bulb column gave 77, 77 and 91% yields of 3-diethylamino-1-propanol, boiling at 93–95° (28 mm.) and 88, 81 and 86% yields of di-*n*-butylamino-1-propanol, boiling at 134–136° (23 mm.) for preparations starting with 1, 3 and 3 moles of chlorohydrin. Yields in four mole runs were 65% and 80% for the diethyl and dibutyl derivatives, respectively, when sodium hydroxide was not added to the aqueous solution.

α-Dialkylamino-ω-methylanilinoalkanes.—The dialkylaminopropanols above and di-*n*-butylaminoethanol[8] were converted to the methylanilino compounds by the following general procedure. One mole of aminoalcohol in an equal volume of chloroform at 15–20° was treated for forty-five minutes with 1.15 to 1.40 moles of water-white thionyl chloride dissolved in an equal volume of chloroform. The temperature was raised as rapidly as the evolution of sulfur dioxide would permit, the mixture refluxed one hour, the chloroform removed by distillation first at atmospheric pressure and finally at water pump pressure in an oil-bath at 80–85° until a pressure of 30 mm. was reached. To the residue 3 moles of methylaniline (free of aniline and dimethylaniline) were added, the mixture heated in oil bath to 150° for two hours (five hours for the dibutylaminoethyl chloride hydrochloride), cooled and washed with an excess of 6*N* sodium hydroxide. It was necessary to wash the 1-diethylamino- and 1-di-*n*-butylamino-3-methylanilinopropane with alkali by stirring in a flask in order to avoid emulsions which formed in the use of a separatory funnel. The organic layer was washed with water, dried by refluxing with benzene or in benzene over potassium carbonate and finally vacuum fractionated through a 2 or 3 bulb column. A column could not be used with the di-*n*-butylamino-1-methylanilinopropane because of decomposition caused apparently by a chlorine-containing solid which appeared in the condenser and receiver. Nevertheless vacuum distillation in this case was continued, the solid, amounting to 2% was removed from the distillate by filtration. The chlorine-free filtrate was redistilled through a 3-bulb column. Attempts to obtain dibutylaminomethylaminopropane from the undistilled substance gave poor yields, 31 and 37%.

The yield of 1-diethylamino-3-methylanilinopropane, boiling at 121–123° (3.5 mm.) was 90%. Heating of the reaction mixture to 170–200° lowered the yield to 77%.

Anal. Calcd. for $C_{14}H_{24}N_2$: N, 12.72. Found: N, 12.37.

The yield of 1-di-*n*-butylamino-3-methylanilinopropane, boiling at 163–168° (4 mm.) was 75%. Heating of the reaction mixture to 80° for twelve hours gave only a 30% yield.

Anal. Calcd. for $C_{18}H_{32}N_2$: C, 78.18; H, 11.68; N, 10.14; neut. equiv., 278. Found: C, 77.75; H, 11.49; N, 10.29; neut. equiv., 276.

The yield of 1-di-*n*-butylamino-2-methylanilinoethane boiling at 155° (4.4 mm.) was 93%. A 97% yield may be obtained by isolating the aminochloride and treating it with methylaniline substantially according to Mason and co-workers.[9]

Anal. Calcd. for $C_{17}H_{30}N_2$: N, 10.68. Found: N, 10.48.

2-Di-*n*-butylaminoethyl Chloride.—This substance, boiling at 121° (33 mm.) was prepared in 74% yield by the method of Mason and Block.[9]

Anal. Calcd. for $C_{10}H_{22}ClN$: Cl, 18.40. Found: Cl, 18.35, 18.41.

Nitrosation of the α-Dialkylamino-ω-methylanilinoalkanes.—The method of Bennett and Bell[10] was adapted. 1-Dibutylamino-2-methylanilinoethane (2.38 moles) was dissolved in 16.7 moles of concd. hydrochloric acid and 1850 g. of ice was added. During addition of 2.50 moles of sodium nitrite as a 30% solution the temperature was held below −6°. The time of addition was five hours. When the time of addition was shortened by maintaining a temperature of +8° no hydrolysis product could be obtained.

The nitrosation of the other two aniline derivatives was very similar except for the diethylaminopropane derivative which was treated with 9 moles of hydrochloric acid per mole.

Hydrolysis of the Nitroso Derivatives.—These hydrolyses were accomplished by a much modified method of Braun and Muller.[3] The nitroso compound was extracted from the nitrosation mixture with ether, the ether solution dried over potassium carbonate and the ether removed by distillation from a water-bath held below 66°. The residue, a calculated 2.38 moles, was treated in a 12-liter one-necked flask, fitted with a stirrer and thermometer, with 14.3 moles of sodium bisulfite as a 26% solution of sodium metabisulfite. Some heat was evolved, the color changed from a green to a deep red brown and a small amount remained as a separate layer. After stirring at room temperature for one hour, the mixture was heated on a water-bath to 76° for fifteen minutes, cooled to room temperature and treated with a 50% excess of sodium hydroxide over that required to neutralize the sodium bisulfite. The mixture, which had a distinct ammonia odor, was extracted once manually with a liter of ether and further in a continuous extractor. After drying over potassium hydroxide and removal of the ether the product was fractionated through a 3 or 5 bulb column.

In order to lighten the load on our continuous extractors an alternate procedure was used. Hydrochloric acid, instead of alkali, was added, the solution was concentrated to one-third of its original volume by distillation in a bath, 50% sodium hydroxide was added and the resulting mixture of salts and solution extracted in a continuous extractor. The use of higher ratios of bisulfite to nitroso derivative or of longer time of heating does not increase the yield.

The yield of 1-di-*n*-butylamino-2-methylaminoethane, boiling at 91.0–91.7° (7–8 mm.), was 66–70%. The substance was soluble in the common organic solvents and soluble to the extent of 1.15 g. per 100 ml. of water; d^{20}_{20} 0.8125, $n^{20}D$ 1.4391.

Anal. Calcd. for $C_{11}H_{26}N_2$: C, 70.91; H, 14.07; N, 15.04; neut. equiv., 93.2. Found: C, 71.18; H, 14.50; N, 14.87; neut. equiv., 93.7.

The phenylthiourea derivative softened at 49.9° and melted at 50.3–50.7°.

Anal. Calcd. for $C_{19}H_{31}N_3S$: C, 67.25; H, 9.72. Found: C, 67.10; H, 9.38.

The yield of 1-diethylamino-3-methylaminopropane, boiling at 58–60° (8 mm.) or 75° (23 mm.) was 65%; d^{18}_{18} 0.8128, $n^{19}D$ 1.4390. Neutral equiv. calcd.: 72.15.

(6) Generously supplied by Proctor and Gamble Company, Ivorydale, Ohio.

(7) Campbell and Campbell, *Proc. Indiana Acad. Sci.*, **49**, 101–104 (1939).

(8) Generously supplied by Sharples Chemicals, Inc. We are also indebted to Calco Chemical Company and to United States Rubber Company for gifts from their storerooms while getting this work started.

(9) Mason and Block, THIS JOURNAL, **62**, 1443 (1940); Mason and Malkiel, *ibid.*, **62**, 1448 (1940).

(10) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1941, 2nd ed., p. 223.

Found: 72.18, 72.24. Because of its hygroscopic nature, the elementary analyses were not satisfactory.

The yield of 1-di-*n*-butylamino-3-methylaminopropane, boiling at 102–103° (6 mm.), was 64%; d^{25}_{18} 0.8206, $n^{21}D$ 1.4480.

Anal. Calcd. for $C_{12}H_{28}N_2$: C, 71.93; H, 14.09. Found: C, 71.85; H, 13.89.

Summary

1-Di-*n*-butylamino-2-methylaminoethane was prepared in 63% over-all yield starting with di-*n*-butylaminoethanol. 1-Diethylamino- and 1-di-*n*-butylamino-3-methylaminopropane were prepared in 38% over-all yields starting with diethyl- and di-*n*-butylamine. The classical method of alkylating methylaniline and hydrolyzing the *p*-nitroso derivative was used. Much higher yields were obtained by hydrolysis by the sodium bisulfite than by the better known sodium hydroxide method.

NEW BRUNSWICK, NEW JERSEY RECEIVED APRIL 5, 1946

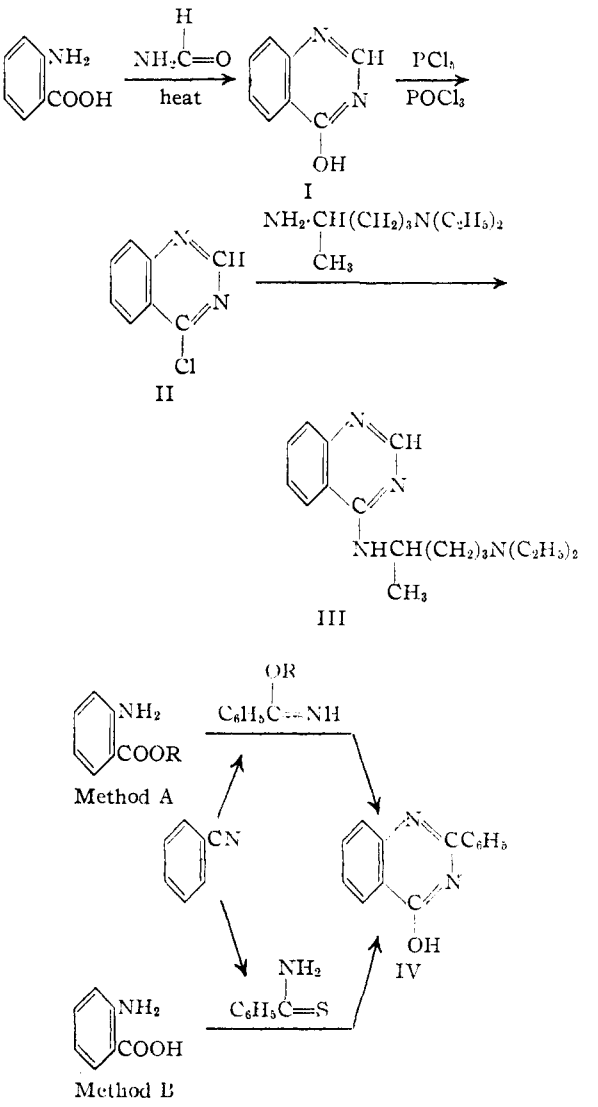
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF MOUNT HOLYOKE COLLEGE]

Quinazoline Derivatives.[1] I. The Synthesis of 4-(4′-Diethylamino-1′-methylbutylamino)-quinazoline (SN 11,534) and the Corresponding 2-Phenylquinazoline (SN 11,535)[2]

BY MARGARET M. ENDICOTT, EMILY WICK, MARIE L. MERCURY AND MARY L. SHERRILL

The investigation of quinazoline derivatives with an alkyl diamine side chain as potential antimalarial drugs was based in part on the similarity of quinazoline (benzopyrimidine) to quinoline (benzopyridine). The two compounds are very similar in reactivity, the heterocyclic ring in each having aromatic properties. The quinazolone nucleus has been found in certain alkaloids[3] and quinazoline derivatives have been reported as pharmaceuticals which affect blood pressure,[4] produce local anesthesia[4] and are active toward blood parasites.[5]

The synthesis of the two dialkylaminoalkylaminoquinazolines reported in this paper required the preparation from anthranilic acid of 4-quinazolone (I), 4-chloroquinazoline (II) and the condensation of the latter with 1-diethylamino-4-aminopentane to give the aminoquinazoline (III) as indicated in the chart. The 2-phenylquinazolone (IV) was prepared by two methods, the second being more satisfactory. Methyl or ethyl anthranilate was condensed with the corresponding alkyl imidobenzoate (Method A) and anthranilic acid with thiobenzamide (Method B). Subsequent reactions for the preparation of 2-phenyl-4-chloroquinazoline (V) and 4-(4′-diethylamino-1′-methylbutylamino) - 2 - phenylquinazoline (VI) were analogous to those for II and III.



(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Mount Holyoke College.

(2) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(3) Asahina, Manske, Robinson, *J. Chem. Soc.*, 1708 (1927).

(4) Paal and Busch, *Ber.*, **22**, 2683 (1889); Gabriel and Colman, German Patent 161,401, *Chem. Zentr.*, **76**, II, 182 (1905); British Patent 346,118, *Chem. Zentr.*, **102**, II, 87 (1931); Maffei, German Patent 525,653, *C. A.*, **25**, 4664 (1931).

(5) I. G. Farbenind. A. G. British Patents 287,179, 288,159, *C. A.*, **23**, 396 (1929); British Patent 330,583, *Chem. Zentr.*, **101**, II, 1773 (1930).