diethylaminohexan-2-one (VIII), the corresponding oxime (IX) and the latter reduced to give the 1-diethylamino-5-aminohexane (X).

SOUTH HADLEY, MASSACHUSETTS RECEIVED APRIL 5, 1946

[CONTRIBUTION NO. 212 FROM THE CHEMICAL DEPARTMENT, E. I. DU PONT DE NEMOURS & COMPANY]

Synthesis of Alicyclic Diamines[1]

BY L. C. BEHR, J. E. KIRBY, R. N. MACDONALD AND C. W. TODD

The superiority of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline[2] over quinacrine in the treatment of malaria prompted the preparation of other 7-chloroquinolines containing a basic side chain in the 4-position. The two amino groups in the quinacrine side chain are separated by an open chain of four carbon atoms. To our knowledge, analogous compounds in which the carbon atoms joining the two amino groups form elements of an alicyclic structure had not been tested as antimalarials. Accordingly, this work was undertaken to supply the requisite alicyclic diamines for the preparation of compounds of this type.[3]

It was found that N-substituted *p*-phenylenediamines and *p*-nitroanilines could be hydrogenated to substituted cyclohexanediamines using either ruthenium dioxide or cobalt-on-alumina as the catalyst. It is known that 1,4-disubstituted cyclohexanes may exist in *cis* and *trans* forms. Although in our work the geometric isomers of the diamines have not been separated, the final drug, 7-chloro-4-(4-diethylaminocyclohexylamino)-quinoline, prepared from samples of our N,N-diethyl-1,4-cyclohexanediamine obtained by reduction over ruthenium and over cobalt-on-alumina has been separated by Drake[3] into two isomeric forms of different melting points. The isolation of larger amounts of the high melting form from the drug prepared from the cobalt-reduced diamine indicates that reduction over cobalt-on-alumina at high temperatures (200–210°) favors the formation of the *trans* isomer, whereas reduction over ruthenium at lower temperatures (100–110°) favors the formation of the *cis* isomer of the diamine. This is in agreement with the studies of other investigators[4] on the isomeric forms of related compounds obtained by reduction over other hydrogenation catalysts.

The preparation of 1-piperazinepropylamine and 1,4-piperazinebispropylamine by the reduction of the acrylonitrile adducts of piperazine for use as side chains in the preparation of other antimalarial drugs is also described.

(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 E. I. du Pont de Nemours and Company.

(2) *Science*, **103**, 8 (1946).

(3) The coupling of these diamines with 4,7-dichloroquinoline was done by N. L. Drake, THIS JOURNAL, **68**, 1214 (1946).

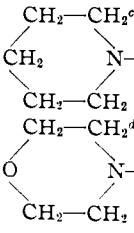
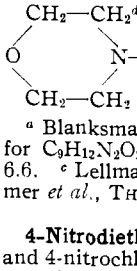
(4) Linstead, *et al.*, *ibid.*, **64**, 1985 (1942); Farkas, *Trans. Faraday Soc.*, **35**, 910 (1939).

Experimental

Preparation of Substituted Nitroanilines.—The N-substituted nitroanilines required in this work were prepared by the reaction of 4-nitrochlorobenzene with the appropriate amine in the absence of a solvent. A typical preparation is described below. The preparations of the other substituted nitroanilines are summarized in Table I.

TABLE I

SUBSTITUTED NITROANILINES X—C$_6$H$_4$—NO$_2$

X	Reaction temp., °C.	Time, hours	Yield, %	M. p., °C.
$(C_2H_5)_2N$—[5]	175	8	94	76
C_2H_5NH—[a]	160	5	75	96
$(CH_3)_2CHNH$—[b]	175	10	40	81–82
	145	3	83	103.5–104.5
	145	4	67	150–151

[a] Blanksma, *Rec. trav. chim.*, **21**, 271 (1902). [b] Calcd. for $C_9H_{12}N_2O_2$: C, 59.8; H, 6.7. Found: C, 59.8; H, 6.6. [c] Lellmann and Geller, *Ber.*, **21**, 2282 (1888). [d] Kremer *et al.*, THIS JOURNAL, **61**, 2552 (1939).

4-Nitrodiethylaniline.[5]—Diethylamine (100 g., 1.4 mole) and 4-nitrochlorobenzene (97.8 g., 0.6 mole) were heated in an agitated Parr bomb for eight hours at 175°. The contents of the bomb were then added to one liter of water. The precipitate was filtered, washed with water, dissolved in 200 ml. of 20% hydrochloric acid at 60°, and the solution filtered through sintered glass. The addition of ammonium hydroxide to the filtrate precipitated crude 4-nitrodiethylaniline (114 g., 94% yield), melting at 71–73°. Recrystallization from ethyl alcohol yielded the 4-nitrodiethylaniline (85 g.) as light yellow plates melting at 76°.

Preparation of Alicyclic Diamines.—The preparations of the alicyclic diamines are summarized in Table II. As typical examples, the reductions of 4-aminodiethylaniline to N,N-diethyl-1,4-cyclohexanediamine and of 4-nitroisopropylaniline to N-isopropyl-1,4-cyclohexanediamine are described below.

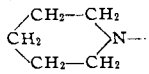
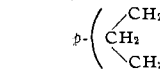
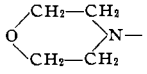
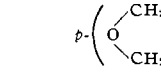
N,N-Diethyl-1,4-cyclohexanediamine.—4-Aminodiethylaniline (175 g., 1.07 mole) was reduced at 200° and 2000 to 2500 lb. sq. in. of hydrogen pressure in the presence of 17 g. of cobalt-on-alumina.[6] The theoretical amount of hydrogen was absorbed over three and one-half hours. The catalyst was then removed by filtration and the product distilled. There was obtained 126 g. (70% yield) of

(5) Holleman and de Mooy, *Rec. trav. chim.*, **35**, 32 (1915).

(6) This catalyst was prepared by treating a 1:1 cobalt-aluminum alloy with an amount of aqueous sodium hydroxide insufficient to dissolve the alumina formed.

TABLE II

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

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.