zidines may be obtained. When copper chromite was employed as catalyst for reductive cyclizations, examples of both skeletal cleavage and rearrangement were found.

Compounds, having the simple quinolizidine nucleus, were found not to possess appreciable curariform activity.

ROCHESTER, NEW YORK RECEIVED SEPTEMBER 13, 1948

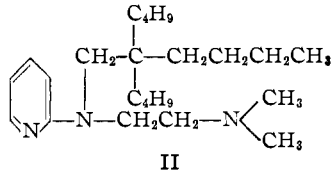
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Quaternary Carbon Compounds. II. N,N-Dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine and the Diethyl Homolog

BY NATHAN SPERBER AND DOMENICK PAPA

In a publication[1] describing the synthesis of N′-benzyl-N′-(2-pyridyl)-N,N-dimethylethylenediamine (I) and related compounds, several substances in which the benzyl group of I was replaced by lower alkyl radicals such as ethyl, isopropyl and propyl are reported. The latter substances showed a low order of antihistaminic activity in experimental animals as compared with the benzyl compound.

In the course of studies on trialkyl-substituted compounds of pharmacological importance,[2] we have prepared a highly branched compound related to I, namely, N,N-dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine (II), in order to establish whether this type of substitution would show appreciably greater antihistaminic activity than the lower alkyl derivatives. In animal experiments, II has shown approximately $^1/_{250}$ the antihistaminic activity of I. The diethyl homolog (III) of II was also prepared and was $^1/_5$–$^1/_{10}$ as active as II.



II

The synthesis of II and the diethyl homolog was carried out in two steps. The condensation of 2-bromopyridine, (2,2-dibutylhexyl)-amine and anhydrous sodium carbonate in xylene or cymene yielded, after prolonged refluxing, N-(2,2-dibutylhexyl)-2-aminopyridine. The latter on alkylation with dimethylaminoethyl chloride or diethylaminoethyl chloride gave good yields of II and III, respectively.[3] Attempts to condense N,N-diethyl-N′-(2,2-dibutylhexyl)-ethylenediamine and 2-bromopyridine with sodamide were unsuccessful.

(1) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(2) (a) Junkmann and Allardt, U. S. 2,186,976, Jan. 16, 1940; (b) Allardt and Junkmann, U. S. 2,361,524, Oct. 31, 1944; (c) Sperber, Papa and Schwenk, Quaternary Carbon Compounds. I, THIS JOURNAL, **70**, 3091 (1948).

(3) These experiments were completed prior to the publication of Huttrer, *et al.*, and were based on the directions of Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

Experimental

(2,2-Dibutylhexyl)-amine.—Capronitrile was dialkylated with butyl bromide and sodium amide according to the directions of Ziegler and Ohlinger.[4] The resulting 2,2-dibutylcapronitrile was reduced to (2,2-dibutylhexyl)-amine[2b]; yield 90%; b. p. 123–124° (4 mm.); hydrochloride m. p. 135°.

N-(2,2-Dibutylhexyl)-2-aminopyridine.[5]—A mixture of 32 g. of 2-bromopyridine, 50 g. of (2,2-dibutylhexyl)-amine and 21 g. of anhydrous sodium carbonate in 100 cc. of *p*-cymene was refluxed and stirred for sixty-seven hours. The mixture was poured into water, the cymene layer separated and, after drying, concentrated *in vacuo*. The residue was fractionated. After a forerun of 12.6 g., b. p. 95–163° (1 mm.), the substituted aminopyridine was obtained as a yellow viscous oil; yield 45 g., b. p. 172–174° (2 mm.); $n^{28}D$ 1.5045. Calcd. for $C_{19}H_{34}N_2$: N, 9.65. Found: N, 9.28.

N,N-Dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine.—To a sodium amide suspension[6] (2.5 g. of sodium) in 75 cc. of dry toluene, was added 29 g. (0.1 mole) of N-(2,2-dibutylhexyl)-2-aminopyridine.[7] The mixture was heated with stirring for two hours on the steam-bath. A solution of 12 g. of dimethylaminoethyl chloride in 20 cc. of dry toluene was added dropwise to the stirred suspension and the reaction heated with stirring for twenty hours on the steam-bath. The reaction mixture was cooled and then decomposed with water. The organic layer was separated, dried and the solvent removed *in vacuo*. The residue distilled as a yellow viscous oil; yield 28.5 g., b. p. 175–177° (2 mm.), $n^{23}D$ 1.5002. Calcd. for $C_{23}H_{43}N_3$: C, 76.36; H, 11.99; N, 11.62. Found: C, 76.60; H, 11.99; N, 11.61.

The dihydrochloride was prepared as follows: A solution of 6 g. of the free base in 75 cc. of dry ethyl acetate was saturated with anhydrous hydrogen chloride. Upon cooling and scratching, a crystalline solid was obtained. Dry ether was added, the solid collected and washed with ether: recrystallized twice from alcohol–ether; yield 5.8 g.; m. p. 184.5–185.5°. Calcd. for $C_{23}H_{45}N_3Cl_2$: N, 9.67; Cl, 16.33. Found: N, 9.45; Cl, 16.00.

N,N-Diethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine.—N-(2,2-Dibutylhexyl)-2-aminopyridine was alkylated with diethylaminoethyl chloride and sodium amide as described for the corresponding dimethyl compound; yield 70%; yellow viscous oil; b. p. 190–195° (2 mm.); $n^{21}D$ 1.5005. The free base was converted to

(4) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(5) The reaction of 16 g. of 2-bromopyridine, 39 g. of (2,2-dibutylhexyl)-amine and 50 cc. of pyridine for ten hours at 155–160° essentially as described by Whitmore[3] did not yield any of the substituted aminopyridine.

(6) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 99.

(7) Although King, King and Muir (*J. Chem. Soc.*, 5 (1946)) alkylated diphenylamine with diethylaminoethyl chloride by means of the Grignard reagent, N-(2,2-dibutylhexyl)-2-aminopyridine with methylmagnesium iodide and dimethylaminoethyl chloride yielded none of the expected tertiary amine.

the dihydrochloride in ethyl acetate and was recrystallized twice from a mixture of alcohol-ether; m. p. 205–205.5°. Calcd. for $C_{25}H_{49}N_3Cl_2$: N, 9.08; Cl, 15.34. Found: N, 9.18; Cl, 15.76.

N,N-Diethyl-N'-(2,2-dibutylhexyl)-ethylenediamine.—A mixture of 21 g. (0.1 mole) of 2,2-dibutylhexylamine, 14 g. (0.1 mole) of diethylaminoethyl chloride and 11 g. of anhydrous sodium carbonate in 50 cc. of dry xylene was refluxed with stirring for sixty-five hours. The cooled reaction product was poured into water, the xylene layer separated, and the solvent removed *in vacuo*. The brown oily residue was distilled; yield 29 g.; b. p. 155–156° (2 mm.); $n^{23}D$ 1.4540. The analytical sample showed the following constants: b. p. 151–152° (1.5 mm.); $n^{23}D$ 1.4513. Calcd. for $C_{20}H_{44}N_2$: C, 76.82; H, 14.20; N, 8.97. Found: C, 76.71; H, 13.74; N, 9.26.

Acknowledgment.—We wish to express our appreciation to Dr. Richard Tislow and Mrs. Annette LaBelle of our Pharmacology Laboratory for the pharmacological data reported herein.

Summary

Replacement of the benzyl group in N'-benzyl-N'-(2-pyridyl)-N,N-dimethylethylenediamine by a highly branched aliphatic radical resulted in a considerable decrease in antihistaminic activity.

BLOOMFIELD, N. J. RECEIVED SEPTEMBER 9, 1948

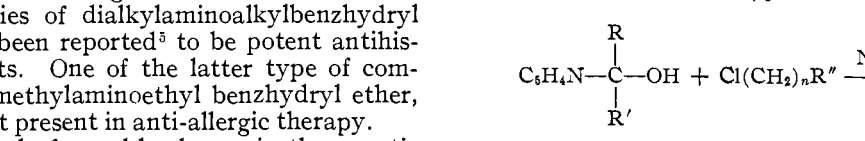
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Pyridyl-Substituted Alkamine Ethers as Antihistaminic Agents[1]

BY NATHAN SPERBER, DOMENICK PAPA, ERWIN SCHWENK AND MARGARET SHERLOCK

Although Fourneau and co-workers[2] demonstrated that dialkylaminoalkylaryl ethers[3] possessed antihistaminic activity, these substances proved too toxic for general clinical use. Recently, a series of dialkylaminoalkylbenzhydryl ethers[4] have been reported[5] to be potent antihistaminic agents. One of the latter type of compounds, β-dimethylaminoethyl benzhydryl ether, is employed at present in anti-allergic therapy.

The extremely favorable change in therapeutic index which resulted from the replacement of the phenyl group by a pyridyl group[6] in N'-phenyl-N'-benzyl-N,N-dimethylethylenediamine seemed of sufficient interest to warrant the study of a similar substitution in the benzhydrylalkamine ether series. A number of substituted dialkylaminoalkylpyridylmethyl ethers of the general formula I (Table II) wherein R is a pyridyl radical, R' is alkyl, aryl or heterocyclic, R'' is hydrogen or a lower alkyl group, n is 2 or 3 and R''' is a dialkylamino group, were synthesized by the condensation of the appropriately substituted carbinols with dialkylaminoalkyl halides and sodium amide in toluene. In general, the yields of ethers varied from about 45–88%. In the case of (2-pyridyl)-(2-thienyl)-methylcarbinol, only 22% of the dimethylaminoethyl ether was obtained.



$$R-C(R')(R'')-O(CH_2)_nR''' \quad \text{I}$$

$$C_5H_4N-C(R)(R')-OH + Cl(CH_2)_nR''' \xrightarrow{NaNH_2} \text{I}$$

The requisite carbinols (Table I) were synthesized by the following three methods[7]: (I) the reaction of aldehydes with 2-pyridylmagnesium bromide as described by Overhoff and Proost[8]: (II) The condensation of picolinic acid and aromatic aldehydes and ketones to yield the secondary and tertiary pyridylarylcarbinols,[9] respectively; (III) tertiary carbinols were also prepared by the reaction of 2- or 3-acetylpyridine with aryl or aralkylmagnesium halides.

Although method I is reported to give 40–55% of the carbinols, we have not been able to duplicate these yields. Furthermore, this synthesis required the use of large volumes of solvent for extraction and, frequently, troublesome emulsions were encountered.

A more satisfactory method for the preparation of the secondary substituted 2-pyridylcarbinols is based on the decarboxylation of picolinic acid in the presence of an aromatic aldehyde at a temperature above 140° (Method II). The products of

(1) The major portion of this paper was presented in abstract before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, April 21, 1948. Similar amino ethers have been reported by Tilford, Van Campen and Shelton, abstract of Papers of 114th Meeting of the American Chemical Society, pg. 2K (August 31, 1948).

(2) Forneau and Bovet, *Arch. internat. de pharmacodyn. et de therap.*, **46**, 178 (1933); Staub, *Ann. Inst. Pasteur*, **63**, 400 (1939).

(3) 929F, 2-isopropyl-5-methylphenoxyethyldiethylamine; 1379F, 2-methyl-5-isopropylphenoxyethyldiethylamine; 1464F, 2-isopropyl-5-methylphenoxyethylpiperidine.

(4) Abstracts of the Atlantic City Meeting of the American Chemical Society, p. 50K (1946); Rieveschl, U. S. Patent 2,421,714, June 3, 1947.

(5) Loew, Kaiser and Moore, *J. Pharmacol. and Exp. Therap.*, **83**, 120 (1945); Loew and Kaiser, *Proc. Soc. Exper. Biol. and Med.*, **58**, 235 (1945).

(6) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(7) (a) Chichibabin oxidized 2-benzylpyridine to phenyl-2-pyridyl ketone (*J. Russ. Phys.-Chem. Soc.*, **33**, 701 (1901)). The latter was reduced to the corresponding carbinol with zinc dust and sodium ethoxide (*Ber.*, **37**, 1371 (1904)); (b) Emmert and Asendorf (*Ber.*, **72**, 1188 (1939)) have prepared several 2-pyridyl-substituted carbinols by the reaction of a ketone and mercuric chloride with pyridine and magnesium.

(8) Overhoff and Proost, *Rec. trav. chim.*, **57**, 179 (1938).

(9) Ashworth, Daffern and Hammick, *J. Chem. Soc.*, 809 (1939); Mislow, THIS JOURNAL, **69**, 2559 (1947).