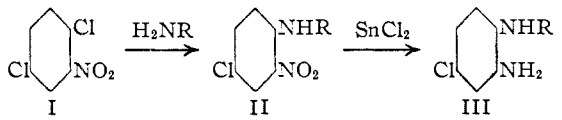
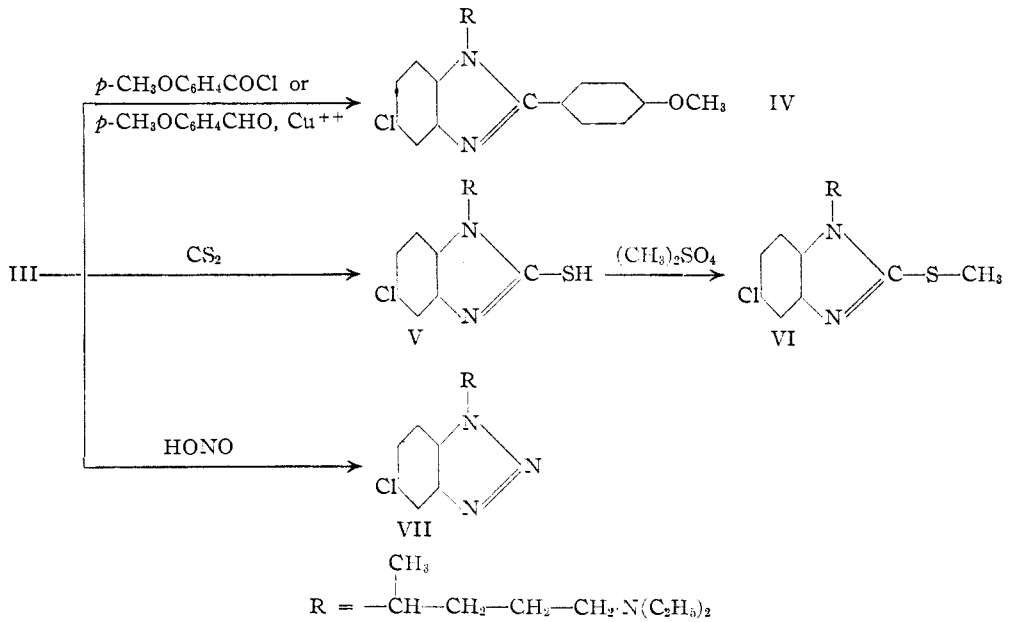
[Contribution from the Venable Chemical Laboratory of the University of North Carolina]

Some Derivatives of 3-Amino-4-(1-diethylamino-4-pentylamino)-chlorobenzene

By R. L. McKee,[1] M. K. McKee and R. W. Bost

In the course of a program of antimalarial research, two derivatives of benzimidazole and one of benztriazole were prepared according to the scheme





2,5-Dichloronitrobenzene (I) was obtained in 95% yield from *p*-dichlorobenzene according to the procedure of Kiprianov and Mikhailenko.[2]

The conversion of I into 4-(1-diethylamino-4-pentylamino)-3-nitrochlorobenzene (II) in 65% yield is in interesting contrast to the reaction between 4-bromo-3-nitroanisole and 1-diethylamino-4-aminopentane which has been reported[3] and confirmed in this Laboratory to proceed in 19% yield.

5 - Chloro - 1 - (1 - diethylamino- 4 - pentyl) - 2-(*p*-methoxyphenyl)-benzimidazole (IV) was obtained from III ether by the action of *p*-anisoyl chloride (94% yield) or by interaction with *p*-anisaldehyde and cupric acetate[4] (53% yield).

In the reaction between III and carbon disulfide,[5] the intermediate sulfhydral benzimidazole (V) proved to be highly water-soluble and unstable; consequently, it was methylated without isolation to yield 5-chloro-1-(1-diethylamino-4-pentyl)-2-thiomethoxybenzimidazole (VI).

Nitrous acid[6] reacted upon III normally to form 5-chloro-1-(1-diethylamino-4-pentyl)-benztriazole (VII) in 76% yield.

Antimalarial studies of these compounds will be reported elsewhere.

Experimental

4-(1-Diethylamino-4-pentylamino)-3-nitrochlorobenzene (II).—1-Diethylamino-4-aminopentane (8.5 g., 0.054 mole), 11.0 g. (0.057 mole) of 3,5-dichloronitrobenzene, 4.5 g. of potassium carbonate, 0.1 g. of copper powder and 30 cc. of nitrobenzene were heated in an oil-bath maintained at 195° for six hours. After cooling, 100 cc. of ether was added, and the base was extracted with dilute hydrochloric acid. The acidic solution was made strongly alkaline with 50% aqueous sodium hydroxide and extracted three times with 100-cc. portions of ether. After drying (solid sodium hydroxide), the ether was evaporated and the base distilled under diminished pressure. The main fraction boiled at 191–197° (3 mm.), and on redistillation, 11.0 g. (65% yield) of material boiling at 193–195° (3 mm.) was obtained. The compound is a viscous, deep red oil.

Anal. Calcd. for $C_{15}H_{24}ClN_3O_2$: N, 13.41. Found: N, 13.46.

4-(1-Diethylamino-4-pentylamino)-3-amino-chlorobenzene (III).—The above nitro compound (9.6 g., 0.030 mole) was dissolved into a solution of 21 g. (0.093 mole) of stannous chloride in 35 cc. of concentrated hydrochloric acid. After standing for six hours, this was poured into an excess of 40% aqueous sodium hydroxide with cooling. The product was extracted with ether and the ethereal

(1) The Wm. S. Merrell Co., Postdoctoral Fellow.

(2) Kiprianov and Mikhailenko, *Ukrain. Khem. Zhur.*, **5**, Tech. Pt. 225 (1930), through *C. A.*, **25**, 5033 (1931).

(3) Clemo and Swan, *J. Chem. Soc.*, 274 (1944).

(4) Weidenhagen, *Ber.*, **69**, 2263 (1936).

(5) Lillmann, *Ann.*, **221**, 8 (1883).

(6) Hofmann, *ibid.*, **115**, 251 (1860); Ladenburg, *Ber.*, **9**, 219 (1876).

solution was dried over potassium carbonate and distilled. The product appeared as 7.5 g. (86% of theoretical) of a pale yellow oil boiling at 174–176° (3 mm.). This diamine is reasonably stable but begins to darken when kept for a few weeks.

Anal. Calcd. for $C_{15}H_{26}ClN_3$: N, 14.80. Found: 14.71.

5-Chloro-1-(1-diethylamino-4-pentyl)-2-*p*-methoxyphenylbenzimidazole (IV).—A. The above diamine (III) (7.5 g., 0.026 mole) was dissolved in 50 cc. of methyl alcohol containing 2.4 cc. of concentrated hydrochloric acid. To this was added a solution of 11.2 g. (0.056 mole) of cupric acetate in 150 cc. of water, followed by a solution of 3.8 g. (0.028 mole) of *p*-anisaldehyde in 50 cc. of methyl alcohol. On warming, the original intense blue color disappeared and a copper-colored precipitate formed. After heating for three hours, the solution was diluted to 750 cc. with water, 6.0 g. of sodium sulfide nonahydrate was added, and a mixture of equal volumes of glacial acetic acid and concentrated hydrochloric acid was added dropwise until the solution was slightly acid (litmus). After filtering and extracting once with ether, the acidic solution was made strongly alkaline (sodium hydroxide), resulting in the separation of a greenish-brown oil. This was taken up in ether, dried over potassium carbonate and distilled. The main fraction boiled at 230–240° (2.5 mm.) and on redistillation, 5.5 g. (53% yield) of a light red-brown oil was obtained, boiling at 236° (2.5 mm.).

B. Seventeen grams (0.06 mole) of the diamine (III) was dissolved in 15 cc. of dry pyridine and 12.2 g. (0.07 mole) of *p*-anisoyl chloride was added with cooling in ice. After standing at room temperature for one hour, the mixture was heated on a steam-bath for twelve hours. Dilute sodium hydroxide was added and the resulting oil extracted with ether (1.5 g. of anisic acid was recovered from the aqueous layer by acidification). The ether layer was dried and distilled as in (A), giving 22.6 g. (94% of the theoretical) of the benzimidazole.

Anal. Calcd. for $C_{23}H_{30}ClN_3O$: N, 10.51. Found: N, 10.22.

5-Chloro-1-(1-diethylamino-4-pentyl)-2-thiomethoxybenzimidazole (VI).—Fifteen grams (0.053 mole) of the diamine (III) was dissolved in a mixture of 20 cc. of carbon disulfide and 20 cc. of 95% ethyl alcohol and refluxed overnight on a steam-bath, after which the excess carbon disulfide and most of the alcohol was distilled. A solution of 4.3 g. (0.11 mole) of sodium hydroxide in 50 cc. of water was added, followed by 5 cc. (0.053 mole) of dimethyl sulfate, the latter in 1-cc. portions, with vigorous shaking. The oil so produced was extracted with a mixture of equal volumes of ether and ethyl acetate, dried over sodium sulfate, and distilled. The product appeared as a light brown viscous oil, boiling at 194–198° (3 mm.). A yield of 12 g. (66% of the theoretical) was obtained.

Anal. Calcd. for $C_{17}H_{26}ClN_3S$: N, 12.36. Found: N, 12.46.

5-Chloro-1-(1-diethylamino-4-pentyl)-benzotriazole (VII).—Twelve grams (0.042 mole) of the diamine (III) was dissolved in 100 cc. of water containing 14 cc. of concentrated hydrochloric acid. After adding about 400 g. of ice, a solution of 3.1 g. (0.045 mole) of sodium nitrite in 50 cc. of water was added dropwise with vigorous stirring. The solution was allowed to stand for twelve hours and then made alkaline (sodium hydroxide). The oil was extracted with ether, dried over potassium carbonate and distilled. The fraction boiling at 162–178° (3 mm.) was redistilled, giving 9.5 g. (76% of the theoretical) of a viscous light brown oil boiling at 177–178° (3 mm.).

Anal. Calcd. for $C_{15}H_{23}ClN_4$: N, 19.00. Found: N, 18.90.

Acknowledgment.—The authors wish to express their appreciation to The Wm. S. Merrell Company through whose generous support this work was carried out.

Summary

3 - Amino - 4 - (1 - diethylamino - 4 - pentylamino)-chlorobenzene has been synthesized and converted into three basically substituted heterocycles.

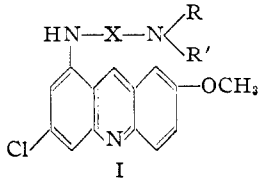
CHAPEL HILL, NORTH CAROLINA RECEIVED MAY 17, 1946

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

N-Substituted 2-Methoxy-6-chloro-9-aminoacridines Derived from Unsymmetrical Aliphatic Amines[1]

BY JOSEPH CORSE, J. T. BRYANT[2] AND H. A. SHONLE

A number of 2-methoxy-6-chloro-9-(dialkylaminoalkylamino)-acridines (I), related to quinacrine (II), have been made for antimalarial studies.[3] However, although there has been considerable variation in the type of side chain (—X—), there has been but little work reported



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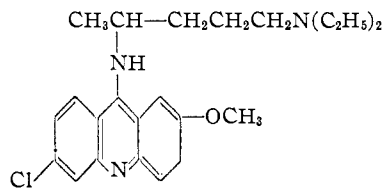

II

on variations in the dialkylamino part of the molecule.[4] This paper reports a few compounds we have made wherein R and R′ are dissimilar.

The unsymmetrical secondary amines used were obtained from commercial sources or made by known methods, usually by high pressure reduction of mixtures of primary amines and ketones

(1) Reported at the 108th Meeting of the American Chemical Society, September 11 to 15, 1944, New York, N. Y.

(2) Deceased December 30, 1943.

(3) Mietzsch and Mauss, *Angew. Chem.*, **47**, 633 (1934); German Patents 553,072 and 571,449.

(4) Burckhalter, Jones, Holcomb and Sweet, THIS JOURNAL, **65**, 2012 (1943).