[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# UNSYMMETRICALLY DISUBSTITUTED PIPERAZINES. II. HISTAMINE ANTAGONISTS[1]

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When tested by the tracheal chain method (1, 2) the known benzylmethyl and benzylethyl piperazines (3) were found to have about 1% and 0.4% respectively of the antihistaminic activity of dimethylaminoethyl benzhydryl ether (Benadryl). This suggested that N-methylpiperazines having N′-substituents containing two or three rings might show activities comparable to those of currently available histamine antagonists and that among such substituents the benzhydryl group would be close to the optimal size.

A variety of derivatives of methylpiperazine, whose properties are shown in Table I, were therefore prepared to ascertain (a) whether the benzhydryl radical was in fact of the optimal size and (b) whether it would be possible to combine the features of antihistaminic and bronchodilator drugs. This latter point early received a negative answer which was not unexpected since attempts to combine in one compound the virtues of two physiologically active types usually result in a substance lacking the advantages of either. Compound XI was much less potent than benzhydrylmethylpiperazine and Compounds XII and XIII had only vestigial activity. Bronchodilator action was also negligible.

In respect to point (a), Compounds I–VI had activities intermediate between those of benzylmethylpiperazine and benzhydrylmethylpiperazine (4). Compounds VII–X and XIV–XV again showed little or no activity. It is evident that the benzhydryl group is, at any rate, close to the optimal size. The inferior potency of Compounds XI–XIII can be interpreted as meaning that hydrophilic groups in this portion of the molecule are undesirable.

## EXPERIMENTAL

With the exception of Compounds III and XII, all the substances listed in Table I were prepared by the direct reaction of methylpiperazine with the appropriate halide. The intermediates for I, II, and XIII were bromides, the rest chlorides. The reactions leading to Compounds IV–VI and XIV–XV were carried out in ethanol, the others without solvent except that a little benzene was usually added to ensure adequate mixing. The benzhydryl chloride precursors to Compounds VII–X react by the $SN_1$ scheme requiring absence of hydroxylic solvents. It is probable from the poor yield of Compound V that α-naphthylmethyl chloride also reacts largely by the "unimolecular" mechanism. In the preparation of Compounds XI and XIII hydroxylic solvents presumably would not be objectionable. Aside from these variations the preparations were of standard type and can be generalized. Two equivalents of methylpiperazine were employed to one of halide and the mixture was heated on the steam-bath for two to ten hours dependent on the expected reactivity of the halide. When ethanol was present it was evaporated at this point. The reaction mixture was then partitioned between ether and water, the ethereal layer being washed with water

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TABLE I

SALTS OF UNSYMMETRICALLY DISUBSTITUTED PIPERAZINES, MeN($CH_2$—$CH_2$)NR($CH_2$—$CH_2$)

| COMP. NO. | R | M.P., °C.[a] | YIELD, % | EMPIRICAL FORMULA | ANALYSES | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Carbon | | Hydrogen | |
| | | | | | Calc'd | Found | Calc'd | Found |
| I | 2-Nitrophenyl | 234–235[b] | 60 | $C_{11}H_{15}N_3O_2 \cdot HCl$ | 51.24 | 50.94 | 6.25 | 6.13 |
| II | 4-Nitrophenyl | 269–270[b] | 90 | $C_{11}H_{15}N_3O_2 \cdot HCl$ | 51.24 | 51.46 | 6.25 | 6.06 |
| III | 4-Aminophenyl | 272–274[c] | 61[i] | $C_{11}H_{17}N_3 \cdot HCl$ | 58.00 | 58.34 | 7.95 | 7.73 |
| IV | 2,4-Dinitrophenyl | 233–234[d] | 100 | $C_{11}H_{14}N_4O_4 \cdot HCl$ | 43.62 | 43.33 | 4.99 | 4.76 |
| V | α-Naphthylmethyl | 244–245[e] | 20 | $C_{16}H_{20}N_2 \cdot 2HCl$ | 61.30 | 61.35 | 7.09 | 7.06 |
| VI | 2-Lepidyl | dec. over 295 | 85 | $C_{15}H_{19}N_3 \cdot 2HCl$ | 22.60[k] | 22.82[k] | | |
| VII | α-(α-Naphthyl)benzyl | 211.5–213[e] | 90 | $C_{22}H_{24}N_2 \cdot 2HCl$ | 67.86 | 67.55 | 6.74 | 6.78 |
| VIII | α-(β-Naphthyl)benzyl | 219–220[e] | 65 | $C_{22}H_{24}N_2 \cdot 2HCl$ | 67.86 | 67.68 | 6.74 | 6.72 |
| IX | 4-Phenylbenzhydryl | 219.5–220[e] | 85 | $C_{24}H_{26}N_2 \cdot 2HCl$ | 69.37 | 69.18 | 6.80 | 6.71 |
| X | 4-Phenoxybenzhydryl | 203–204[f] | 65 | $C_{24}H_{26}N_2O \cdot 2HCl$ | 66.78 | 66.72 | 6.54 | 6.44 |
| XI | α-Phenylphenacyl | 227–228[e] | 90 | $C_{19}H_{22}N_2O \cdot 2HCl$ | 62.10 | 61.92 | 6.59 | 6.51 |
| XII | α-Phenyl-β-hydroxyphenethyl | 233.5–234.5[e] | 60 | $C_{19}H_{24}N_2O \cdot 2HCl$ | 61.77 | 62.06 | 7.10 | 7.45 |
| XIII | α-Phenyl-4-hydroxyphenacyl | 214–216 (dec.) | 65 | $C_{19}H_{22}N_2O_2 \cdot 2HCl$ | 56.85 | 56.80 | 6.55 | 6.72 |
| XIV | 9-Phenanthridylmethyl | 222–223 | 80 | $C_{19}H_{21}N_3 \cdot 2HCl \cdot 2H_2O$[g] | 56.97 | 57.33 | 6.80 | 6.11 |
| XV | 2-Chloro-6-methoxyacridyl | 290–293[h] | 50 | $C_{19}H_{20}ClN_3O \cdot 2HCl$ | 54.98 | 55.33 | 5.35 | 5.68 |

[a] Melting points below 230° are corrected. [b] Yellow needles. [c] Needles. [d] Yellow prisms. [e] Leaflets. [f] The base melts at 90–90.5°. [g] Cl. Calc'd: 17.74. Found: 17.62. [h] Orange powder. [i] By hydrogenation of II with Adams' catalyst in methanol. Reduction was incomplete probably because of insolubility of the substrate and the product. [k] Chlorine.

until the washings were neutral. The basic material was then extracted from the ethereal layer with dilute hydrochloric acid and the base was liberated by addition of alkali. In a few cases the products could be crystallized as bases from petroleum ether. The general procedure, however, was to dry the base in ethereal solution over potassium carbonate, and transform it to the hydrochloride with ethanolic hydrogen chloride solution. Compounds I–IV were isolated as monohydrochlorides, the rest as dihydrochlorides. These salts were purified by crystallization from methanol or ethanol or from mixtures of those alcohols with ether.

Compound III was prepared by catalytic hydrogenation of II. When Compound XI was hydrogenated with Adams' catalyst, cleavage (debenzylation) resulted. Compound XII was subsequently obtained by reduction of XI with aluminum isopropoxide.

The reaction of trityl chloride with methylpiperazine was also attempted and was probably successful. However, in the step of extraction of basic material with *N* hydrochloric acid, cleavage ensued, and only an additional quantity of methylpiperazine could be found in the aqueous extract. Since *tritylmethylpiperazine* would be of no physiological interest if so easily degraded, no further attempts were made to prepare it.

### PREPARATION OF INTERMEDIATES

The *halides* required for Compounds I, II, IV–VI, XI, and XV require no comment. Compound XIV was prepared from 9-chloromethylphenanthridine (5). The substituted benzhydryl chlorides corresponding to Compounds VII–X were prepared by the method of Norris and Blake (6) who described 4-phenoxybenzhydryl chloride and $\alpha$-naphthylphenylchloromethane. Norris and Banta (7) have reported 4-phenylbenzhydryl chloride. $\beta$-Naphthylphenylchloromethane, prepared from the known carbinol, crystallizes from benzene-hexane mixture in colorless needles, m.p. 75.5°.

*Anal.* Calc'd for $C_{17}H_{13}Cl$: C, 80.76; H, 5.19.

Found: C, 80.78; H, 5.22.

The intermediate for Compound XIII, $\alpha$-phenyl-4-hydroxyphenacylbromide, was prepared by the method of Weisl (8) but was found to melt at 165–166° (dec.) whereas Weisl gives 108° for the melting point. The composition was confirmed by analysis and the ability to react with methylpiperazine establishes the position of the bromine.

*Anal.* Calc'd for $C_{14}H_{11}BrO_2$: C, 57.73; H, 3.81.

Found: C, 57.77; H, 3.83.

*Methylpiperazine.* A preparation of this substance has been published recently from the Cyanamid laboratories (9) which is very similar to that we had worked out. The chief differences are in the reductive methylation step (monocarbethoxypiperazine → N′-methyl-N-carbethoxypiperazine) for which we employed the Clarke-Eschweiler procedure (10), and in the isolation of the base which we accomplished by the addition of sodium methoxide solution to the dihydrochloride followed by fractional distillation of the filtered methanolic solution. This procedure gives about 80% recovery of the base, while most of the remainder, contained in intermediate fractions, can be added to later runs. As the reductive methylation gives 99% of pure carbethoxymethylpiperazine hydrochloride the isolation of this substance can be omitted.

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### SUMMARY

1. A series of unsymmetrically disubstituted piperazines has been prepared.

2. Antihistaminic activity is manifested fairly generally in the series. When the N′-substituent is methyl, the optimal size for the N-substituent is close to that of a benzhydryl group.

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## REFERENCES

(1) CASTILLO AND DE BEER, *J. Pharmacol. Exptl. Therap.*, **90**, 104 (1947).
(2) CASTILLO AND DE BEER, *Federation Proc.*, **6**, 315 (1947).
(3) BALTZLY, BUCK, LORZ, AND SCHOEN, *J. Am. Chem. Soc.*, **66**, 263 (1944).
(4) BALTZLY, DUBREUIL, IDE, AND LORZ, *J. Org. Chem.* following article.
(5) MORGAN AND WALLS, *J. Chem. Soc.*, 2447 (1931).
(6) NORRIS AND BLAKE, *J. Am. Chem. Soc.*, **50**, 1808 (1928).
(7) NORRIS AND BANTA, *J. Am. Chem. Soc.*, **50**, 1804 (1928).
(8) WEISL, *Monatsh.*, **26**, 997 (1905).
(9) STEWART, TURNER, DENTON, KUSHNER, BRANCONE, MCEWEN, HEWITT, AND SUBBAROW, *J. Org. Chem.*, **13**, 134 (1948).
(10) CLARKE, GILLESPIE, AND WEISSHAUS, *J. Am. Chem. Soc.*, **55**, 4571 (1933).