[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

UNSYMMETRICALLY DISUBSTITUTED PIPERAZINES. III. N-METHYL-N′-BENZHYDRYLPIPERAZINES AS HISTAMINE ANTAGONISTS[1]

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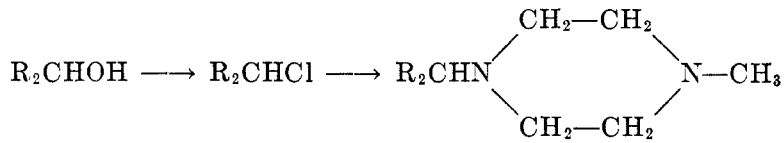
Testing of N-methyl-N′-benzhydrylpiperazine by the tracheal chain method (1, 2) revealed antihistaminic potency almost identical with that of dimethylaminoethyl benzhydryl ether (Benadryl). The toxicity was also very similar. Exploratory experiments reported separately (3) showed that the benzhydryl group was close to the optimal size and that hydrophilic substitution thereon was undesirable. Chief attention was given therefore to variations of the benzhydryl group, the results of which are the subject of this paper.

Synthesis of the benzhydrylmethylpiperazines was along the general line:



Some of the required carbinols were prepared directly from the appropriate aldehydes and Grignard reagents. The others were obtained by reduction of the corresponding ketones.

Quaternization of the methyl-bearing nitrogen atom (Compound II) largely abolished activity. Compounds III and XVIII, in which one phenyl group is replaced by a cyclohexyl radical, also showed diminished potency.

The first substituted benzhydrylmethylpiperazines prepared were Compounds VI, XV, and XVII, having *p*-chloro, *o*-methoxy, and *p*-methoxy substitution respectively. All of these were less toxic than the parent substance, VI being about one-half and XVII about one-third as toxic. Compounds XV and XVII appeared respectively to be slightly less and slightly more potent than I. Compound VI was hard to evaluate by the tracheal chain method since the onset of its action was slow and its action persisted through a number of washings. Tested on live guinea pigs it was found to be very potent and persistent in action, some pigs being protected from histamine shock as long as twenty-four hours. On the other hand, Compound XVII was virtually impotent when tested *in vivo*.

This anomalous behavior of Compound XVII is probably the result of instability since it is rapidly cleaved in warm aqueous and alcoholic solutions to methylpiperazine dihydrochloride and neutral fragments (presumably *p*-methoxybenzhydrol or its ether). In the absence of heat, cleavage is slower and the compound can be purified by careful recrystallization, but dilute aqueous solutions

[1] The work here reported is part of a joint program carried out in collaboration with a pharmacological group in these laboratories.

become turbid within two hours even in the refrigerator. The *o*-methoxy compound, XV, is considerably more stable.

This cleavage is presumably to be written as $R_2CH\overset{+}{N}H\langle \rightarrow R_2\overset{+}{C}H + HN\langle$ which is entirely analogous to the cleavage: $(C_6H_5)_2CH\overset{+}{N}Me_3 \rightarrow (C_6H_5)_2\overset{+}{C}H + NMe_3$ studied by Hughes and Ingold (4) and shown to be independent of $[OH^-]$. Such a cleavage is of the same nature as the rate determining step in SN_1 substitutions,[2] which for benzhydryl halides is: $(C_6H_5)_2CHX \rightarrow (C_6H_5)_2\overset{+}{C}H + X^-$.

Norris and co-workers (8, 9, 10) determined alcoholysis rates for a number of benzhydryl halides and showed that methoxy substitution in the *para* position stimulated alcoholysis tremendously.[3] In the *ortho* position the influence of the methoxyl group was much less. Halogen substitution tended to stabilize the benzhydryl halides, most markedly when in the *ortho* position. These findings are in general accord with theoretical expectations.

Since the rates of cleavage of substituted benzhydryl ammonium salts should parallel the rates of alcoholysis of the corresponding benzhydryl halides, it was hoped that compounds with both alkoxyl and halogen substitution in the benzhydryl moiety would be more stable than Compound XVII and might combine the advantages of the two types of substitution. At the same time a variety of benzhydrylmethylpiperazines with halogen substitution in *ortho* and *meta* positions and with several halogen substitutions were prepared. Data on these substances are presented in Table I.

The expectation that halogen substitution would counteract the labilizing effect of methoxyl substitution was partially fulfilled. Compounds XIX–XXVI are considerably more stable than XVII, although cleavage does take place with

[2] Swain (5) has recently shown that the solvolysis of trityl chloride (and very likely of other halides normally considered to be reacting by the SN_1 mechanism) involves solvation of the halogen by a hydrogen-bonding mechanism. Key evidence in this paper is the existence of third-order reaction rates in indifferent solvents and especially the fact that in solutions containing both phenol and methanol solvolysis is first-order with each and much more rapid than with either alone.

The ion $R_2CH\overset{+}{N}\langle$ might be considered equivalent to $(C_6H_5)_3C—Cl \ldots HOC_6H_5$ of Swain's mechanism, on which basis it would be predicted that cleavage of benzhydrylamine salts in indifferent solvents would be first-order with respect to an alcohol or water present in small amount and would not be affected by added phenol.

Whether these reactions are supposed to proceed by a true ionization or by Swain's mechanism, the effect of electron attracting or repelling substituents on the rates should be the same.

Cantarel (6, 7) has reported certain cleavages of N-substituted benzhydrylamines and their salts. In a qualitative sense the mechanism we suggest can account for the cleavages and the products of secondary reactions he reported but Cantarel informs us that he is not as yet satisfied with a detailed interpretation on this basis.

[3] Norris found the rate for *p*-methoxybenzhydryl chloride about 1200 times that for benzhydryl chloride. The rate determinations of Norris and his group have been criticized rather severely (11, 12, 13), but it is unlikely that their results are seriously in error in respect to the general extent of the larger effects observed.

TABLE I

N-Methyl-N′-Benzhydrylpiperazine Dihydrochlorides

Comp. No.	Benzhydryl Substitution	M.P., °C.*	Empirical Formula	PK_{a1}	PK_{a2}	Analyses, %			
						Carbon		Hydrogen	
						Calc'd	Found	Calc'd	Found
I	None	dec. > 255[a, d]	$C_{18}H_{24}Cl_2N_2$	2.54	7.92	63.72	63.83	7.13	6.88
II	Methochloride hydrochloride	240 (dec.)	$C_{19}H_{26}Cl_2N_2$			64.56	64.37	7.42	7.56
III	1,2,3,4,5,6 hexahydro	249 (dec.)[b]	$C_{18}H_{30}Cl_2N_2$	3.05	8.09	62.57	62.59	8.76	8.38
IV	2-Cl	248	$C_{18}H_{23}Cl_3N_2$	2.38	7.87	57.84	57.72	6.21	6.04
V	3-Cl	250–252	$C_{18}H_{23}Cl_3N_2$	2.39	7.79	57.84	57.46	6.21	6.07
VI	4-Cl	216–216.5[b, e]	$C_{18}H_{23}Cl_3N_2$	2.44	7.78	57.84	57.96	6.21	5.91
VII	2-Br	252 (dec.)[f]	$C_{18}H_{23}BrCl_2N_2$	2.33	7.78	51.68	52.02	5.55	5.80
VIII	4-Br	227–228	$C_{18}H_{23}BrCl_2N_2$	2.43	7.88	51.68	51.53	5.55	5.76
IX	4-Me-4′-Cl	226	$C_{19}H_{25}Cl_3N_2$	2.32	7.78	58.83	59.07	6.50	6.33
X	2,4-Cl_2	233	$C_{18}H_{22}Cl_4N_2$	2.22	7.67	52.94	52.70	5.43	5.06
XI	3,4-Cl_2	237–238.5	$C_{18}H_{22}Cl_4N_2$	2.24	7.65	52.94	52.71	5.43	5.69
XII	4,4′-Cl_2	249[f]	$C_{18}H_{22}Cl_4N_2$	2.33	7.71	52.94	52.82	5.43	5.24
XIII	4-Cl-4′-Br	241–243[g]	$C_{18}H_{22}BrCl_3N_2$	2.27	7.66	47.74	47.66	4.90	4.89
XIV	2,4,4′-Cl_3 monohydrochloride	257–258[a]	$C_{18}H_{20}Cl_4N_2$	2.11	7.46	53.21	53.60	4.97	4.65
XV	2-MeO	196 (dec.)	$C_{19}H_{26}Cl_2N_2O$	2.60	7.93	61.77	61.71	7.10	6.93
XVI	3-EtO	226–228[h]	$C_{20}H_{28}Cl_2N_2O$			62.64	62.48	7.37	7.13
XVII	4-MeO	191–192[a]	$C_{19}H_{26}Cl_2N_2O$	2.44	7.85	61.77	61.88	7.10	6.99
XVIII	4′-MeO-1,2,3,4,5,6,-hexahydro	218 (dec.)	$C_{19}H_{32}Cl_2N_2O$	3.14	8.09	60.77	60.47	8.50	8.40
XIX	2-MeO-5-Cl	225–227[i]	$C_{19}H_{25}Cl_3N_2O$	2.42	7.82	56.50	56.28	6.24	6.02
XX	4-MeO-3-Cl	221 (dec.)	$C_{19}H_{25}Cl_3N_2O$	2.24	7.71	56.50	56.27	6.24	6.10
XXI	4-MeO-4′-Cl	182–184 (dec.)[j]	$C_{19}H_{25}Cl_3N_2O \cdot \frac{1}{2}H_2O$	2.30	7.77	55.26	54.92	6.38	6.57
XXII	4-MeO-3-Br	208.5–209.5	$C_{19}H_{25}BrCl_2N_2O$			50.89	50.42	5.62	5.65
XXIII	4-MeO-2′-Br	211–213 (dec.)[c]	$C_{19}H_{25}BrCl_2N_2O$			50.89	50.82	5.62	5.40
XXIV	4-MeO-2,4′-Cl_2	172[k]	$C_{19}H_{24}Cl_4N_2O$			52.05	52.01	5.52	5.43
XXV	4-MeO-3,4′-Cl_2	210–211.5[k]	$C_{19}H_{24}Cl_4N_2O$			52.05	51.68	5.52	5.79
XXVI	4,4′-$(MeO)_2$-3,3′-Cl_2	225–227[a, l]	$C_{20}H_{26}Cl_4N_2O_2$			51.27	51.27	5.60	5.64

* Melting points below 230° are corrected.

[a] Needles.

[b] Prisms.

[c] Platelets.

[d] M.p. of base, 105.5–107.5°.

[e] The base distills at 137–145° at 0.10–0.15 mm. (bath temperature, 185–197°); at 0.0002–0.0003 mm. pressure it distills from a bath at 90–93°.

[f] M.p. of base, 77–78°.

[g] M.p. of base, 99–101°.

[h] M.p. of base, 75–77°, b.p., 140–150° at 0.03–0.05 mm.

[i] M.p. of base, 124–125°.

[j] M.p. of base, 63–65°.

[k] The base distills at 0.0002–0.0003 mm. from a bath at 140°.

[l] M.p. of base, 99–99.5°.

all of them in aqueous solution. Anti-histaminic activity, however, diminished. Of the methoxy-halogen derivatives, only Compound XXI showed appreciable activity and it was less potent than I. At the same time, examination of the halogenated compounds (IV–XIV) revealed the interesting fact that substitution elsewhere than in the *para* position was not advantageous. Compounds X and XI as well as XX and XXII were less potent than the unsubstituted compound. All the substances having only *para* halogen substitution (VI, VIII, XII, and XIII) manifested the same type of physiological behavior, differences being relatively insignificant.

Two explanations for these findings suggest themselves. The prolonged action of the *para*-halogen derivatives might be due to inhibition of metabolic oxidation, which would probably lead to physiologically inert substances. The other explanation, which is especially reinforced by the observation that repeated washings of the tracheal chains (in the screening tests) do not abolish the effect of these drugs, is that these antihistaminics function by being absorbed on (and blocking the action of) some enzyme whose matrix admits the presence of *para*-substituents only.

The electron-attracting or -releasing effect of these polar substituents ought to be reflected to some extent in the basicity of the benzhydrylmethylpiperazines Electrometric titrations were carried out with about half of the compounds in 50% methanol. The results, expressed as PK_{a1} and PK_{a2} (apparent) for the conjugate acids, are given in Table I. Certain definite trends are evident, although the effect of variations on the basicity of the benzhydrylamino nitrogen tends to be masked by the presence of the more strongly basic methylamino group—itself little affected by substitution in the benzhydryl portion. One halogen substitution (Compounds IV–VIII) diminishes PK_{a1} by 0.1–0.15 PK units. The influence of two or three halogens is greater in about the same ratio.

The influence of methoxyl substitution on PK_{a1} is less than had been expected and is largely negative. The resonance of a methoxyl could be expected to increase electron concentration *para* to itself and thus to increase basicity. This tendency, if present, is of minor importance and the methoxyl seems to function mainly through its inductive action, electron attraction being dominant. This suggests that the methoxyl resonance while important in activated or transition states, has little influence on continuing, unactivated properties of the molecule.

EXPERIMENTAL

The *synthesis* employed by us is not the only one possible but is the most convenient for the preparation of a series. Benzhydryl halides tend to react by the SN_1 mechanism, wherefore hydroxylic solvents must be avoided, and in common non-polar solvents reaction is slow. Monobenzhydrylpiperazines are obtainable by direct reaction of anhydrous piperazine and benzhydryl halides but the operation is far less convenient than that between the halides and methylpiperazine. It is advantageous, though not essential, to use the latter substance in about 100% excess, the unreacted material being subsequently recoverable.

Another objection to the initial preparation of monobenzhydrylpiperazines is that

methylation of the secondary nitrogen by alkylating agents gives poor yields. Reductive methylation carries the risk of removal of the benzhydryl group.[4]

PREPARATION OF INTERMEDIATES

Data on new compounds prepared as intermediates are presented in Table II; melting points are corrected.

Carbinols. The substituted benzhydrols corresponding to Compounds III–VI, IX, and XV–XVIII were obtained from the reactions of phenyl-, *p*-tolyl-, and cyclohexyl-magnesium bromides with the appropriate aldehydes. The other benzhydrols required were prepared by reduction of the corresponding ketones. For this purpose the classical procedure using zinc dust and alcoholic alkali (15) is usually adequate. Ketones containing bromine were reduced by the Meerwein-Ponndorf method to avoid loss of halogen. Ketones having substituents *ortho* to the carbonyl are reduced rather slowly and with these also the Meerwein-Ponndorf method was preferable since the course of the reduction could be followed. The carbinols corresponding to Compounds X, XI, XIV, XX, and XXII–XXV were not crystalline although presumably substantially pure.

Benzophenones. These were prepared by the Friedel-Crafts reaction. Several reactions in this series involving substitution of chloro- and bromo-benzene were found to give poor yields by the usual procedure employing carbon disulfide as solvent. In the preparation of 2,4,4′-trichlorobenzophenone from 2,4-dichlorobenzoyl chloride and chlorobenzene, an excess (3 mols) of the latter was used as solvent. The acid halide was added last, with no temperature control during addition, and the reaction mixture was heated at 80° for an hour thereafter. The yield by this procedure was 90%.

Benzyhydryl chlorides. With one exception the benzhydryl chlorides were prepared by the method of Norris and Blake (10). This procedure was apparently inadequate with the unreactive 2,4,4′-trichlorobenzhydrol, which was accordingly treated with thionyl chloride by the method of Levene and Mikeska (16) (for α-cyclohexylbenzyl chloride). The oily product was reacted directly with methylpiperazine. The neutral fraction from this reaction amounted to 20–25% of the starting carbinol and may be presumed from the odor to have contained sulfur derivatives. Nevertheless, Compound XIV was obtained in 75% yield. The method of Levene and Mikeska would also presumably have given better results than that of Norris and Blake in the preparation of α-cyclohexylbenzyl chloride. The product from the Norris and Blake procedure could be transformed into Compound III in only about a 25% yield. The rather large neutral fraction from this reaction still contained much halogen which was relatively unreactive and is suspected to have been mainly *1-benzyl-1-chlorocyclohexane.*

In all the other preparations the Norris and Blake method appeared to give a nearly quantitative transformation, as judged by the yield of pure benzhydryl chloride or of benzhydrylmethylpiperazine when the chloride was used without purification. Because of the sensitivity of the benzhydryl chlorides they were not subjected to extended manipulations. While many of them undoubtedly could be distilled in a good vacuum this was attempted only with *p*-chlorobenzhydryl chloride, which was known to survive such treatment. With that exception, attempts were made to crystallize the halides from hexane and if these attempts failed, the solvent was evaporated and the oily residue used directly in the next step.

Benzhydrylmethylpiperazines. When the required benzhydryl chloride was available in pure form, 0.02 mole of that substance was added to 0.04 mole of methylpiperazine (3) together with a little benzene to facilitate mixing. When a crude benzhydryl chloride was to be used, a quantity equal in weight to 0.03 mole was taken and 0.06 mole of methylpiperazine. Thereafter the manipulations were identical. Each reaction mixture, covered loosely

[4] *Cf.*, Clarke, Gillespie, and Weisshaus (14) on the reductive methylation of dibenzylamine.

TABLE II

INTERMEDIATES IN THE PREPARATION OF BENZHYDRYLMETHYLPIPERAZINES

COMPOUND[a]	M.P., °C.	APPEARANCE	EMPIRICAL FORMULA	ANALYSES, %			
				Carbon		Hydrogen	
				Calc'd	Found	Calc'd	Found
2,4-$Cl_2C_6H_3COC_6H_4Cl$-4	64–64.5	Needles	$C_{13}H_{17}Cl_3O$	54.66	54.40	2.47	3.00
4-MeO-3-Cl-$C_6H_3COC_6H_5$	82–84	Leaflets or prisms	$C_{14}H_{11}ClO_2$	68.39	68.17	4.46	4.37
4-MeO-2-Cl-$C_6H_3COC_6H_4Cl$-4	68–70	Silky needles	$C_{14}H_{10}Cl_2O_2$	59.79	59.50	3.50	3.72
4-MeO-3-Cl-$C_6H_3COC_6H_4Cl$-4	127.5–128	Silky needles	$C_{14}H_{10}Cl_2O_2$	59.79	59.70	3.50	3.65
4-$ClC_6H_4CHOHC_6H_4Br$-4	103–104	Fine meshed needles	$C_{13}H_{10}BrClO$	52.45	52.60	3.39	3.63
3-$EtOC_6H_4CHOH$-C_6H_5	51.5–52	Needles	$C_{15}H_{16}O_2$	78.91	78.83	7.07	7.16
2-MeO-5-ClC_6H_3CHOH-C_6H_5	70–71.5	Prisms	$C_{14}H_{13}ClO_2$	67.59	67.68	5.27	5.12
4-$ClC_6H_4CHClC_6H_4Br$-4	78	Prisms	$C_{13}H_9BrCl_2$	49.38	49.31	2.87	2.93

[a] All compounds crystallized for analysis from hexane or ether-hexane mixtures.

with a watch-glass, was heated in the steam-bath for 4 to 48 hours, depending on the expected reactivity of the halide. In most cases a deposit of solid, presumably a hydrochloride of methylpiperazine, formed within an hour.

When reaction was believed complete, the flasks were cooled and the contents partitioned between ether and water, the ethereal layers being washed with water until the washings were neutral. The products were then extracted by washing with successive portions of dilute hydrochloric acid until the extracts were strongly acid to Congo Red paper. The ethereal layers, containing only neutral material, were evaporated. The neutral residues usually amounted to less than 1 g. The aqueous solutions were basified and the liberated bases were taken into ether and dried over potassium carbonate. Thereafter procedures varied somewhat. A number of bases could be crystallized from hexane and advantage was taken of this method of purification where possible. Some, perhaps most, of the bases can also be distilled in high vacuum but this was usually unnecessary and distillation was seldom attempted save when other methods failed to give analytically-pure material. Most frequently the base in ethereal solution was poured into ethanol containing an excess of hydrogen chloride.

Most of the *dihydrochlorides* crystallized readily and all could be recrystallized from alcohol or alcohol-ether mixtures. Compound XXV was induced to crystallize only after the base had been distilled, but thereafter behaved normally. Many of the dihydrochlorides came down as fine powders with no grossly visible crystalline form.

In the preparation of Compound XIV, a salt, presumably a *monohydrochloride hydrate*, crystallized during the acid extraction. This salt came out of aqueous solution acid to Congo Red but dissolved in more concentrated acid. It could be crystallized as platelets from water and melted below 112° when immersed in a bath at that temperature. When heated more slowly it sintered at about 103°, gave off gas and did not melt below 200°. It was readily soluble in absolute ethanol at 25° from which solution needle-like crystals separated spontaneously. No other water-insoluble hydrochlorides were encountered but benzhydrylmethylpiperazine itself forms a monohydrochloride with only moderate solubility in water.

Quite a number of the dihydrochlorides offered considerable difficulty in the matter of analysis, apparently due to obstinate retention of water. Compound XXI, for example, appeared to form a hemi-hydrate and gave satisfactory analyses for that composition. The calculated weight (for $\frac{1}{2}$ H_2O) was lost only on drying at 0.0003 mm. Compound XXIII liquefied by absorption of moisture when placed in a vacuum desiccator that contained calcium chloride as the desiccant. The water was removed by evacuation on the oil pump.

Electrometric titrations. These were performed on a Beckmann *p*H meter machine by the usual technique. The solvent was 50% methanol and the concentration was 0.02 molar.

SUMMARY

1. A series of N-methyl-N′-benzhydrylpiperazines has been prepared.

2. A number of these substances, especially those with halogen substitution in the *para* position, show marked activity as histamine antagonists.

3. Those members of the series with methoxyl substitution in the *para* position tend to suffer cleavage when present as the bivalent cations in hydroxylic solvents.

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