[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Unsymmetrically Substituted Piperazines. IX. Quaternary Salts of Benzhydrylpiperazines as Spasmolytics[1]

BY RICHARD BALTZLY, WALTER S. IDE AND EMIL LORZ

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Monoquaternary salts have been prepared from a number of N-benzhydryl-N'-alkylpiperazines. Spasmolytic activity of a high order is shown by many of these substances and is favored by *ortho* or *meta* substitution in one of the phenyl residues.

A considerable number of N-benzhydryl-N'-alkylpiperazines have been prepared in the search for antihistaminic compounds.[2,3] In that series, antihistaminic activity was favored notably by *para* substitution in one of the rings of the benzhydryl portion and was largely abolished by *ortho* or *meta* substitution.

More recently in the course of a search for compounds exhibiting spasmolytic action (specifically of the neurotropic or anti-acetylcholine type) most of these compounds were retested. Further, since quaternization of cholinergic drugs usually, though not always, enhances their activity, quaternary salts were prepared. None of the tertiary amines previously reported showed interesting activity nor did quaternary salts from the important antihistaminic substances (*e.g.*, compounds I, II, XIV–XIX in Table I). However, the quaternary salt XXXII derived from an inactive member of the antihistaminic series was about a third as active as atropine in the screening test.[4]

Consideration of a number of reviews on spasmolytic compounds[5] reveals that while there is a general belief in this field that substitution in the aromatic rings of a spasmolytic is undesirable, this belief is founded largely on observations with a very limited number of substances, mostly substituted in the *para* position. It was decided consequently to examine quaternary salts derived from *ortho*- and *meta*-substituted benzhydrylpiperazines—which as antihistaminics are substantially inactive. The compounds prepared are shown together with various related quaternary salts in Table I. A large number of the *ortho*- and *meta*-substituted compounds have sufficient activity in the screening test to suggest possible utility. In particular, compounds IX, X, XX and XXI are assayed as more than ten times as active as atropine. In intact animals such activity is less pronounced but potency is still very high.

The quaternary salts shown in Table I were prepared by conventional methods from the corresponding N-benzhydryl-N'-alkylpiperazines, most of which already were known. It is assumed without specific proof that quaternization has taken place at the nitrogen atom not attached to the benzhydryl group. This assumption appears to us reasonable for the following reasons: (a) it has already been shown that substitution in the benzhydryl moiety of benzhydrylmethylpiperazines affects principally the dissociation constant of the less basic nitrogen.[2a] Consequently the nitrogen atom that is less likely electronically to be quaternized is that attached to the benzhydryl. (This would, of course, be expected on general considerations). (b) Hindrance is more pronounced at this less basic nitrogen atom. (c) We have never observed diquaternization in the course of these experiments. Derived merely from preparative experiments, this indicates only that one nitrogen is quaternized with considerably less ease than the other. A specific attempt, however, to convert compound XVII to the dimethiodide resulted in recovery of 80% of the starting compound. Since the mother liquors contained some further monomethiodide and some dark tarry material we believe ourselves justified in saying that the second quaternization step is extremely slow and probably attended by decomposition.[6]

Experimental

The benzhydryl chlorides required to prepare the N-benzhydryl-N'-alkylpiperazines all have been reported previously.[2,3,7,8] The less reactive chlorides (corresponding to compounds VIII–XIII and XX–XXII) were prepared from the carbinols by the action of thionyl chloride.[8] The more reactive chlorides are obtained readily by the method of Norris and Blake.[7b]

The ditertiary amines were prepared by methods previously described.[2a] Methylpiperazine being the most accessible N-alkylpiperazine, in most cases the benzhydrylmethylpiperazine was made and quaternized with the requisite alkyl iodide. Compounds II, V, VI, XI, XIII, XXVI, XXX and XXXV were prepared from N-ethylpiperazine[9] to yield a benzhydrylethylpiperazine. An alternative route to the N'-isopropyl derivative is through N-isopropylpiperazine (b.p. 172–176°) which can be prepared by hydrogenation of carbethoxypiperazine in the presence of acetone followed by hydrolysis and isolation by conventional methods. A few of these intermediates appear to be new.

(1) The work here reported is part of a joint project with the Pharmacology Department of these laboratories.

(2) (a) R. Baltzly, S. Dubreuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, **14**, 775 (1949); (b) L. P. Albro, R. Baltzly and A. P. Phillips, *ibid.*, **14**, 771 (1949).

(3) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., THIS JOURNAL, **74**, 2731, 2734 (1949).

(4) The primary screen is against acetylcholine-induced spasm in isolated guinea pig ileum. Drugs showing activity are later tested more extensively in intact animals. It should be emphasized that no direct correlation can be expected between the results of different laboratory tests or between any of them and clinical tests in humans. The latter is the chief concern of the investigator but with the best methods available it is extremely difficult to decide which drug of a series is really to be preferred. Since in clinical practice most compounds are given orally and the oral dosage is ten to a hundred times that required by injection, it is evident that efficiency in absorption and susceptibility to destruction are of no less practical importance than inherent activity.

(5) *Cf.* especially R. R. Burtner, "Medicinal Chemistry," Edited by C. M. Suter, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951.

(6) A slow cleavage in the sense $Ph_2CHNR_3 \rightarrow Ph_2\overset{+}{C}H + NR_3$ has been studied by E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 69 (1933). A comparable cleavage of *p*-methoxybenzhydryl piperazine dihydrochloride also has been reported (ref. 2a).

(7) (a) J. F. Norris and C. Banta, THIS JOURNAL, **50**, 1804 (1928); (b) J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928).

(8) S. Altscher, R. Baltzly and S. W. Blackman, *ibid.*, **74**, 3649 (1952).

(9) W. S. Ide, E. Lorz and R. Baltzly, *ibid.*, **77**, 3142 (1955).

TABLE I

MONOQUATERNARY SALTS OF N-BENZHYDRYLPIPERAZINES Ph_2CHN I^-

Compd. no.	Substns. in phenyl groups	R	R'	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	None	Me	Et	252[a,b]	$C_{20}H_{27}IN_2$	56.9	56.9	6.5	6.3
II	None	Et	Et	255 d.	$C_{21}H_{29}IN_2$	57.8	57.8	6.7	6.8
III	None	Me	*i*-Pr	238	$C_{21}H_{29}IN_2$	57.8	57.6	6.7	6.7
IV	None	Me	*n*-C_4H_9	198	$C_{22}H_{31}IN_2$	58.6	58.0	6.9	7.2
V	None	Et	*n*-Pr	258	$C_{22}H_{31}IN_2$	58.6	58.5	6.9	7.0
VI	None	Et	*i*-Pr	196	$C_{22}H_{31}IN_2$	58.6	58.5	6.9	7.0
VII	Ph_2CH = fluorenyl	Me	Me	228 d.	$C_{19}H_{23}IN_2$	56.1	55.9	5.7	5.6
VIII	2-Cl	Me	Me	226	$C_{19}H_{24}ClIN_2$	51.5	51.7	5.5	5.3
IX	2-Cl	Me	Et	232[c]	$C_{20}H_{26}ClIN_2$	52.6	52.7	5.7	5.6
X	2-Cl	Me	*i*-Pr	236[d]	$C_{21}H_{28}ClIN_2$	53.6	53.9	6.0	6.2
XI	2-Cl	Et	Et	256	$C_{21}H_{28}ClIN_2$	53.6	53.6	6.0	6.0
XII	3-Cl	Me	Et	210	$C_{20}H_{26}ClIN_2$	52.6	52.3	5.7	5.8
XIII	3-Cl	Et	Et	238	$C_{21}H_{28}ClIN_2$	53.6	53.6	6.0	6.1
XIV	4-Cl	Me	Me	125	$C_{19}H_{24}ClIN_2 \cdot EtOH$	51.6	51.7	6.2	6.2
XV	4-Cl	Me	Et	194–198	$C_{20}H_{26}ClIN_2$	52.6	52.1	5.7	5.7
XVI	4-Cl	Me	*i*-Pr	198	$C_{21}H_{28}ClIN_2$	53.6	53.7	6.0	5.9
XVII	4-Cl	Me	*n*-C_4H_9	204	$C_{22}H_{30}ClIN_2$	54.5	54.9	6.2	6.5
XVIII	4,4'-Cl_2	Me	Et	138	$C_{20}H_{25}Cl_2IN_2$	48.9	49.3	5.1	5.5
XIX	4,4'-Cl_2	Me	*i*-Pr	222	$C_{21}H_{27}Cl_2IN_2$	49.9	50.5	5.4	5.4
XX	2-Br	Me	Et	254	$C_{20}H_{26}BrIN_2$	47.9	48.0	5.2	5.5
XXI	2-Br	Me	*i*-Pr	216	$C_{21}H_{28}BrIN_2$	48.9	48.9	5.5	5.6
XXII	4-NO_2	Me	Et	168	$C_{20}H_{26}IN_3O_2 \cdot {}^1/_2H_2O$[e]	50.4	50.1	5.7	5.9
XXIII	2-Me	Me	Me	204	$C_{20}H_{27}IN_2$	56.9	56.8	6.5	6.7
XXIV	2-Me	Me	Et	190	$C_{21}H_{29}IN_2$	57.8	58.2	6.7	6.7
XXV	2-Me	Me	*i*-Pr	225	$C_{22}H_{31}IN_2$	58.7	58.6	6.9	7.0
XXVI	2-Me	Et	Et	242[f]	$C_{22}H_{31}IN_2$	58.7	58.5	6.9	7.2
XXVII	3-Me	Me	Me	218	$C_{20}H_{27}IN_2$	56.9	57.1	6.5	6.6
XXVIII	3-Me	Me	Et	212	$C_{21}H_{29}IN_2$	57.8	57.8	6.7	6.4
XXIX	3-Me	Me	*i*-Pr	226	$C_{22}H_{31}IN_2$	58.7	59.1	6.9	7.1
XXX	3-Me	Et	Et	236	$C_{22}H_{31}IN_2$	58.7	58.9	6.9	6.9
XXXI	2-MeO	Me	Et	188	$C_{21}H_{29}IN_2O$	55.8	55.5	6.4	6.8
XXXII	3-EtO	Me	Et	193–194	$C_{22}H_{31}IN_2O$	56.6	56.9	6.7	6.5
				Derivatives of *trans*-2,5-dimethylpiperazine					
XXXIII	None	Me	Me	219.5–220	$C_{21}H_{29}IN_2$	57.8	58.1	6.7	6.9
XXXIV	None	Me	Et	201–202	$C_{22}H_{31}IN_2$	58.6	59.1	7.0	6.8
XXXV	None	Et	Et	190	$C_{23}H_{33}IN_2$	59.5	60.1	7.2	7.0
				Related piperazinium salts					
XXXVI	β-$C_{10}H_7CH_2N(CH_2CH_2)_2\overset{+}{N}MeEtI^-$			182	$C_{18}H_{25}IN_2$	54.5	54.6	6.4	6.7
XXXVII	α-$C_{10}H_7CHPhN(CH_2CH_2)_2\overset{+}{N}Me_2I^-$			232	$C_{23}H_{27}IN_2$	60.2	60.1	5.9	6.1
XXXVIII	α-$C_{10}H_7CHPhN(CH_2CH_2)_2\overset{+}{N}MeEtI^-$			233	$C_{24}H_{29}IN_2$	61.0	60.9	6.2	6.2
XXXIX	α-$C_{10}H_7CHPhN(CH_2CH_2)_2\overset{+}{N}MeiPrI^-$			246	$C_{25}H_{31}IN_2$	61.8	61.6	6.4	6.4

[a] Some specimens melted at 228°. This is probably a case of dimorphism. [b] The corresponding chloride melts at 174°. *Anal.* Calcd. for $C_{20}H_{27}ClN_2$: C, 72.6; H, 8.2. Found: C, 72.7; H, 8.1. [c] The corresponding chloride melts at 242°. *Anal.* Calcd. for $C_{20}H_{26}Cl_2N_2$: C, 65.7; H, 7.2. Found: C, 65.5; H, 7.2. [d] The corresponding chloride melts at 223°. *Anal.* Calcd. for $C_{21}H_{28}Cl_2N_2$: C, 66.5; H, 7.4. Found: C, 66.3; H, 7.2. [e] Loss in weight when dried at 65–80° and 20 μ pressure: 2%. Calcd. for ${}^1/_2H_2O$: 1.9%. [f] The corresponding bromide melts at 258°. *Anal.* Calcd. for $C_{22}H_{31}BrN_2$: C, 65.5; H, 7.8. Found: C, 65.8; H, 7.8.

N-Benzhydryl-N'-isopropylpiperazine.—From benzhydryl chloride and N'-isopropylpiperazine. The base forms a monohydroiodide melting at 185–187°. *Anal.* Calcd. for $C_{20}H_{27}IN_2$: C, 56.9; H, 6.5. Found: C, 56.5; H, 7.1.

N-[*o*-Chlorobenzhydryl]-N'-ethylpiperazine.—From *o*-chlorobenzhydryl chloride and ethylpiperazine. The dihydrochloride was crystallized from absolute ethanol; m.p. 250°. *Anal.* Calcd. for $C_{19}H_{25}Cl_3N_2$: C, 58.8; H, 6.5. Found: C, 58.6; H, 6.6.

N-*o*-Chlorobenzylpiperazine.—This base was prepared by the reaction of *o*-chlorobenzyl chloride with piperazine in alcohol. It boils at 121–123° at 2 mm. pressure and forms a monohydrochloride that melts at 220°. *Anal.* Calcd. for $C_{11}H_{16}Cl_2N_2$: C, 53.4; H, 6.5. Found: C, 53.8; H, 6.7.

N-[*o*-Chlorobenzhydryl]-N'-[*o*-chlorobenzyl]-piperazine.—To 2.4 g. (0.01 mole) of *o*-chlorobenzhydryl chloride was added 4.2 g. (0.02 mole) of *o*-chlorobenzylpiperazine. The reactants were heated on the steam-bath in a loosely-closed flask for 24 hours. The pasty reaction mixture was filtered and washed well with ether. The combined filtrates were acidified with *N* hydrochloric acid whereupon solid separated from both ethereal and aqueous layers. The solid was collected and recrystallized from absolute alcohol; m.p. 232°. *Anal.* Calcd. for $C_{24}H_{25}Cl_3N_2$: C, 64.4; H, 5.6. Found: C, 64.1; H, 5.7.

N-[*m*-Chlorobenzhydryl]-N'-ethylpiperazine.—From *m*-chlorobenzhydryl chloride and ethylpiperazine. The dihydrochloride crystallizes from abs. alcohol and melts at

262°. *Anal.* Calcd. for $C_{19}H_{25}Cl_3N_2$: C, 58.8; H, 6.5. Found: C, 58.8; H, 6.4.

N-[*o*-Methylbenzhydryl]-N'-methylpiperazine.—From methylpiperazine and *o*-methylbenzhydryl chloride. The dihydrochloride crystallizes from abs. ethanol; m.p. 242°. *Anal.* Calcd. for $C_{19}H_{26}Cl_2N_2$: C, 64.6; H, 7.4. Found: C, 64.2; H, 7.6.

N-[*o*-Methylbenzhydryl]-N'-ethylpiperazine.—From ethylpiperazine and *o*-methylbenzhydryl chloride. The dihydrochloride crystallizes from abs. alcohol and melts at 244°. *Anal.* Calcd. for $C_{20}H_{28}Cl_2N_2$: C, 65.4; H, 7.7. Found: C, 65.4; H, 7.5.

N-[*m*-Methylbenzhydryl]-N'-methylpiperazine.—From methylpiperazine and *m*-methylbenzhydryl chloride, the dihydrochloride crystallized from aqueous ethanol melts at 259°. *Anal.* Calcd. for $C_{19}H_{26}Cl_2N_2$: C, 64.6; H, 7.4. Found: C, 64.5; H, 7.3.

N-[*m*-Methylbenzhydryl]-N'-ethylpiperazine.—From ethylpiperazine and *m*-methylbenzhydryl chloride, the dihydrochloride crystallized from aqueous ethanol melts at 258°. *Anal.* Calcd. for $C_{20}H_{28}Cl_2N_2$: C, 65.4; H, 7.7. Found: C, 65.6; H, 7.8.

N-[*p*-Nitrobenzhydryl]-N'-methylpiperazine.—From methylpiperazine and *p*-nitrobenzhydryl chloride.[8] The hydrochloride prepared in the usual way was recrystallized twice from ethanol–ether mixture and then melted at 192–194°. *Anal.* Calcd. for $C_{18}H_{23}Cl_2N_3O_2$: C, 56.2; H, 6.0. For $C_{18}H_{22}ClN_3O_2$: C, 62.1; H, 6.4. Found: C, 61.7; H, 6.5.

This salt was evidently a monohydrochloride. A specimen of hydrochloride freshly precipitated with excess acid and not recrystallized melted at 215–218° dec. and gave: C, 56.0; H, 6.1. Evidently the dihydrochloride is unstable except in the presence of excess acid.[10]

The derivatives of 2,5-dimethylpiperazine were prepared by a slightly different route.

N-Benzhydryl-2,5-dimethylpiperazine.—Forty grams (0.2 mole) of benzhydryl chloride was added to a solution of 34.5 g. (0.3 mole) of 2,5-dimethylpiperazine (a Carbide and Carbon specimen shown by benzoylation to be at least 85% and probably over 90% the *trans* isomer) in 100 cc. of dioxane (distilled from sodium). The solution was heated on the steam-bath 14 hours and about half the dioxane was distilled off. On cooling, the residue was partitioned between water and ether and the aqueous layers were discarded (washing being continued until the wash water was no longer alkaline). The ethereal layer was then extracted with dilute hydrochloric acid. The neutral material remaining after the acid extraction weighed 10–11 g. (after evaporation of the ether). The acid extracts were basified and the precipitate was taken into ether and dried over potassium hydroxide. On evaporation of the ether, the residue weighed 25.5 g. (0.09 mole calculated as monobenzhydryl derivative). The residue was dissolved in ether–hexane mixture, charcoaled and refrigerated. There separated 12 g. of a yellow solid that melted at 81–82.5°. The mother liquors were evaporated, residue 7.5 g. At this stage the base did not readily yield a homogeneous hydrochloride. Accordingly the base was distilled at 60–80 μ pressure (bath temperature 100–120°). After this treatment, the base crystallized readily from hexane in small stubby prisms that melted at 82.5–83°. *Anal.* Calcd. for $C_{19}H_{24}N_2$: C, 81.4; H, 8.6. Found: C, 81.5; H, 8.5.

In 10 cc. of warm methanol was dissolved 2.8 g. (0.01 mole) of the base. To this was added one equivalent of standard *N* hydrochloric acid and the solution was evaporated *in vacuo*. The residue was dissolved in acetone and 0.1 g. more of the base was added. Dry ether then was added to incipient turbidity and solid separated on scratching. This was recrystallized from ethanol–acetone–ether mixture. It formed fine clumped needles, m.p. 195–196°. *Anal.* Calcd. for $C_{19}H_{25}ClN_2$: C, 72.0; H, 8.0. Found C, 72.1; H, 7.8.

N-Benzhydryl-N'-2,5-trimethylpiperazine.—Five and six-tenths gram (0.02 mole) of crystalline base from the above preparation was dissolved in 20 cc. of ether, 3 cc. of formalin was added and the ether was evaporated. To the residue was added 0.5 cc. more formalin and 1 cc. of 90% formic acid. After 5 minutes warming on the steam-bath, layers had separated and 1 cc. more formic acid was required to restore homogeneity. After a half-hour, 1 cc. more formic acid was added and heating was continued for three hours. The solution then was acidified further with hydrochloric acid and evaporated *in vacuo*. The glassy residue was dissolved in water and the base was liberated and taken into ether. Attempts to crystallize a dihydrochloride were unsuccessful but a monohydrochloride, prepared by accurate neutralization with standard acid, was induced to crystallize. After recrystallization from acetone–ether mixtures it formed rosettes of prisms melting at 162.5–164°. *Anal.* Calcd. for $C_{20}H_{27}ClN_2$: C, 72.5; H, 8.2. Found: C, 72.3; H, 8.3.

Quaternizations.—The quaternary iodides listed in Table I were prepared from the appropriate N-benzhydryl-N'-alkyl ditertiary amines by reaction with the required alkyl iodides in acetone solution. In earlier experiments only one equivalent of alkyl iodide was used in order to avoid formation of diquaternary salts. When later it was found that diquaternization was not an interfering factor, the alkyl iodides were used in excess. The reactions were usually run at around 40° and in most cases the quaternary iodides separated initially in crystalline form. They were recrystallized from absolute ethanol or from alcohol–ether mixtures.

Compound XXXV was prepared from N-benzhydryl-2,5-dimethylpiperazine by refluxing with ethyl iodide in methanol solution over potassium carbonate. Compound XXXVI was prepared by treating *n*-bromomethylnaphthalene with methylpiperazine and quaternizing the resultant ditertiary amine (not further characterized).

Since it was realized that the standard quaternization procedure, resulting in precipitation of monoalkiodide, was not critical as to *possibility* of diquaternization, a specific attempt was made to prepare a diquaternary salt.

In 5 cc. of methanol was dissolved 0.5 g. of the monoquaternary compound XVII. Two cc. of methyl iodide was added and the flask, loosely stoppered, was set near the steam-bath (temp. 30–40°) for 70 hours. Volatile material was taken off *in vacuo* and the yellow sirup remaining was extracted with hot ethyl acetate, which removed most of the color. During these extractions the residue crystallized. It was recrystallized from ethanol–ethyl acetate–ether mixture giving 0.4 g. of solid that melted at 202–203° and at the same temperature when mixed with the starting material (m.p. 204°). A small amount of the same material appeared in the mother liquors which also contained dark tarry material (the color was not extracted by chloroform and was therefore not due to iodine).

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TUCKAHOE 7, NEW YORK

(10) *Cf.* ref. 2a for the influence of substituents on basicity in related compounds.