[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

Histamine Antagonists. II.[1] Unsymmetrical 1,4-Disubstituted Piperazines

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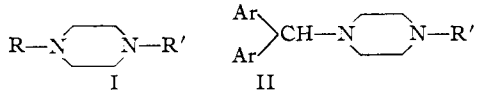
The search for compounds having antihistaminic activity has led to extensive investigations of a wide variety of synthetic compounds which have been included in an excellent review by Huttrer.[2] The substituted ethylenediamines as a class have received special attention from a large group of investigators.[3] In an effort to obtain a superior antihistaminic agent having a longer duration of action and a lower incidence of side effects, new types of amine structures were examined.

In the course of this study, it was considered of interest to synthesize a group of 1,4-disubstituted piperazines for pharmacologic investigation. In this investigation, unsymmetrical 1,4-disubstituted piperazines (I) were prepared in which the group in the 1-position contained one or more aromatic nuclei and the substituent in the 4-position was an alkyl or substituted alkyl group of fairly low molecular weight. In this way the benzohydryl grouping was incorporated into a piperazine structure as represented by II.

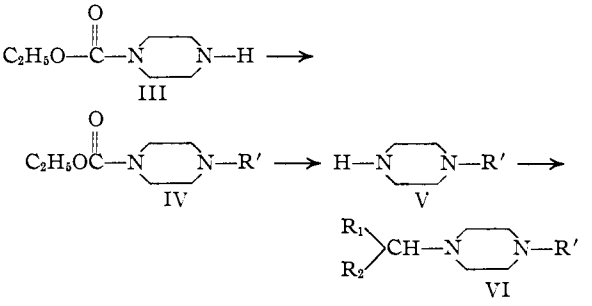
Although the literature discloses a number of instances of the preparation of symmetrical 1,4-disubstituted piperazines,[4] the synthesis of compounds of type I where R and R′ are different is more difficult.



I II

Because of the strongly basic properties of both nitrogen atoms in piperazine, it becomes necessary to introduce a "blocking" group on one nitrogen which can be readily removed subsequent to the introduction of the desired alkyl group. Moore, Boyle and Thorn,[5] and more recently Stewart and co-workers[6] have described such a reaction sequence, involving the use of 1-carbethoxypiperazine (III) as the intermediate. Alternately, it has been shown by Baltzly and co-workers[7] that monoalkylpiperazines (V) can be synthesized by the alkylation of 1-benzylpiperazine with the subsequent removal of the benzyl group by catalytic hydrogenation.

The method of Moore, Boyle and Thorn has been the method of choice for the synthesis of the 1-alkylpiperazines (V) described in this paper. Generally, it was found convenient to add the low molecular weight group to 1-carbethoxy-piperazine (III), to remove the ester grouping from the 1-alkyl-4-carbethoxypiperazine (IV) with concentrated hydrochloric acid, and finally to alkylate with the appropriate halide using, as the acid binding agent, sodium carbonate (Method A) or a second equivalent of 1-substituted piperazine (Method B) thereby forming the unsymmetrical 1,4-disubstituted piperazine (VI). With the more stable benzohydryl chlorides and 1-methylpiperazine, the yields were good (70–95%). As R′ increased in molecular weight, the yields of VI progressively decreased, as was the case for the less stable benzohydryl halides.



III IV V VI

Of the disubstituted piperazines listed in Table II, all were prepared by the method outlined above with the exception of those where R′ is hydrogen, methylol, guanyl and β-dimethylaminoethyl. In these cases, the sequence of introduction of R and R′ groups was reversed. Thus, the alkylation of 1-carbethoxypiperazine with the substituted benzohydryl group was first carried out, with subsequent hydrolysis of the carbethoxy grouping and addition of the smaller group (Method C). However, because of difficulties encountered in the hydrolysis step in these instances, Method A was preferred.

All the unsymmetrical 1,4-disubstituted piperazines found in Table II antagonize the effects of histamine. The most active compound, 1-(*p*-chlorobenzohydryl)-4-methylpiperazine,[8] experimentally, has a potency comparable to that of the antihistamine agents currently used clinically, with a longer duration of action. A more detailed pharmacologic report on the testing of these piperazines will appear elsewhere (Roth, Richards and Shepperd in press)

Experimental

Aldehydes.—*p*-Iodo-,[9] *p*-bromo-[10a] and *m*-chlorobenzaldehyde[10b] were prepared according to the directions

(1) For the preceding paper see Weston, THIS JOURNAL, **69**, 980 (1947).

(2) Huttrer, *Enzymologia*, **12**, 277 (1948).

(3) Viaud, *Produits pharm. France*, **2**, 53 (1947); Huttrer, *et al.*, THIS JOURNAL, **68**, 1999 (1946); Clapp, *et al.*, *ibid.*, **69**, 1549 (1947).

(4) von Braun, Goll and Metz, *Ber.*, **59**, 2416 (1926); Pollard and co-workers, THIS JOURNAL, **56**, 150 (1934); **57**, 199, 1788, 1988 (1935); **58**, 1980 (1936).

(5) Moore, Boyle and Thorn, *J. Chem. Soc.*, 39 (1929).

(6) Stewart, Turner, Denton, *et al.*, *J. Org. Chem.*, **13**, 134 (1948).

(7) Baltzly, Buck, Lorz and Schon, THIS JOURNAL, **66**, 263 (1944).

(8) This compound, designated as AH-289, is undergoing clinical trial.

(9) Patterson, *J. Chem. Soc.*, **69**, 1002 (1896).

(10) (a) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 442; (b) *ibid.*, p. 130.

given in the literature. *p*-Fluorobenzaldehyde, b. p. 96–97° at 57 mm., $n^{24.5}D$ 1.5180, was obtained in a 66% yield by following the procedure described for *p*-bromobenzaldehyde.[11] The preparation of 2-thiophenecarboxyaldehyde has been described recently.[12] The *o*- and *p*-chlorobenzaldehydes were obtained from the Heyden Chemical Corporation.

Alcohols.—The *p*-chloro-,[13] *p*-bromo-,[14] *p*-iodo-,[15] *p*-fluoro-,[15] *o*-chloro-,[13] *m*-chloro-[13] and *p*-methylbenzohydrols[16] were synthesized by the addition of phenylmagnesium bromide to the halogenated benzaldehydes. *p,p'*-Dichlorobenzohydrol[17] was similarly obtained from *p*-chlorophenylmagnesium bromide and *p*-chlorobenzaldehyde. Condensation of phenylmagnesium bromide with 2-thiophenecarboxyaldehyde gave a 79% yield of α-(2-thienyl)-benzyl alcohol.[18] Improved yields (80–95%) were realized by employing excess (50–100%) of the Grignard reagent. The constants found for these compounds agreed with those previously reported.

p-Chlorobenzohydrol was also prepared in an excellent yield from *p*-chlorobenzophenone[19] by reduction with zinc and alkali.[20] A similar reduction of *p*-methoxybenzophenone[21] gave *p*-methoxybenzohydrol which melted at 66–68°; literature value is 59–60°.[22]

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.56; H, 6.59.

α-(2-Pyridyl)-benzyl alcohol was synthesized from picolinic acid and benzaldehyde using the method of Ashworth and co-workers.[23]

α-(*n*-Propyl)-*p*-chlorobenzyl Alcohol.—To the Grignard reagent obtained from 98.4 g. (0.8 mole) of *n*-propyl bromide and 19.2 g. (0.8 mole) of magnesium metal, there was added an ether solution of 56.2 g. (0.4 mole) of *p*-chlorobenzaldehyde at a gentle reflux rate. During the reaction, the solid magnesium complex separated. The resulting mixture was finally refluxed two hours, then hydrolyzed by the addition of 50 g. of ammonium chloride in 200 cc. of water. Any solid that remained, after separation of the ether layer, was warmed with water, then collected on a filter and washed well with ether. The ether extracts of the filtrate were combined with the original ether solution, then dried and concentrated. Distillation of the residual oil gave 56.2 g. (76%) of the desired alcohol, b. p. 113–114° at 1.4 mm., $n^{27}D$ 1.5270.

Anal. Calcd. for $C_{10}H_{13}ClO$: C, 65.04; H, 7.09. Found: C, 64.77; H, 6.89.

α-(Cyclohexyl)-*p*-chlorobenzyl Alcohol.—The Grignard reagent from 114 g. (0.7 mole) of cyclohexyl bromide and 14.4 g. (0.6 mole) of magnesium metal reacted with 70.3 g. (0.5 mole) of *p*-chlorobenzaldehyde. The product, isolated in the foregoing manner, boiled at 122–125° at 0.7 mm., and weighed 72 g. (64%). It solidified and melted at 70–71° after crystallization from Skelly B (b. p. 63–68°).

Anal. Calcd. for $C_{13}H_{17}ClO$: C, 69.47; H, 7.63. Found: C, 69.29; H, 7.52.

α-(2-Thienyl)-*p*-chlorobenzyl Alcohol.—As in the preceding example, the Grignard reagent from 191.5 g. (1 mole) of *p*-chlorobromobenzene and 24.3 g. (1 mole) of magnesium turnings was treated with 112 g. (1 mole) of 2-thiophenecarboxyaldehyde. After isolation in the usual manner, 193 g. (86%) of the alcohol was obtained, b. p. 157–158° at 0.3 mm. The material solidified and after recrystallization from Skelly B (b. p. 63–68°), it melted at 59.5–60°.

Anal. Calcd. for $C_{11}H_9ClOS$: C, 58.80; H, 4.04. Found: C, 58.95; H, 4.12.

Chlorides.—The alcohols were readily converted to the corresponding chlorides by the procedure of Norris and co-workers[16,22] which consists of treating a benzene–Skelly B (b. p. 63–68°) solution of the carbinol with hydrogen chloride gas in the presence of anhydrous calcium chloride. The *p*-methoxybenzohydryl[22] and the thiophene-containing chlorides were too unstable to distil. In these cases, the crude chlorides were used without further purification in the subsequent condensation. The *o*-chloro- and *m*-chlorobenzohydryl chlorides and α-(*n*-propyl)-*p*-chlorobenzyl chloride distilled without decomposition but gave slightly high analytical values for carbon. In Table I, data regarding these chlorides are recorded.

1-Carbethoxy-4-substituted Piperazines

With the exception of 1-carbethoxy-4-methylpiperazine, these intermediates were made by the procedure of Stewart, *et al.*,[6] in which 1-carbethoxypiperazine[5] was treated with the appropriate halide. The constants found for 1-carbethoxy-4-ethylpiperazine agree with those previously reported.[6] The boiling point of 1-carbethoxy-4-*n*-butylpiperazine was 140° at 0.8 mm.[24]

1-Carbethoxy-4-methylpiperazine.—Methylation of 1-carbethoxypiperazine with formaldehyde and formic acid by the method of Clarke and co-workers[25] gave a 96% yield of 1-methyl-4-carbethoxypiperazine,[6] b. p. 116–119° at 10 mm.; $n^{25}D$ 1.4633.

1-Benzohydryl-4-carbethoxypiperazine.—The reaction of benzohydryl bromide and 1-carbethoxypiperazine in the presence of sodium carbonate gave a 60% yield of 1-benzohydryl-4-carbethoxypiperazine, m. p. 114–115° after recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: N, 8.64. Found: N, 8.71.

1-Carbethoxy-4-(δ-hydroxybutyl)-piperazine.—Treatment of 1-carbethoxypiperazine with tetramethylene chlorohydrin in the presence of sodium carbonate resulted in a 60% yield of 1-(δ-hydroxybutyl)-4-carbethoxypiperazine, b. p. 165–170° at 0.4 mm., $n^{25}D$ 1.4838. The hydrochloride prepared in the usual manner melted at 118–119° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{11}H_{22}N_2O_3 \cdot HCl$: N, 10.50. Found: N, 10.99.

TABLE I

CHLORIDES $R_1R_2CH\text{–}Cl$

R_1	R_2	B. p., °C.	Mm.	Ref. index n_D	°C.	Yield, %
C_6H_5	*p*-ClC_6H_4[a]	159–160	2	1.6007	25	93
C_6H_5	*p*-BrC_6H_4[a]	134–135	0.5	1.6186	25.5	88
C_6H_5	*p*-FC_6H_4[b]	125–127	1	1.5726	27	92
C_6H_5	*p*-IC_6H_4[c]	148–149	0.6	1.6470	28	59
C_6H_5	*m*-ClC_6H_4[d]	157–160	1.8	1.5997	28	54
C_6H_5	*o*-ClC_6H_4[a]	142–145	1.5	1.6028	21.5	53
C_6H_5	*p*-$CH_3C_6H_4$[a]	141–142	2.6	1.5861	25	88
p-ClC_6H_4	*p*-ClC_6H_4[a]	159–160	1.3	[e]		90
n-C_3H_7	*p*-ClC_6H_4	101–103	1	1.5296	25	68
C_6H_{11}[f]	*p*-ClC_6H_4	134–136	1.6	1.5514	25.5	91
2-C_5H_4N[g]	C_6H_5	126–131	0.3	1.5927	25.5	92

[a] Norris and Banta, THIS JOURNAL, 50, 1807 (1928). [b] *Anal.* Calcd. for $C_{13}H_{10}ClF$: C, 70.75; H, 4.57. Found: C, 71.27; H, 4.74. [c] *Anal.* Calcd. for $C_{13}H_{10}ClI$: C, 47.52; H, 3.07. Found: C, 47.81; H, 3.26. [d] Norris and Blake, THIS JOURNAL, 50, 1811 (1928). [e] M. p., 63° (reference [a]). [f] Cyclohexyl. [g] Pyridyl.

(11) "Organic Syntheses," *J. Chem. Soc.*, 1947, p. 89.

(12) King and Nord, *J. Org. Chem.* **13**, 635 (1948); Weston and Michaels, in press.

(13) Bachmann, Carlson and Moran, *J. Org. Chem.*, **13**, 917 (1948).

(14) Ullmann and Meyer, *Ann.*, **332**, 78 (1904).

(15) Schiemann and Pillarsky, *Ber.*, **64**, 1345 (1931).

(16) Norris and Banta, THIS JOURNAL, **50**, 1807 (1928).

(17) Norris and Tibbetts, *ibid.*, **42**, 2091 (1920).

(18) Minnis, *ibid.*, **51**, 2143 (1929).

(19) Gomberg and Cone, *Ber.*, **39**, 3278 (1906).

(20) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 90.

(21) Gattermann, Ehrhardt and Marsh, *Ber.*, **23**, 1204 (1890).

(22) Norris and Blake, THIS JOURNAL, **50**, 1811 (1928).

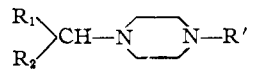
(23) Ashworth and co-workers, *J. Chem. Soc.*, 809 (1939).

(24) Stewart, *et al.*, ref. 6, report b. p. 140° at 8 mm.

(25) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

TABLE II

1,4-DISUBSTITUTED PIPERAZINES



R_1	R_2	R′	B. p., °C.	Mm.	Ref. index n_D	°C.	Method	Nitrogen, % Calcd.	Found	M. p.,[q] °C.	Salt Formula	Nitrogen, % Calcd.	Found
C_6H_5	C_6H_5	CH_3	[a]				A			258–260	$C_{18}H_{22}N_2\cdot 2HCl$	8.26	8.21
C_6H_5	C_6H_5	CH_2OH					C			189–190	$C_{18}H_{22}N_2O\cdot 2HCl$	7.88	7.76
C_6H_5	C_6H_5	C_2H_5					A			241–242	$C_{19}H_{24}N_2\cdot 2HCl$	7.93	7.97
C_6H_5	C_6H_5	CH_2CH_2OH					A			229[b]	$C_{19}H_{24}N_2O\cdot 2HCl$	7.59	7.61
C_6H_5	C_6H_5	C_4H_9-n					A			248[b]	$C_{21}H_{28}N_2\cdot 2HCl$	7.35	7.39
C_6H_5	C_6H_5	$C(=NH)NH_2$					C			294–295	$C_{18}H_{22}N_4\cdot 1/2H_2SO_4$	16.31	15.92[c]
C_6H_5	C_6H_5	$CH_2CH_2N(CH_3)_2$	162–164	0.7	1.5613	26.5	C	12.99	12.84	255–257	$C_{21}H_{29}N_3\cdot 2HCl$	10.60	10.88[d]
C_6H_5	p-F-C_6H_4	CH_3	140–141	0.6[e]	1.5556	27	A	9.85	9.85	230–231	$C_{18}H_{21}FN_2\cdot HCl$	8.73	8.55
C_6H_5	p-Cl-C_6H_4	CH_3	160–161	0.5	1.5777	28	A	9.31	9.23	223–224	$C_{18}H_{21}ClN_2\cdot HCl$	8.31	8.17
C_6H_5	p-Br-C_6H_4	CH_3	175–176	0.8	1.5906	25	A	8.11	8.30	249–250	$C_{18}H_{21}BrN_2\cdot HCl$	7.34	7.46
C_6H_5	p-I-C_6H_4	CH_3	180–181	0.5	[f]		A	7.14	7.21	260–261	$C_{18}H_{21}IN_2\cdot HCl$	6.54	6.54
C_6H_5	o-Cl-C_6H_4	CH_3	179–180	2	1.5803	25	A	9.31	9.44	272–273	$C_{18}H_{21}ClN_2\cdot HCl$	8.31	8.34
C_6H_5	m-Cl-C_6H_4	CH_3	177	1.5	1.5235	29	A	9.31	9.58	249–250	$C_{18}H_{21}ClN_2\cdot HCl$	8.31	8.22
C_6H_5	p-CH_3-C_6H_4	CH_3	159–160	1	1.5665	24.5	A	9.99	9.93[g]	228–229	$C_{19}H_{24}N_2\cdot HCl$	8.84	8.66[h]
C_6H_5	p-CH_3O-C_6H_4	CH_3	168–169	0.7			A			194–195	$C_{19}H_{24}N_2O\cdot 2HCl$	7.59	7.80
C_6H_{11}[i]	p-Cl-C_6H_4	CH_3					A			278–279[b]	$C_{18}H_{27}ClN_2\cdot 2HCl$	7.38	7.30[j]
n-C_3H_7	p-Cl-C_6H_4	CH_3	142–143	1.7	1.5283	29	A	10.50	10.84	176–177	$C_{16}H_{25}ClN_2\cdot HCl$[k]	9.24	8.99
p-Cl-C_6H_4	p-Cl-C_6H_4	CH_3	168	0.3			A			245–246	$C_{18}H_{20}Cl_2N_2\cdot 2HCl$	6.86	6.59
C_6H_5	p-Cl-C_6H_4	C_2H_5					A			227–228	$C_{19}H_{23}ClN_2\cdot 2HCl$	7.30	7.48
C_6H_5	p-Cl-C_6H_4	C_4H_9-n					A			254–255	$C_{21}H_{27}ClN_2\cdot 2HBr$	5.55	5.51
C_6H_5	p-Cl-C_6H_4	$(CH_2)_4OH$					A			211–212	$C_{21}H_{27}ClN_2O\cdot 2HCl$	6.50	6.51
C_6H_5	p-Cl-C_6H_4	$C_{10}H_{21}$-n	245–250	0.4	1.5372	31	A	6.56	6.03[l]		$C_{27}H_{39}ClN_2$[m]		
C_6H_5	2-C_5H_4N[n]	CH_3	[o]				B	15.72	15.60		$C_{17}H_{21}N_3$[m]		
C_6H_5	2-C_4H_3S[p]	CH_3					B			202[b]	$C_{16}H_{20}N_2S\cdot 2HCl$	8.11	8.05
p-Cl-C_6H_4	2-C_4H_3S[p]	CH_3					B			216[b]	$C_{16}H_{19}ClN_2S\cdot 2(COOH)$	5.76	5.71

[a] Melting point 105–108°. [b] Melted with decomposition. [c] Calcd.: C, 62.97; H, 6.75. Found: C, 62.80; H, 6.97. [d] Calcd.: C, 63.63; H, 7.88. Found: C, 63.55; H, 7.78. [e] Melting point, 62–64°. [f] Melting point, 80–81°. [g] Calcd.: C, 81.38; H, 8.63. Found: C, 81.05; H, 8.19. [h] Calcd.: Cl, 11.19. Found: Cl, 11.31. [i] Cyclohexyl. [j] Calcd.: C, 56.92; H, 7.70. Found: C, 56.67; H, 7.63. [k] Dihydrochloride, m. p. 256–257° dec. Calcd. for $C_{15}H_{19}ClN_2\cdot 2HCl$: N, 8.25. Found: N, 8.17. [l] Calcd.: C, 75.93; H, 9.21. Found: C, 76.35; H, 9.12. [m] No satisfactory salts could be obtained. Formula of base. [n] Pyrridyl. [o] Melting point, 95–97°. [p] Thienyl. [q] The melting points of these salts vary considerably with the rate of heating.

1-Carbethoxy-4-*n*-decylpiperazine.—Reaction of 1-carbethoxypiperazine with *n*-decyl bromide gave an 85% yield of 1-*n*-decyl-4-carbethoxypiperazine, b. p. 168–169° at 0.4 mm.; $n^{29}D$ 1.4628.

Anal. Calcd. for $C_{17}H_{34}N_2O_2$: N, 9.39. Found: N, 9.45.

1-Substituted Piperazines

With the exception of 1-(β-hydroxyethyl)-piperazine which was synthesized by the method of Baltzly and coworkers,[7] the 1-substituted piperazines were prepared by hydrolyzing the corresponding 1-carbethoxy-4-substituted piperazine by the method of Moore, Boyle and Thorn.[5] Where the 4-substituent was of fairly low molecular weight, this hydrolysis was satisfactorily accomplished with concentrated hydrochloric acid. For substituents such as the benzhydryl group, it was necessary to use ethanolic potassium hydroxide. The physical constants for 1-methyl-[6] and 1-ethylpiperazine[5,7] agree with those in the literature.

1-Benzohydrylpiperazine.—Hydrolysis of 1-benzohydryl-4-carbethoxypiperazine by refluxing with ethanolic potassium hydroxide for twenty-two hours gave a 75% yield of 1-benzohydrylpiperazine, b. p. 189–190° at 1 mm.; m. p. 70–72°. On treating this base with ethanolic *d*-tartaric acid, the *d*-tartrate salt was formed, m. p. 194.5–195° from absolute ethanol.

Anal. Calcd. for $C_{17}H_{22}N_2\cdot C_4H_6O_6$: N, 6.93. Found: N, 6.75.

1-*n*-Butylpiperazine.—Hydrolysis of 1-*n*-butyl-4-carbethoxypiperazine using concentrated hydrochloric acid formed 1-*n*-butylpiperazine in an 81% yield; b. p. 186–192° at 747 mm.; $n^{25}D$ 1.4630.

Anal. Calcd. for $C_8H_{18}N_2$: N, 19.70. Found: N, 19.62.

1-(δ-Hydroxybutyl)-piperazine.—By hydrolyzing 1-carbethoxy-4-(δ-hydroxybutyl)-piperazine with concentrated hydrochloric acid, a 20% yield of 1-(δ-hydroxybutyl)-piperazine was obtained; b. p. 142° at 6 mm.; $n^{21}D$ 1.4985.

Anal. Calcd. for $C_8H_{18}N_2O$: N, 17.71. Found: N, 17.74.

1-*n*-Decylpiperazine.—Hydrolysis of 1-*n*-decyl-4-carbethoxypiperazine by means of concentrated hydrochloric acid gave a 77% yield of 1-*n*-decylpiperazine, b. p. 115–120° at 0.4 mm.; $n^{23}D$ 1.4660.

Anal. Calcd. for $C_{14}H_{30}N_2$: N, 12.38. Found: N, 12.83.

The dihydrochloride was prepared in the usual manner, and melted at 271–274° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{14}H_{30}N_2\cdot 2HCl$: N, 9.37. Found: N, 9.05.

Unsymmetrical 1,4-Disubstituted Piperazines

Method A. 1-(*p*-Chlorobenzohydryl)-4-methylpiperazine.—A solution of 11.8 g. (0.05 mole) of *p*-chlorobenzohydryl chloride in 75 cc. of dry xylene was added dropwise, with stirring, to a refluxing mixture of 5.0 g. (0.05 mole) of 1-methylpiperazine and 5.3 g. (0.05 mole) of anhydrous sodium carbonate in 30 cc. of dry xylene. The mixture was refluxed for sixty hours. The acidic extracts of the xylene layer were made alkaline and the resulting oil removed with ether. The ether extracts were dried, concentrated and the residual oil was distilled. There was obtained 12 g. (80%) of product, b. p. 160–161° at 0.5 mm.; $n^{28}D$ 1.5777. The monohydrochloride salt, prepared by adding the base to one equivalent of hydrogen chloride gas dissolved in isopropyl alcohol, melted at 220–

224°. One crystallization from absolute alcohol gave pure material, m. p., 223–224°.

Anal. Calcd. for $C_{18}H_{21}ClN_2 \cdot HCl$: C, 64.09; H, 6.58. Found; C, 63.89; H, 6.78.

The dihydrochloride melted at 220–221°.

Anal. Calcd. for $C_{18}H_{21}ClN_2 \cdot 2HCl$: N, 7.50. Found: N, 7.56.

The mono-methiodide quaternary salt separated from an ether solution containing equivalent amounts of the free base and methyl iodide. It melted at 119–120° (dec.) after crystallization from absolute alcohol.

Anal. Calcd. for $C_{19}H_{24}ClIN_2$: C, 51.54; H, 5.46; N, 6.33. Found: C, 51.22; H, 5.54; N, 6.35.

Method B. 1-Methyl-4-(α-2-thienylbenzyl)-piperazine.—A solution of 10.4 g. (0.05 mole) of α-2-thienylbenzyl chloride in 50 cc. of anhydrous ether was added dropwise to a stirred solution of 10 g. (0.1 mole) of 1-methylpiperazine in 100 cc. of anhydrous ether. The resulting mixture was allowed to stand at room temperature for twenty-four hours. The dihydrochloride of 1-methylpiperazine was then removed by filtration. After extraction of the filtrate with dilute hydrochloric acid, the acid extracts were made strongly alkaline. The oil which separated was extracted with ether. On treatment of dry ether solution with gaseous hydrogen chloride, the dihydrochloride of 1-methyl-4-(α-2-thienylbenzyl)-piperazine was obtained in 35% yield, m. p. 202° (dec.) after recrystallization from ethanol–pentane.

Method C. 1-Benzohydryl-4-guanylpiperazine Sulfate.—To a refluxing mixture of 2.52 g. (0.01 mole) of 1-benzohydrylpiperazine and 1.38 g. (0.01 mole) of S-methylisothiourea sulfate in 20 cc. of alcohol, there was added sufficient water to give a clear solution which was then refluxed three hours. The solid material which separated from the cooled reaction mixture was crystallized from dilute alcohol; m. p. 294–295° (dec.).

1-Benzohydryl-4-(β-dimethylaminoethyl)-piperazine.—The N-lithio derivative of 1-benzohydrylpiperazine was prepared by slowly adding 4.7 g. (0.019 mole) of the amine dissolved in 25 cc. of ether, to 35 cc. (0.021 mole) of a 0.6 *M* solution of methyllithium in ether and refluxing the mixture two hours. A solution of 2.15 g. (0.02 mole) of β-dimethylaminoethyl chloride in 25 cc. of ether was then slowly added. The reaction mixture was refluxed several hours, then hydrolyzed with dilute acid. The acidic extracts of the ether layer were combined with the original acid layer and made alkaline. The ether extracts of the basic material were combined, dried and concentrated. Distillation of the residue gave 4.4 g. of crude material, b. p. 158–168° at 0.7 mm. The addition of two equivalents of hydrogen chloride to an isopropyl alcohol solution of the distilled material gave the dihydrochloride which melted at 255–257° (dec.) after further purification from an isopropyl alcohol–ether mixture.

1-Benzohydryl-4-methylolpiperazine.—To a solution of 1.8 g. (0.007 mole) of 1-benzohydrylpiperazine in 25 cc. of 50% methanol, there was added 2.2 cc. of formalin. An oil separated immediately. The mixture was heated for fifteen minutes on the steam-bath, cooled and the liquid decanted from the insoluble oil which was then dissolved in warm ethanolic hydrogen chloride. On cooling the alcohol solution, the dihydrochloride separated which melted at 189–190° after two crystallizations from an absolute alcohol–ether mixture; weight 1 g. (41%). The product assumed a bluish cast on standing.

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Summary

The synthesis of twenty-five unsymmetrical 1,4-disubstituted piperazines as histamine antagonists is described. These compounds were prepared by one of three methods each of which utilized 1-carbethoxypiperazine as the starting material. 1-(*p*-Chlorobenzohydryl)-4-methylpiperazine proved to be the most potent of the group as an antihistaminic agent.

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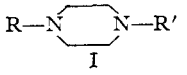
Histamine Antagonists. III. 1- and 1,4-Substituted Piperazine Derivatives

BY K. E. HAMLIN, ARTHUR W. WESTON, FRANCIS E. FISCHER AND R. J. MICHAELS, JR.

In the previous paper[1] of this series, the preparation of unsymmetrical 1,4-disubstituted piperazines as antihistaminic agents was disclosed. In connection with this investigation, the piperazines described in this paper were also prepared. Included in the present series, are the compounds represented by formula I in which R is an aralkyl or heterocyclic group and R′ is hydrogen, methyl, β-hydroxyethyl or is identical with R.



I

The synthesis of these products which are listed in Table I was accomplished by several methods. With the exception of 1-(9-fluorenyl)-piperazine, all the 1-substituted and symmetrical 1,4-disubstituted piperazines were prepared in a manner essentially paralleling that of Baltzly and co-workers[2] (Method A), where the appropriate halide was reacted with anhydrous piperazine. When the reactivity of the halide was not too great, both the 1- and 1,4-substituted piperazines were isolated in satisfactory yields. With the more reactive 9-bromofluorene and 9-chloromethylphenanthrene, only the disubstituted products were formed in practically quantitative yields. In the case of 2-bromopyridine, autoclave conditions were used and both the 1- and 1,4-substituted piperazines were isolated. To prepare the 1,4-disubstituted compounds in which R′ is methyl, one of two methods was used. Certain 1-substituted piperazines were conveniently methylated by the procedure of Clarke and co-workers[3] using formal-

(1) Hamlin, Weston, Fischer and Michaels, THIS JOURNAL, **71**, 2731 (1949).

(2) Baltzly, Buck, Lorz and Schon, *ibid.*, **66**, 263 (1944).

(3) Clarke, Gillespie and Weisshaus, *ibid.*, **55**, 4571 (1933).