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.

Acknowledgment.—The authors wish to thank Mr. E. F. Shelberg and the members of the Microanalytical Department for the microanalyses and Mr. Robert W. DeNet and Dr. Karl M. Beck for their technical assistance in the preparation of some of the intermediates.

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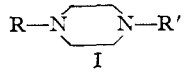
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

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).

dehyde and formic acid (Method B). Alternately, 1-methylpiperazine[1] (or 1-(2-hydroxyethyl)-piperazine[1]), when alkylated with the appropriate aralkyl halide in the presence of sodium carbonate (Method C), yielded the unsymmetrical 1,4-disubstituted piperazines in satisfactory yields.

To synthesize 1-(9-fluorenyl)-piperazine, it was necessary to prepare 1-(9-fluorenyl)-4-carbethoxypiperazine by a modification of the method of Stewart and co-workers[4] and then to remove the ester grouping with concentrated hydrochloric acid by the method of Moore, Boyle and Thorn.[5]

The pharmacology of these compounds will be reported elsewhere.

Experimental

2,2-Diphenylethanol.—This alcohol was obtained in a 93% yield by reducing diphenylacetic acid with lithium aluminum hydride.[6] The product boiled at 144–145° at 1 mm. and melted at 54–55° after repeated crystallization. The literature[7,8,9] reports a variety of melting points which range from 59–65°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.98; H, 7.05.

The benzoate of our material melted at 90-92° which agrees with the value previously reported.[8]

Halides.—In all cases, the halides used in these experiments were prepared by methods paralleling those in the literature. 2,2-Diphenylethyl chloride,[10] b. p. 136–137° at 2.8 mm. was prepared from the alcohol described above using thionyl chloride in the presence of pyridine.[11] Chloromethylation of naphthalene and phenanthrene according to the method of Cambron[12] gave 1-chloromethylnaphthalene and 9-chloromethylphenanthrene.[13] 2-Chloromethylnaphthalene was obtained by the chlorination of 2-methylnaphthalene according to Tarbell's[14] directions. 3,3-Diphenylallyl chloride was prepared from ethyl β-chloropropionate and phenylmagnesium bromide following the method of Weizmann and Bergmann.[15] The procedure of Wittig and Felletschin[16] for the bromination of fluorene by means of bromosuccinimide was improved by the use of catalytic amounts of benzoyl peroxide.[17] In this manner good yields of 9-bromofluorene were obtained. The 2-bromopyridine was prepared from 2-aminopyridine according to the published directions.[18]

Method A. 1-(1-Naphthylmethyl)-piperazine and 1,4-Di-(1-naphthylmethyl)-piperazine.—A solution of 8.6 g. (0.1 mole) of anhydrous piperazine and 17.7 g. (0.1 mole) of 1-chloromethylnaphthalene in 150 cc. of anhydrous ethanol was allowed to stand at room temperature for seventeen hours. The crystalline precipitate was removed by filtration and the filtrate concentrated *in vacuo*. The residue was made alkaline and then extracted with ether. After being dried, the ether extract was distilled. The product, 1-(1-naphthylmethyl)-piperazine, b. p. 154–156° at 1 mm., was a yellow, semi-solid material; yield 8.3 g. (37%). The monohydrochloride prepared from this base melted at 227–228° after recrystallization from ethanol.

The crystalline precipitate which was separated from the reaction mixture represented a 27% (10 g.) yield of 1,4-di-(1-naphthylmethyl)-piperazine. After recrystallization from ethanol, it melted at 163–165°.

1-(2-Pyridyl)-piperazine and 1,4-Di-(2-pyridyl)-piperazine.—A mixture of 31.6 g. (0.2 mole) of 2-bromopyridine, 34.4 g. (0.4 mole) of piperazine and 20 g. of pyridine was heated in an autoclave for six hours at 155°. The reaction mixture was made strongly alkaline and extracted well with ether. The ether extract was dried and distilled. The fraction boiling at 114–116° at 1.4 mm. and weighing 12.9 g. (40% yield) was 1-(2-pyridyl)-piperazine. The monohydrochloride, prepared from this base and recrystallized from anhydrous ethanol, melted at 232–233°. The dihydrochloride was prepared and melted at 275–276° after recrystallization from ethanol.

Anal. Calcd. for $C_9H_{13}N_3.HCl$: N, 21.15. Found: N, 20.90.

In the distillation just described, the fraction boiling at 135–140° at 1.4 mm. was 1,4-di-(2-pyridyl)-piperazine; 7 g. (15% yield). This material solidified and after recrystallization from ethanol melted at 124–126° (lit.,[19] 124–126°). The dihydrochloride, prepared from this base and recrystallized from anhydrous ethanol, melted at 281–283°.

Method B. 1-(*p*-Bromobenzyl)-4-methylpiperazine.—An aqueous solution of 5 g. (0.017 mole) of 1-(*p*-bromobenzyl)-piperazine hydrochloride[20] was treated with 0.72 g. (0.017 mole) of sodium hydroxide. To this mixture was added 12.5 cc. of anhydrous formic acid and 2.5 cc. of formalin. The resulting solution was refluxed four hours and then concentrated *in vacuo*. The residue was made alkaline and extracted with ether. The dried ether extracts were treated with ethereal hydrogen chloride to precipitate the dihydrochloride of 1-(*p*-bromobenzyl)-4-methylpiperazine. After recrystallization from ethanol, the salt melted at 292–294° and weighed 5 g. (86% yield).

Method C. 1-(1-Naphthylmethyl)-4-(2-hydroxyethyl)-piperazine.—A mixture of 6.5 g. (0.05 mole) of 1-(2-hydroxyethyl)-piperazine,[1] 14 g. (0.075 mole) of 1-chloromethylnaphthalene, 5.3 g. (0.05 mole) of sodium carbonate and 100 cc. of anhydrous xylene was refluxed and stirred for eighteen hours. The mixture was cooled and then acidified with concentrated hydrochloric acid. The xylene and water were removed *in vacuo* and the residue was treated with solid sodium hydroxide. The liberated oil was extracted with ether and dried. The ether solution was next treated with ethereal hydrogen chloride to precipitate 14 g. (81% yield) of 1-(1-naphthylmethyl)-4-(2-hydroxyethyl)-piperazine dihydrochloride. After recrystallization from ethanol-ether, the salt melted at 206–206.5° dec.

1-(9-Fluorenyl)-4-carbethoxypiperazine.—A mixture of 15.8 g. (0.1 mole) of 1-carbethoxypiperazine, 27 g. (0.11 mole) of 9-bromofluorene and 5.8 g. (0.05 mole) of sodium carbonate in 100 cc. of butanol was heated for four hours on a steam-bath. The reaction mixture was cooled and the resulting crystalline mass was filtered and washed with butanol. This solid material was dissolved in dilute hydrochloric acid and washed with ether. The acid layer was made alkaline and the liberated oil solidified. After one recrystallization from ethyl acetate, the yield of 1-(9-fluorenyl)-4-carbethoxypiperazine was 22 g. (70%); after further recrystallization from ethyl acetate, m. p. 152–153°.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: N, 8.69. Found: N, 8.65.

The hydrochloride of this base was prepared in the usual manner and after recrystallization from ethanol–ether, it melted at 219–220° dec.

Anal. Calcd. for $C_{20}H_{22}N_2O_2.HCl$: N, 7.81. Found: N, 7.77.

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

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

(6) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(7) Bergmann, *J. Chem. Soc.*, 412 (1936).

(8) Whitmore, *et al.*, THIS JOURNAL, **63**, 652 (1941).

(9) Kharasch, Steinfeld and Mayo, *J. Org. Chem.*, **5**, 362 (1940).

(10) Hepp, *Ber.*, **6**, 1439 (1873).

(11) Human and Mills, *Nature*, **158**, 877 (1946).

(12) Cambron, *Can. J. Research*, **17B**, 10 (1939).

(13) Cook, *et al.*, *J. Chem. Soc.*, 1323 (1935).

(14) Tarbell, *et al.*, THIS JOURNAL, **67**, 197 (1945).

(15) Weizmann and Bergmann, *J. Chem. Soc.*, 401 (1936).

(16) Wittig and Felletschin, *Ann.*, **555**, 133 (1943).

(17) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(18) "Organic Syntheses," Vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 16.

(19) Denton and Howard, U. S. Patent 2,459,367.

(20) This material was supplied us by Dr. Marlin T. Leffler who prepared it in the course of another investigation.

TABLE I

1- AND 1,4-SUBSTITUTED PIPERAZINES, R—N⟨⟩N—R′

R	R′	B. p. °C.	Mm.	Ref. index n_D	°C.	Method	Yield, %	Nitrogen, % Calcd.	Found	M. p., °C.	Salt Formula	Nitrogen, % Calcd.	Found
p-Br-C_6H_4-CH_2	CH_3					B	86			292–294	$C_{12}H_{17}BrN_2$·2HCl	8.19	8.05
$(C_6H_5)_2CH$-CH_2	CH_3					C	40			278–279	$C_{18}H_{24}N_2$·2HCl	7.93	7.80[a]
$(C_6H_5)_2C{=}CHCH_2$	CH_3	167–170	0.9	1.5807	30.5	C	71	9.58	9.85	139–140	$C_{20}H_{24}N_2$·HCl[b,c]	8.52	8.58
1-$C_{10}H_7CH_2$[d]	H	154–156	1			A	37			227–228	$C_{18}H_{18}N_2$·HCl	10.67	10.45
1-$C_{10}H_7CH_2$[d]	CH_3					B	Quant.			241[e]	$C_{16}H_{20}N_2$·2HCl	8.94	8.73
1-$C_{10}H_7CH_2$[d]	CH_2CH_2OH					C	81			206–206.5[e]	$C_{17}H_{22}N_2O$·2HCl	8.16	8.10
1-$C_{10}H_7CH_2$[d]	1-$C_{10}H_7CH_2$[d]			[f]		A	27	7.65	7.79[g]		$C_{26}H_{26}N_2$[h]		
2-$C_{10}H_7CH_2$[d]	H	155–160	1	1.6101	25	A	33			193–195	$C_{18}H_{18}N_2$·HCl	10.67	10.31
2-$C_{10}H_7CH_2$[d]	CH_3					B	82			281[e]	$C_{16}H_{20}N_2$·2HCl	8.94	8.83
2-$C_{10}H_7CH_2$[d]	CH_2CH_2OH					C	33			241[e]	$C_{17}H_{22}N_2O$·2HCl	8.16	8.05
2-$C_{10}H_7CH_2$[d]	2-$C_{10}H_7CH_2$[d]			[i]		A	23	7.65	7.46[j]		$C_{26}H_{26}N_2$[h]		
9-$C_{13}H_9$[k]	H					..	89			283–285[e]	$C_{17}H_{18}N_2$·2HCl	8.67	8.47
9-$C_{13}H_9$[k]	CH_3					C	57			265–268[e]	$C_{18}H_{20}N_2$·2HBr	6.57	6.66
9-$C_{13}H_9$[k]	CH_2CH_2OH			[l]		C	68	9.52	9.65	243–244[e]	$C_{19}H_{22}N_2O$·2HCl	7.63	7.54
9-$C_{13}H_9$[k]	9-$C_{13}H_9$[k]			[m]		A	Quant.	6.76	6.63		$C_{30}H_{26}N_2$[h]		
9-$C_{14}H_9CH_2$[n]	CH_3					C	43			254–255[e]	$C_{20}H_{22}N_2$·2HCl	7.71	7.49
9-$C_{14}H_9CH_2$[n]	9-$C_{14}H_9CH_2$[n]			[o]		A	Quant.	6.01	6.14	283–286	$C_{34}H_{30}N_2$·2HCl	5.20	5.25
2-C_5H_4N[p]	H	114–116	1.4	1.5888	27	A	40	25.75	25.74	275–276	$C_9H_{13}N_3$·2HCl	17.79	17.51
2-C_5H_4N[p]	CH_3	106–107	2.7	1.5625	25	B	82			258–259	$C_{10}H_{15}N_3$·2HCl	16.80	16.55
2-C_5H_4N[p]	2-C_5H_4N[p]	135–140	1.4	[q]		A	15	23.32	23.06	281–283	$C_{14}H_{16}N_4$·2HCl	17.87	17.73

[a] Calcd.: C, 64.58; H, 7.42. Found: C, 64.58; H, 7.70. [b] This compound readily forms a monohydrate, m. p. 86–87° (isopropyl alcohol). [c] Calcd. for $C_{20}H_{24}N_2HCl\cdot H_2O$: C, 69.24; H, 7.85. Found: C, 69.30; H, 7.89. [d] Naphthylmethyl. [e] Melted with decomposition. [f] Solid, m. p. 163–164.5°. [g] Calcd.: C, 85.20; H, 7.16. Found: C, 85.20; H, 7.10. [h] Formula of base. [i] Solid, m. p. 159–60.5°. [j] Calcd.: C, 85.20; H, 7.16. Found: C, 85.20; H, 7.18. [k] Fluorenyl. [l] Solid, m. p. 143–144°. [m] Solid, m. p. 291–292° dec. [n] Phenanthryl. [o] Solid, m. p. 253–254°. [p] Pyridyl. [q] Solid, m. p. 124–126°.

1-(9-Fluorenyl)-piperazine.—A solution of 10 g. (0.03 mole) of 1-(9-fluorenyl)-4-carbethoxypiperazine in 100 cc. of concentrated hydrochloric acid was refluxed for sixty hours. The acid solution was concentrated *in vacuo* to yield 7 g. (89%) of crystalline 1-(9-fluorenyl)-piperazine which after recrystallization from anhydrous ethanol melted at 283–285° dec.

Acknowledgment.—The authors wish to thank Mr. E. F. Shelberg and the members of the Microanalytical Department for the microanalyses and Mr. Morris Freifelder for conducting the autoclave experiment.

Summary

The synthesis of a number of 1-substituted, 1,4-symmetrical disubstituted and 1,4-unsymmetrical disubstituted piperazines as histamine antagonists is described. These compounds were prepared by one of three methods from piperazine or 1-carbethoxypiperazine.

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[CONTRIBUTION FROM ROHM & HAAS COMPANY]

Transetherification Reactions. Alcohols with Certain β-Alkoxy Esters

BY W. J. CROXALL, J. O. VAN HOOK AND R. LUCKENBAUGH[1]

The condensation of acetylene with ethyl carbonate[2] provides a convenient synthesis for ethyl β,β-diethoxypropionate (I)[3] and ethyl α,α-diethoxysuccinate. This paper is the first of a series concerned with the chemistry of these esters.

During work on the isolation of the pure propionate (I) from the reaction of acetylene with ethyl carbonate,[2] it was observed that a mixture of ethyl β-ethoxyacrylate (IV) and the propionate (I) was completely converted to the latter compound by treatment with ethanol and a catalytic amount of sodium ethoxide. It was also shown that acrylate–propionate mixtures upon distillation from a catalytic amount of sodium bisulfate were readily converted to ethanol and the acrylate (IV).[2] Further verification of the reversible nature of this system was obtained in the present work when it was demonstrated that mixtures of ethanol and the acrylate (IV) in the presence of sodium bisulfate, boron trifluoride or sulfuric acid were converted to ethyl β,β-diethoxypropionate. Similar results were realized with 1-butanol and the acrylate in which case ethyl β-ethoxy-β-butoxypropionate was isolated as the main product.

The mobility of the above acrylate–propionate system suggested that the beta ethoxy groups of these esters should be capable of replacement by other alkoxy groups. Actually, this supposition has been realized, the results of which are herein reported.

(1) Present address: University of Maryland, College Park, Md.

(2) Croxall and Schneider, THIS JOURNAL, 71, 1256 (1949).

(3) McElvain and Clarke (*ibid.*, 69, 2657 (1947)) have shown the difficulties encountered in preparing this compound in good yield.