[CONTRIBUTION FROM THE CALCO CHEMICAL DIVISION AND THE LEDERLE LABORATORIES DIVISION OF THE AMERICAN CYANAMID COMPANY]

EXPERIMENTAL CHEMOTHERAPY OF FILARIASIS. IV. THE PREPARATION OF DERIVATIVES OF PIPERAZINE[1]

H. W. STEWART, R. J. TURNER, AND J. J. DENTON; S. KUSHNER, L. M. BRANCONE, W. L. McEWEN, R. I. HEWITT, AND Y. SUBBAROW

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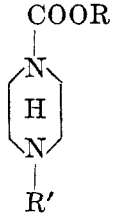
The general term "filariasis" includes several diseases in man and other vertebrates caused by slender, parasitic, nematode worms located in the circulatory and lymphatic systems, muscles, serous cavities or connective tissues. The microfilariae or prelarval forms are discharged by the adult worms into the blood, lymphatics, or tissues of the hosts. Intermediate hosts (mosquitoes or biting flies) are required for the completion of the life cycle.

In man, several species of filaria are known, the most important being *Wuchereria bancrofti*, *Wuchereria malayi*, and *Onchocerca volvulus*. The former two are widely distributed in Africa, India, China, Japan, the East Indies, and the West Indies. The latter is found only in Africa and certain parts of central America. In animals, filarial diseases are widespread, even in the United States.

Though compounds containing heavy metals, particularly those of antimony (1), and certain cyanine dyes (18) have shown anti-filarial activity in laboratory animals, their use in the treatment of human filariasis leaves much to be desired.

During a recent course of investigation in our laboratories, certain piperazines having the following structure



were found to be quite active as anti-filarial agents on both micro- and macrofilariae.

Of the carbalkoxyl groups studied in this type of molecule, the carbethoxyl seemed to be more effective than the carbomethoxyl, carbo-*n*-butoxyl, or carboisobutoxyl. By retaining the carbethoxyl group in the 1-position, the substituent in the 4-position was varied in order to obtain a compound with the greatest apparent antifilarial activity for this type of structure. Of the phenyl, benzyl, and saturated and unsaturated alkyl groups tried in the 4-position, the methyl group gave a compound with maximum antifilarial activity, 1-carbethoxy-4-methylpiperazine.

During this study a number of piperazine derivatives, having the above as

[1] For paper III of this series see Hewitt, Kushner, Stewart, Wallace, White, and SubbaRow.

well as other structures, were prepared. The accompanying table lists compounds synthesized, along with the physical properties for both the piperazine base and its hydrochloride salt. The superscript numbers in the table correspond to the numbered references at the end of the paper, while the superscript letters refer to procedures in the experimental part by which the compounds were synthesized. The last column shows the relative activity of these compounds as antifilarial agents; 1-carbethoxy-4-methylpiperazine, being the most active, is represented by ++. The antifilarial activity is described more completely in paper number II of this series (17). The preparation of other piperazines is presented in the following paper of this series (8).

There are but a few types of compounds known to react with piperazine to produce a reasonable yield of a monosubstituted piperazine; an alkyl chlorocarbonate is one such type of reagent (2, 3). We have utilized this method in preparing several 1-carbalkoxypiperazines which served as intermediates for a number of the compounds reported here. The position of the carbethoxyl group in the monosubstitution product from the reaction of 2-methylpiperazine and ethyl chlorocarbonate was not determined.

Most of the 1-carbalkoxy-4-alkylpiperazines were prepared from the corresponding 1-carbalkoxypiperazines by alkylation, either with an alkyl halide or an alkyl *p*-toluenesulfonate (2). 1-Carbethoxy-4-methylpiperazine, however, was prepared by reductive alkylation of 1-carbethoxypiperazine with formaldehyde in the presence of zinc dust and hydrochloric acid. 1-Carbethoxy-4-phenylpiperazine was synthesized from 1-phenylpiperazine by reacting it with ethyl chlorocarbonate.

Certain 1-alkylpiperazines have been made by Baltzly, *et al.* (3) by the alkylation of 1-benzylpiperazine in the 4-position with subsequent removal of the benzyl group by catalytic hydrogenation (16). A more indirect procedure has been used by Prelog and Stepan (4) for the preparation of 1-methylpiperazine from 1-methyl-4-phenylpiperazine. Moore, Boyle, and Thorn (2) obtained 1-ethylpiperazine from the hydrolysis of 1-carbethoxy-4-ethylpiperazine in concentrated hydrochloric acid. We have used the latter method for preparing the 1-alkylpiperazines reported in this article.

Several media were tried in an attempt to find a more rapid and convenient procedure than that of Moore, *et al.* (2) for the hydrolysis of 1-carbethoxy-4-methylpiperazine. Aqueous acetic acid containing sulfuric acid, 50% sulfuric acid, and aqueous alcoholic sodium hydroxide were all inferior to concentrated hydrochloric acid. One experiment with the latter indicated, however, that a shorter heating period might be used, since about 80% hydrolysis, based on recovered starting material, had occurred after heating for only six hours.

Although Abderhalden and Haas (13) reported the preparation of 1,4-dimethylpiperazine from piperazine and methyl iodide, our attempts to repeat the work were unsuccessful. A quaternary salt appeared to form instead. Several other methods have been reported (14) for the synthesis of this compound. We have prepared 1,4-dimethylpiperazine by the methylation of piperazine with formaldehyde in formic acid (15).

2,3-Diphenyl-5,6-dihydropyrazine was prepared according to Mason (12) by reacting ethylenediamine with benzil. Catalytic hydrogenation of this compound appeared to give only one diastereoisomeric form (the lower-melting, *beta* form) of 2,3-diphenylpiperazine.

EXPERIMENTAL[2]

Procedure (a). Preparation of 1-alkylpiperazines. The 1-alkylpiperazines, as dihydrochlorides, were prepared by hydrolyzing the appropriate 1-carbethoxy-4-alkylpiperazine with concentrated hydrochloric acid using the method of Moore, Boyle, and Thorn (2). They may be purified by crystallization from absolute ethyl alcohol.

1-Methylpiperazine dihydrochloride. Crystallization of 1-methylpiperazine dihydrochloride from absolute ethyl alcohol gave a product which, when dried at 40°, melted at 82.5–83° (corr.).

Anal. Calc'd for $C_5H_{12}N_2 \cdot 2HCl \cdot H_2O$: Cl, 37.1 Found: Cl, 37.2.

Further crystallization of 1-methylpiperazine dihydrochloride monohydrate and a long period of drying (2 days) at 50° gave a product, which by a Volhard titration corresponded to a partially dehydrated form, that softened at 83° and completely melted at 191°. Two other melting points, 110° (3) and 242° (4), have been reported in the literature.

1-Methylpiperazine. 1-Methylpiperazine was liberated from a solution of the dihydrochloride monohydrate (150 g.) in 100 cc. of water by using 50% sodium hydroxide solution. The base was separated without a solvent. It contained a large amount of dissolved water which was difficult to remove. By placing it repeatedly over fresh portions of solid potassium hydroxide, it was freed of water. On distillation of the dried liquid, 57.5 g. of 1-methylpiperazine was obtained.

1-Isopropylpiperazine dihydrochloride. The dihydrochloride was crystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_7H_{16}N_2 \cdot 2HCl$: C, 41.5; H, 8.0; N, 13.9.
Found: C, 41.2; H, 8.7; N, 14.1.

Procedure (b). Preparation of 1-phenyl-4-methylpiperazine dihydrochloride. To a solution of 43.2 g. of 1-phenyl-4-methylpiperazine (0.245 mole) in 500 cc. of absolute ether, there was added 80 cc. of ethyl alcohol containing 0.49 mole of anhydrous hydrogen chloride. The precipitate was isolated by filtration, washed with ether, and dried at 50°; yield 57.7 g., 94.5% calculated as the anhydrous dihydrochloride. It was purified by crystallization from absolute ethyl alcohol which contained a slight excess of anhydrous hydrogen chloride. When taken in the usual manner the melting point was 193–200° (corr.) with some color produced but no noticeable gases. When immersed at 175°, it melted at 178–182° (corr.) with strong evolution of gas, but with no coloration.

Anal. Calc'd for $C_{11}H_{16}N_2 \cdot 2HCl \cdot H_2O$: Cl, 26.55. Found: Cl, 26.3.

Procedure (c). Preparation of 1,4-dimethylpiperazine (7, 14). The procedure was the same as that used for the methylation of 1-diethylcarbamylpiperazine with formaldehyde and formic acid (8). No solvent was used to extract the oil before distillation. It codistilled somewhat with diethyl ether.

1,4-Dimethylpiperazine dihydrochloride. The dihydrochloride salt was made in the usual manner from an ether solution of the base and anhydrous hydrochloric acid and crystallized from methyl alcohol-isopropyl acetate. It was dried at 50°.

Anal. Calc'd for $C_6H_{14}N_2 \cdot 2HCl \cdot 2/3H_2O$: C, 36.19; H, 8.77; N, 14.07; Cl, 35.61; H_2O, 6.03.
Found: C, 36.0; H, 8.6; N, 14.1; Cl, 35.6; H_2O, 5.98 (Karl Fischer).

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[2] The microchemical analyses were carried out by O. E. Sundberg, M. E. Nielsen, and I. H. Prokul.

Procedure (d). Preparation of 1-carbalkoxypiperazines and 1,4-dicarbalkoxypiperazines in a water solution. The procedure was that used by Moore, Boyle, and Thorn (2) for the reaction of ethyl chlorocarbonate with piperazine in a buffered water solution. The yields of the 1,4-dicarbalkoxypiperazines given in Table I are based on the amount of starting piperazine.

1-Carbomethoxypiperazine.

Anal. Calc'd for $C_6H_{12}N_2O_2$: C, 50.0; H, 8.3; N, 19.5.
Found: C, 49.4; H, 8.1; N, 18.9.

1,4-Dicarbomethoxypiperazine.

Anal. Calc'd for $C_8H_{14}N_2O_4$: N, 13.9. Found: N, 13.7.

1-Carbo-n-butoxypiperazine.

Anal. Calc'd for $C_9H_{18}N_2O_2$: C, 58.2; H, 9.7.
Found: C, 58.7; H, 10.0.

1,4-Di(carbo-n-butoxy)piperazine.

Anal. Calc'd for $C_{14}H_{26}N_2O_4$: N, 9.8. Found: N, 9.7.

1-Carboisobutoxypiperazine.

Anal. Calc'd for $C_9H_{18}N_2O_4$: C, 58.2; H, 9.7; N, 15.1.
Found: C, 58.0; H, 10.0; N, 15.0.

1,4-Di(carboisobutoxy)piperazine.

Anal. Calc'd for $C_{14}H_{26}N_2O_4$: C, 58.7; H, 9.1; N, 9.8.
Found: C, 58.8; H, 9.4; N, 9.7.

1-Carbethoxy-2-(or 3)methylpiperazine. To 17 g. of 2-methylpiperazine was added 150 cc. of water and enough hydrochloric acid to bring the solution to *p*H 3. During a period of one hour, 18 cc. of ethyl chlorocarbonate was added along with sodium acetate to maintain a *p*H of 3 to 3.5. The solution was extracted with ether and the extract was discarded. The aqueous layer was then cooled, saturated with potassium carbonate and extracted thoroughly with ether. This ethereal solution was dried over magnesium sulfate and then distilled; yield, 10.1 g. of a yellow oil.

Anal. Calc'd for $C_8H_{16}N_2O_2$: N, 16.3. Found: N, 16.4.

1,4-Dicarbethoxy-2-methylpiperazine. The preparation of 1,4-dicarbethoxy-2-methylpiperazine was carried out in a slightly different manner. To 20 g. of 2-methylpiperazine dihydrochloride was added a solution of 16.5 g. of potassium hydroxide pellets in 100 cc. of water. Then a total of 30 cc. of ethyl chlorocarbonate was added in six 5-cc. portions, while at the same time there was slowly added another 16.5-g. portion of potassium hydroxide in 100 cc. of water, so that the reaction remained slightly alkaline to phenolphthalein. The oil that separated was taken up in ether, dried over magnesium sulfate and distilled; yield 21.7 g.

Anal. Calc'd for $C_{11}H_{20}N_2O_4$: N, 11.5. Found: N, 11.3.

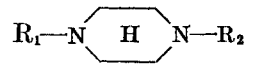
Procedure (e). Preparation of 1-carbethoxypiperazine hydrochloride and 1,4-dicarbethoxypiperazine in an 85% ethyl alcohol solution. This procedure is a modification of that used by Baltzly and co-workers (3). Ten moles (860 g.) of anhydrous piperazine (b.p. 142–147°) was dissolved in 5 liters of 85% ethanol. To this was added, with mechanical stirring, 953 cc. (10 moles) of ethyl chlorocarbonate, keeping the temperature below 50° by means of external cooling; this addition required about 50 minutes. The solution was stirred for one-half hour after the addition of ethyl chlorocarbonate, and then was made acid to Congo Red with concentrated hydrochloric acid.

The piperazine dihydrochloride which had precipitated was washed with alcohol, and dried at 50°. The total amount of piperazine dihydrochloride collected was 525 g. (3.3 moles), 33%.

The filtrate from the piperazine dihydrochloride was treated with 100 g. of Darco and clarified. The clarified filtrate was evaporated *in vacuo* to a volume of 1 liter, and the material which precipitated upon cooling was collected and washed with isopropyl acetate. By this method, 910 g. (4.7 moles) of 1-carbethoxypiperazine hydrochloride, m.p. 145–148°,

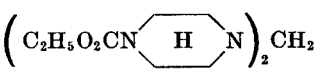
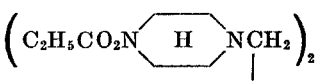
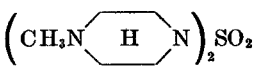
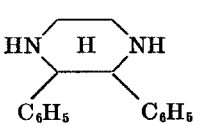
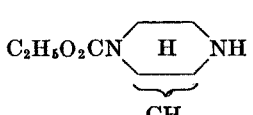
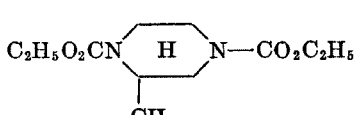
TABLE I

PIPERAZINE DERIVATIVES



COMPOUND	R_1	R_2	B.P. OF BASE, °C.	MM.	YIELD, %	M.P. OF HCl, °C.	ACTIVITY
I	CH_3	H	134–136*, [4]	760	74[a, 4]		−
					96.6[a]	82.5–83*, [3, 4]	
II	CH_3	CH_3	131–133*, [7]	760	70[c]	251.5–253*, [7] (dec.)	−
III	CH_3	$CH_2CH_2N(CH_3)_2$			58[c]	262–264	−
IV	C_2H_5	H					−
V	$(CH_3)_2CH$	H			90[a]	274–275 (dec.)	−
VI	C_6H_5	H	161–164*, [5, 6]	15	31.5[6]	245–247*, [6]	+
VII	C_6H_5	CH_3	130–131*, [4, 7]	8	70.5[7]		−
					94.5[b]	180–182* (dec.)	
						178–182* (dec.)	
VIII	CO_2CH_3	H	112–116	7	37[d]		−
IX	CO_2CH_3	CH_3	116–121 (m.p.)		16[g]		−
X	CO_2CH_3	CO_2CH_3	163	11	2[d]		−
XI	$CO_2C_2H_5$	H			47[c]	156.5–157*, [9, 3]	+
XII	$CO_2C_2H_5$	CH_3	97–98*	8	96[f]		++
					96[f]	168.5–169*	
XIII	$CO_2C_2H_5$	C_2H_5	132	28	82[g]		+
XIV	$CO_2C_2H_5$	*n*-C_3H_7	136	16	73[g]	189–192	+
XV	$CO_2C_2H_5$	*iso*-C_3H_7	138–144	19	75[g]		+
XVI	$CO_2C_2H_5$	*n*-C_4H_9	139–140	8	64[g]		+
XVII	$CO_2C_2H_5$	*iso*-C_4H_9	93.5–94	1	63[g]		−
XVIII	$CO_2C_2H_5$	*sec*-C_4H_9	139–147	18	40[g]	218–221 (dec.)	+
XIX	$CO_2C_2H_5$	*n*-C_7H_{15}	159–161*	4	86[h]		−
XX	$CO_2C_2H_5$	$CH_2{=}CHCH_2$	113–115*	6	81.7[h]		−
XXI	$CO_2C_2H_5$	CH_2CH_2OH	175–177	12	72[2]		−
XXII	$CO_2C_2H_5$	$CH_2CO_2C_2H_5$	123–125	2	75[2]		−
XXIII	$CO_2C_2H_5$	C_6H_5	61–61.5* (m.p.)		92[1]	197–198* (dec.)	−
XXIV	$CO_2C_2H_5$	$C_6H_5CH_2$			86[h]	218–218.5*	−

TABLE I—*Continued*

XXV	$CO_2C_2H_5$	COC_2H_5	131–133[2, 3, 10, 11] 45–46 (m.p.)	3	8[e]		−
XXVI	$CO_2C_4H_9(n)$	H	141–143	10	46[d]		−
XXVII	$CO_2C_4H_9(n)$	$CO_2C_4H_9(n)$	205–208	10	5.2[d]		−
XXVIII	$CO_2C_4H_9(iso)$	H	138–142	13	52[d]		−
XXIX	$CO_2C_4H_9(iso)$	$CO_2C_4H_9(iso)$	203–205	15	7.3[d]		−
		MISCELLANEOUS					
XXX			61.5–62.5* (m.p.)	95.7[h]			+
XXXI			258–262* 80–80.5 (m.p.)	12	86.4[h]		−
XXXII			89–90.5 (m.p.)		32[k]		−
XXXIII					72.5[j]	310–311* (dec.)	−
XXXIV			127–129	18	60[d]		−
XXXV			173–175	16	74[d]		+

* Corrected temperature.

was obtained; 47%. A portion was crystallized from absolute ethyl alcohol to the constant melting point 156.5–157° (corr.). The *p*H of a 1% water solution was 5.1 at 25°; its approximate solubility was 360 g./100 cc. of water at 25°.

Anal. Calc'd for $C_7H_{14}N_2O_2 \cdot HCl$: C, 43.17; H, 7.77; N, 14.39; Cl, 18.21.
Found: C, 43.3; H, 7.9; N, 14.6; Cl, 17.9.

1,4-Dicarbethoxypiperazine was obtained from the alcohol-isopropyl acetate filtrate by concentration of it *in vacuo* and recrystallization of the residue from petroleum ether. The yield of 1,4-dicarbethoxypiperazine, m.p. 43.5–45.5°, was 184 g. (0.8 mole); 8% based on starting piperazine. A portion was crystallized from petroleum ether (b.p. 35–60°) to the constant melting point 45–46° (corr.); b.p. 131–133° (corr.)/3 mm. The *p*H of a 1% water solution was 6.5; approximate solubility 4.3 g./100 cc. water at 25°.

Procedure (f). Preparation of 1-carbethoxy-4-methylpiperazine. To a 5-liter, 3-necked flask there were added 291.8 g. (1.5 moles) of 1-carbethoxypiperazine hydrochloride, 600 cc. of water, and 196.5 g. (3.0 moles) of zinc dust. The flask was immersed in an ice-bath and while the temperature of the solution was kept at 10–15°, 192 g. (2.3 moles) of 36% aqueous formaldehyde solution was added with good agitation over a period of 15 minutes.

At the end of this time, 600 cc. of concentrated hydrochloric acid (sp. gr. 1.18, 7.5 moles) was added slowly, keeping the temperature below 20°. After the addition of the hydrochloric acid, which required about one hour, the solution was stirred for 10 hours at 20–25° without cooling.

Aqueous sodium hydroxide solution (50%) was added with stirring until soluble sodium zincate was obtained and no more oil separated, while the temperature of the solution was kept below 20°. The oil layer was separated and the lower caustic layer was extracted six times with diethyl ether. The oil and ether extracts were combined and dried over sodium sulfate. After removal of the ether the product was distilled under reduced pressure. The base was found to be soluble in water.

Anal. Calc'd for $C_8H_{16}N_2O_2$: C, 55.80; H, 9.30; N, 16.28.
Found: C, 56.1; H, 9.29; N, 16.1.

The hydrochloride was prepared by introducing anhydrous hydrochloric acid into an ether solution of the base. It was purified by crystallization from absolute ethyl alcohol. The *p*H of a 1% water solution was 4.40 at 25°; its approximate solubility was 280 g./100 cc. of water at 25°.

Anal. Calc'd for $C_8H_{16}N_2O_2 \cdot HCl$: C, 46.03; H, 8.21; N, 13.42; Cl, 16.98.
Found: C, 46.5; H, 8.1; N, 13.3; Cl, 17.1.

Procedure (g). Preparation of 1-carbalkoxy-4-alkylpiperazines. The procedure was that used by Moore, Boyle, and Thorn (2) for the preparation of 1-carbethoxy-4-ethylpiperazine. The 1-carbalkoxypiperazine was treated with the appropriate alkyl ester of *p*-toluenesulfonic acid.

1-Carbomethoxy-4-methylpiperazine.

Anal. Calc'd for $C_7H_{14}N_2O_2$: C, 53.1; H, 8.9; N, 11.4.
Found: C, 52.7; H, 8.5; N, 11.0.

1-Carbethoxy-4-n-propylpiperazine. The free base was not analyzed. The hydrochloride was prepared in the usual manner and crystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_{10}H_{20}N_2O_2 \cdot HCl$: C, 50.7; H, 8.9; N, 11.8.
Found: C, 50.6; H, 9.3; N, 11.7.

1-Carbethoxy-4-isopropylpiperazine.

Anal. Calc'd for $C_{10}H_{20}N_2O_2$: C, 60.0; H, 10.0.
Found: C, 60.1; H, 9.9.

1-Carbethoxy-4-n-butylpiperazine.

Anal. Calc'd for $C_{11}H_{22}N_2O_2$: C, 61.7; H, 10.3; N, 13.1.
Found: C, 61.4; H, 10.3; N, 13.5.

1-Carbethoxy-4-isobutylpiperazine.

Anal. Calc'd for $C_{11}H_{22}N_2O_2$: C, 61.68; H, 10.28; N, 13.08.
Found: C, 61.6; H, 10.5; N, 13.3.

1-Carbethoxy-4-sec.-butylpiperazine. The free base was not analyzed. The hydrochloride was prepared in the usual manner and crystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_{11}H_{22}N_2O_2 \cdot HCl$: C, 52.6; H, 9.2; N, 11.1.
Found: C, 52.3; H, 9.4; N, 10.6.

Procedure (h). Reaction of 1-carbethoxypiperazine with alkyl halides. The halides used were *n*-heptyl bromide, allyl chloride, benzyl chloride, methylene bromide, and ethylene bromide. One mole of 1-carbethoxypiperazine hydrochloride, three moles of sodium bicarbonate, 300 cc. of 95% ethyl alcohol, and one mole of the halide (1.2 moles with allyl chloride and 0.5 mole with methylene bromide or ethylene bromide) were heated, while stirring, at the refluxing temperature for seven hours. (The reaction with benzyl chloride was refluxed for only two hours. The reaction with allyl chloride was not refluxed but was stirred at 45–50°.)

Most of the alcohol was removed by distillation and then the product was stirred into 1 liter of water to dissolve the inorganic salts. The solution was made strongly basic to phenolphthalein with potassium carbonate. The oil which separated was extracted with ether, dried over sodium sulfate, and after the ether was removed, was distilled as indicated in Table I.

1-Carbethoxy-4-benzylpiperazine. The free base was not distilled but the hydrochloride salt was prepared in the usual manner and crystallized (113 g.) from absolute ethyl alcohol (360 cc.).

Anal. Calc'd for $C_{14}H_{20}N_2O_2 \cdot HCl$: C, 59.05; H, 7.43; N, 9.84; Cl, 12.46.
Found: C, 58.9; H, 7.6; N, 9.99; Cl, 12.3.

1-Carbethoxy-4-allylpiperazine. In this reaction, in order to minimize the loss of the volatile allyl chloride by entrainment with the evolved carbon dioxide, the reaction was heated to the boiling point and then cooled before the allyl chloride was added.

Anal. Calc'd for $C_{10}H_{18}N_2O_2$: C, 60.54; H, 9.15; N, 14.13.
Found: C, 60.5; H, 8.9; N, 14.3.

Bis(1-carbethoxy-4-piperazyl)methane. This compound distilled with some decomposition at 4 mm. A quantity of 124 g. was crystallized from 250 cc. of petroleum ether (b.p. 35–60°) to the constant melting point 61.5–62.5° (corr.). The *p*H of a 1% water solution was 9.8 at 27°; approximate solubility was 4.7 g./100 cc. water at 27°. It gave oily salts with hydrochloric, sulfuric, and phosphoric acids.

Anal. Calc'd for $C_{15}H_{28}N_4O_4$: C, 54.86; H, 8.59; N, 17.06.
Found: C, 54.8; H, 8.7; N, 17.0.

1,2-Bis(1-carbethoxy-4-piperazyl)ethane. After distillation, 125 g. of this compound was crystallized from 350 cc. of mixed hexanes, m.p. 80–80.5° (corr.). The *p*H of a 1% water solution was 8.7 at 27°; approximate solubility was 1.9 g./100 cc. water at 27°. When treated with a small amount of water it dissolved completely and then precipitated, probably as a less soluble hydrate; this redissolved after the addition of more water.

Anal. Calc'd for $C_{16}H_{30}N_4O_4$: C, 56.13; H, 8.83; N, 16.36.
Found: C, 56.1; H, 8.7; N, 16.1.

Procedure (i). Preparation of 1-carbethoxy-4-phenylpiperazine. To 150 cc. of absolute ethyl alcohol were added 54.7 g. of 1-phenylpiperazine hydrochloride (0.275 mole), 29.8 g. of ethyl chlorocarbonate (0.275 mole), and 69.2 g. of sodium bicarbonate (0.83 mole). The reaction was heated, while stirring, at the refluxing temperature for three hours. The alcohol was removed by distillation, 500 cc. of warm water (above 60°) was added and the reaction was stirred till the inorganic salts had dissolved. A small amount of sodium hydroxide was added to make the reaction basic to phenolphthalein and the oil-water slurry was cooled while stirring. The solid was isolated by filtration, washed with water until neutral and dried at room temperature. The yield was 59.2 g. It was crystallized from petroleum ether (2.3 cc./g.) (b.p. 35–60°); m.p. 61–61.5° (corr.).

Anal. Calc'd for $C_{18}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96.
Found: C, 66.9; H, 7.5; N, 11.9.

The hydrochloride was prepared from anhydrous hydrogen chloride and an absolute ethyl alcohol solution of the base. It was crystallized from the same solvent (5.8 cc./g.). The salt was insoluble in water due to hydrolysis but was readily soluble in very dilute hydrochloric acid.

Anal. Calc'd for $C_{18}H_{18}N_2O_2 \cdot HCl$: C, 57.65; H, 7.07; N, 10.35; Cl, 13.09.
Found: C, 58.4; H, 7.0; N, 10.2; Cl, 12.6.

Procedure (j). Preparation of beta-2,3-diphenylpiperazine[3] *(12).* The 2,3-diphenyl-5,6-dihydropyrazine used in this procedure was prepared by the method used by Mason (12); yield 92%.

To 350 cc. of absolute ethyl alcohol were added 150 g. of 2,3-diphenyl-5,6-dihydropyrazine (0.63 mole) and 15 g. of copper chromite. This was hydrogenated in an autoclave at 150° and 1,000 lbs. until no more hydrogen was taken up (two hours). After cooling, the catalyst was removed and the filtrate was heated and water added to give 50% aqueous alcohol. When cool, the crystals which separated were washed with 50% aqueous alcohol and dried at 50°; yield 131.2 g.; m.p. 92.5–101° (corr.). Another crystallization from 50% aqueous alcohol gave 110.4 g. (72.5%); m.p. 108–109° (corr.). The filtrate, on dilution to give 25% aqueous alcohol, gave 6.4 g.; m.p. 97.5–103°. No evidence of the *alpha* isomer, m.p. 122–123°, was found.

The dihydrochloride (12) was prepared by adding anhydrous hydrogen chloride to a solution of the base in absolute ethyl alcohol. The dihydrochloride was insoluble in ethyl alcohol. Two crystallizations from water gave a product which melted at 310–311° (dec.) (corr.). The *p*H of a 1% water solution was 2.04 at 25°; its approximate solubility was 11.4 g./100 of cc. water at 25°.

Anal. Calc'd for $C_{16}H_{18}N_2 \cdot 2HCl$: C, 61.73; H, 6.48; N, 9.00; Cl. 22.78.
Found: C, 61.6; H, 6.5; N, 9.04; Cl, 22.6.

Some of the base was liberated from a small amount of the dihydrochloride by the addition of dilute sodium hydroxide to a water solution of the salt. After washing and drying, the base melted at 110–110.5° (corr.).

Procedure (k). Preparation of 1,1'-sulfonyl-bis(4-methylpiperazine). Ten g. of 1-methylpiperazine (0.1 mole) was dissolved in 30 g. of chloroform and immersed in an ice-bath; to the chilled chloroform solution, 4 g. of sulfuryl chloride (0.025 mole), technical grade, was cautiously added. The temperature of the solution was kept below 40° throughout the addition of sulfuryl chloride.

The chloroform was removed by evaporation on a steam-bath. To the residual liquid dilute sodium hydroxide was added until a pink spot was obtained on Brilliant Yellow test paper. The aqueous solution was extracted thoroughly with chloroform, which was subsequently evaporated to leave an orange oil; yield 2.1 g. (32%, based on sulfuryl chloride). This solidified on standing and was crystallized from mixed hexanes.

Anal. Calc'd for $C_{10}H_{22}N_4O_2S$: C, 45.8; H, 8.4; N, 21.3; S, 12.2.
Found: C, 45.8; H, 8.4; N, 21.0; S, 12.2.

Procedure (l). Preparation of 1-methyl-4-(2-dimethylaminoethyl)piperazine. To 100 cc. of 95% ethyl alcohol there were added 10 g. of N,N-dimethyl-2-chloroethylamine hydrochloride (0.07 mole), 13.4 g. of 1-methylpiperazine dihydrochloride monohydrate (0.07 mole), and 14.9 g. of sodium carbonate (0.14 mole). The reaction was stirred at the refluxing temperature for 18 hours. The inorganic salts were removed by filtration and the product was isolated from filtrate by concentration and crystallization from ethyl alcohol, m.p. 262–264°.

Anal. Calc'd for $C_9H_{21}N_3 \cdot 2HCl$: C, 44.3; H, 9.4; N, 17.2.
Found: C, 44.5; H, 9.6; N, 17.4.

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[3] This compound was prepared by Virginia (Mrs. J. J.) Lawson.

SUMMARY

Several new derivatives of piperazine have been prepared. The activity of these and other derivatives of piperazine as antifilarial agents has been reported.

BOUND BROOK, NEW JERSEY
PEARL RIVER, NEW YORK

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