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

EXPERIMENTAL CHEMOTHERAPY OF FILARIASIS. V. THE PREPARATION OF DERIVATIVES OF PIPERAZINE

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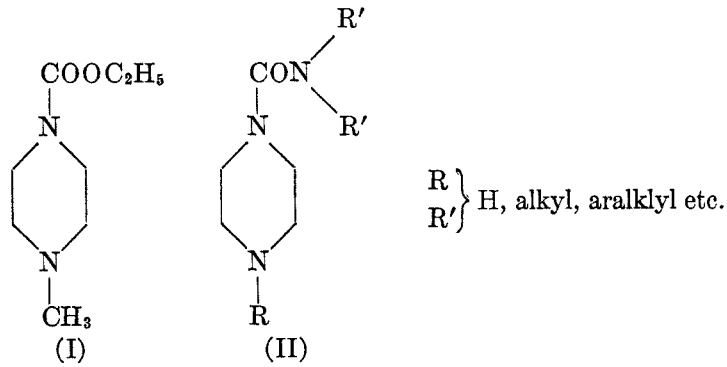
In a preceding paper we have shown that certain carbethoxypiperazines are active filaricides. Of these the most important was 1-carbethoxy-4-methylpiperazine (I), with high antifilarial activity (1).

In the syntheses of a number of carbamyl and other derivatives of piperazine we have found that 1-alkyl-4-dialkylcarbamylpiperazines (II) give the most pronounced oral activity.



In Table I are listed the piperazine derivatives and their relative activity (2). 1-Guanyl-4-carbethoxypiperazine (V) is an active compound, but when converted to 1,4-diguanylpiperazine (VI) it becomes inactive.

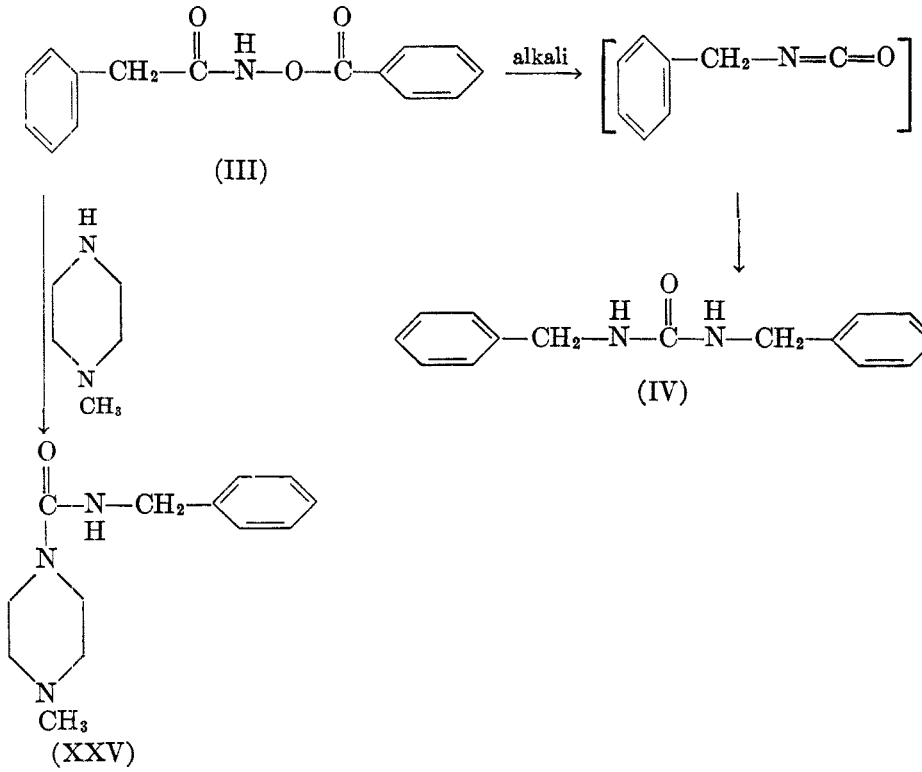
Activity reaches maximum in 1-dimethylcarbamyl-4-methylpiperazine (XIX), and 1-diethylcarbamyl-4-methylpiperazine (XXI). As in the 1-carbethoxy-4-alkyl series it will be noted that activity decreases as the size of the substituents increases.

Preliminary observations on twenty-six human patients infected with filariasis demonstrate that 1-diethylcarbamyl-4-methylpiperazine (XXI) produces a marked and rapid effect against microfilariae in the peripheral blood, and a suggestive effect against adult filariae. These and further results from human cases will be reported elsewhere (3). This compound also shows ascaricidal activity in the dog (4).

The 1-substituted carbamyl-4-alkylpiperazines were prepared by reacting the required carbamyl chloride usually in water or chloroform with the corresponding alkyl piperazine prepared by the method of Moore and co-workers (5). For large scale preparative work as in the case of 1-diethylcarbamyl-4-methylpiperazine (XXI), diethylcarbamyl chloride was reacted with piperazine in alcohol to

give 1-diethylcarbamylpiperazine (XII) which was then treated with formaldehyde and formic acid to give the required product in good yield.

The synthesis of 1-benzylcarbamyl-4-methylpiperazine was effected by a modification of the procedure of James (6) wherein the benzoate of phenylacethydroxamic acid (III), when heated with aqueous alkali gives symmetrical dibenzylurea (IV) presumably through the intermediate benzylisocyanate.



Instead of heating the benzoate (III) with alkali, two moles of 1-methylpiperazine are added, one mole causes the intermediate formation of the isocyanate which immediately reacts with the remaining 1-methylpiperazine to give the desired 1-benzylcarbamyl-4-methylpiperazine (XXV).

Acknowledgment. The authors wish to thank Mr. William Fumor and Mr. S. Modes for the microanalyses.

EXPERIMENTAL

1-Carbethoxy-4-guanylpiperazine sulfate (V). A mixture of 15.7 g. (0.12 mole) of 1-carbethoxypiperazine and 13.9 g. (0.1 mole) of methylisothiourea sulfate in 50 ml. of 65% alcohol was refluxed for 2.4 hours until no more methylmercaptan was evolved and then concentrated to dryness. The resinous mass crystallized when triturated with ether, wt. 19.1 g. It melted at 171° when recrystallized from alcohol-ether.

Anal. Calc'd for $C_{16}H_{34}N_8O_8S$: N, 22.5. Found: N, 23.0.

1-Carbethoxy-4-nitrosopiperazine (VII). To a stirred mixture, maintained at −10°, of

TABLE I

1,4-DISUBSTITUTED PIPERAZINES

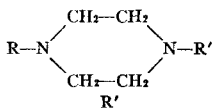
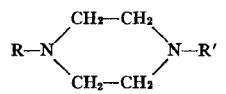
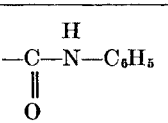
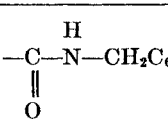
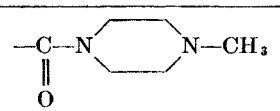
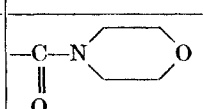
R	 R′	B. P. °C. / PRESSURE MM.	M. P. °C.	YIELD, %	ACTIVITY*
V C_2H_5OOC—	$\begin{matrix}NH\\\|\\-C-NH_2\end{matrix}$		171	77	+
VI $\begin{matrix}NH\\\|\\H_2N-C-\end{matrix}$	$\begin{matrix}NH\\\|\\-C-NH_2\end{matrix}$ (13)		>300	28	–
VII C_2H_5OOC—	—N=O	180–183 / 14		38	–
VIII C_2H_5OOC—	$-NH_2$		190–191[B]	43	–
IX C_2H_5OOC—	$\begin{matrix}O\\\|\\-C-NH_2\end{matrix}$		116–161.5[A]	73	–
X C_2H_5OOC—	$-CON(C_2H_5)_2$	163–167 / 3		66	–
XI H—	$-CON(CH_3)_2$	144–146 / 15		35	D
XII H—	$-CON(C_2H_5)_2$	113.5–115.5[A] / 3	147–151[B]	34	–

TABLE I—*Continued*

XIII H—	—CON[CH(CH$_3$)$_2$]$_2$	146 9		26	—
XIV H—	—CON(*n*—C$_4$H$_9$)$_2$	158–162 5		40	—
XV H—	—CON(*i*—C$_5$H$_{11}$)$_2$	200–202 35		17	—
XVI (C$_2$H$_5$)$_2$NOC—	—CON(C$_2$H$_5$)$_2$	174–178 2	55.7–56.0[A]	15	—
XVII CH$_3$—	O ‖ —C—NH$_2$		189–190[A,B]	72	—
XVIII CH$_3$—	S ‖ —C—NH$_2$		131–132[A,B]	64	—
XIX CH$_3$—	—CON(CH$_3$)$_2$		180–181[B]	33	++
XX CH$_3$—	—CONHC$_2$H$_5$		177 dec.[B]	33	+
XXI CH$_3$—	—CON(C$_2$H$_5$)$_2$	108.5–111[A] 3	156.5–157[A,B] 47–49[A]	93[C] 65 80	++
XXII CH$_3$—	—CON[CH(CH$_3$)$_2$]$_2$		200–203[B]	61	+
XXIII CH$_3$—	—CON(*n*—C$_4$H$_9$)$_2$		151–152[B]	30	—

TABLE I—*Continued*

R		B. P.°C. / Pressure mm.	M. P. °C.	Yield, %	Activity*
XXIV CH_3—			126–130	90	–
XXV CH_3—			188–192	54	–
XXVI CH_3—			303–304	60	–
XXVII CH_3—		178–179 / 17	52–55	61	+
XXVIII *i*—C_3H_7—	—$CON(C_2H_5)_2$	160 / 16	206–208.5	32	–

* Tested against microfilaria in cotton rats.
[A] Corrected temperatures.
[B] Hydrochloride.
[C] Prepared by three methods described below.
[D] Not tested.

189 g. (1.2 moles) of 1-carbethoxypiperazine, 480 g. of ice, and 300 ml. of concentrated hydrochloric acid was added over a period of one and one-half hours 168 g. of sodium nitrite dissolved in the minimum amount of water. The solution was neutralized with ice-cold alkali and then extracted with successive portions of ether until the yellow color was removed from the aqueous solution. The combined ethereal extracts were dried over magnesium sulfate and then fractionated under reduced pressure. The fraction boiling at 180–183° (14 mm.) was collected as 1-carbethoxy-4-nitrosopiperazine (VII), wt. 84.8 g.

Anal. Calc'd for $C_7H_{11}N_3O_3$: C, 44.9; H, 6.9.
Found: C, 45.4; H, 6.6.

1-Carbethoxy-4-aminopiperazine hydrochloride (VIII). To a stirred slurry (kept at 25–30°) of 7 g. (0.037 mole) of 1-carbethoxy-4-nitrosopiperazine and 19 g. of zinc dust was added over a period of two hours 54 ml. of 85% acetic acid. The reaction mixture was then heated for one hour at 60°, filtered, and the filtrate evacuated to dryness in a water-bath. The residue was made strongly alkaline with concentrated potassium hydroxide solution and extracted thoroughly with ether after saturating the solution with potassium carbonate. The ethereal extracts were dried over magnesium sulfate and evacuated to an oil. The oil was dissolved in ether, filtered from insoluble impurities, and the amine hydrochloride was precipitated from ether by a stream of dry hydrogen chloride, wt. 3.3 g. After recrystallization from alcohol-ether it melted at 190–191°.

Anal. Calc'd for $C_7H_{16}ClN_3O_2$: C, 40.1; H, 7.6; N, 20.0.
Found: C, 40.6; H, 7.8; N, 19.9.

1-Carbamyl-4-carbethoxypiperazine (IX). A solution of 82 g. (1 mole) of potassium cyanate in 75 ml. of water was added to a solution of 195 g. (1 mole) of 1-carbethoxypiperazine hydrochloride in 125 ml. of water. The mixture of solutions was agitated for a few minutes and after standing at room temperature for twenty-four hours it was evaporated to dryness. The residue was extracted with 400 ml. of absolute alcohol, acidified with hydrochloric acid and then evaporated to 125 ml. Upon cooling, crystallization occurred. The solid was recrystallized from alcohol with charcoaling, wt. 146.2 g., m.p. 161–162° (corr.).

Anal. Calc'd for $C_8H_{15}N_3O_3$: C, 47.7; H, 7.5; N, 20.8.
Found: C, 47.4; H, 7.6; N, 20.6.

1-Carbamyl-4-methylpiperazine hydrochloride (XVII). This was prepared in the same manner as compound (IX) with the use of 1-methylpiperazine; m.p. 189–190° (corr.) after recrystallization from alcohol.

Anal. Calc'd for $C_6H_{14}ClN_3O$: N, 23.3; Cl, 19.7.
Found: N, 23.0; Cl, 19.4.

1-Thiocarbamyl-4-methylpiperazine hydrochloride (XVIII). This was prepared similarly to compound (IX), with corresponding use of potassium thiocyanate; m.p. 131–132° (corr.) after recrystallization from alcohol.

Anal. Calc'd for $C_6H_{14}ClN_3S$: C, 36.3; H, 7.2; N, 21.5; S, 16.4.
Found: C, 36.6; H, 7.3; N, 21.8; S, 16.5.

1-Benzylcarbamyl-4-methylpiperazine hydrochloride (XXV). A solution of 10 g. (0.04 mole) of the benzoate of phenylacethydroxamic acid (6), 50 ml. of water, and 8 g. (0.08 mole) of 1-methylpiperazine was heated for seven minutes on a steam cone. A cloudiness developed which was increased by an addition of 50 ml. of water. After saturating with potassium carbonate the *1-benzylcarbonyl-4-methylpiperazine* was extracted thoroughly with ether, dried over magnesium sulfate, filtered, and precipitated as its hydrochloride by a stream of dry hydrogen chloride. The oil crystallized on scratching and weighed 5 g. After recrystallization from alcohol it melted at 188–192°.

Anal. Calc'd for $C_{13}H_{20}ClN_3O$: C, 58.1; H, 7.1.
Found: C, 58.1; H, 7.5.

1-Methyl-4-[(4-morpholine)carbonyl]piperazine (XXVII). To a stirred ice-cold solution of 17.9 g. of 1-methylpiperazine dihydrochloride monohydrate, 13.8 g. of 85% potassium

hydroxide, and 150 ml. of water was added simultaneously over a period of ten minutes 15.5 g. of 4-morpholinecarbamylchloride (7) and 6.9 g. of 85% potassium hydroxide. After stirring in the ice-bath for one hour the solution was saturated with potassium carbonate, extracted with chloroform, dried, and distilled at 178–179° (17 mm.); wt. 13 g.; m.p. 52–55°.

Anal. Calc'd for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 8.9; N, 19.7.
Found: C, 56.7; H, 9.2; N, 20.0.

1,1'-Carbonyl-bis(4-methylpiperazine) dihydrochloride (XXVI). Phosgene was passed into a solution of 5 g. (0.005 mole) of 1-methylpiperazine, 2.8 g. of 85% potassium hydroxide, and 25 ml. of water until neutral, whereupon 2.8 g. more of potassium hydroxide was added and the procedure repeated until the solution was acid to Congo Red. The solution was then saturated with potassium carbonate and extracted with chloroform. The hydrochloride was formed by the introduction of dry hydrogen chloride and recrystallized from absolute alcohol, m.p. 303–304°; wt. 4.5 g.

Anal. Calc'd for $C_{11}H_{20}Cl_2N_4O$: C, 44.2; H, 7.4; N, 18.7.
Found: C, 44.2; H, 7.2; N, 19.2.

1-Phenylcarbamyl-4-methylpiperazine (XXIV). To a solution of 10 g. (0.1 mole) of 1-methylpiperazine in 50 ml. of dry benzene was added 10 g. (0.08 mole) of phenylisocyanate. The benzene was removed under suction and the crystalline residue recrystallized from benzene-petroleum ether, m.p. 126–130°, wt. 6.7 g.

Anal. Calc'd for $C_{12}H_{17}N_3O$: N, 19.1. Found: N, 19.1.

1-Diethylcarbamylpiperazine (XII). A slurry of 696 g. (3.58 moles) of piperazine hexahydrate in 2190 g. of absolute ethanol was stirred at 50° until all of the piperazine had dissolved. While maintaining the temperature at 45–50° with an ice-bath, 485 g. (3.58 moles) of diethylcarbamyl chloride (8) was added in about twenty minutes.

The ice-bath was removed, and after stirring for one-half hour the reaction mixture was kept overnight at room temperature. The stirred reaction mixture was then made acidic to Congo Red with concentrated hydrochloric acid, while maintaining the temperature below 50°. After cooling to 20° the precipitated piperazine dihydrochloride was washed thoroughly with 95% alcohol. The yield of recovered piperazine dihydrochloride was 245 g., 43.0%.

The filtrate and washings from above were combined and concentrated on a steam-bath under reduced pressure to a volume of about 700 ml. To this thick syrup was added with stirring and cooling 50% sodium hydroxide solution until the reaction mixture was alkaline to phenolphthalein, and then solid sodium hydroxide was added with stirring and cooling until an oil separated. The slurry of salt and oil was filtered and the residue washed thoroughly with ether. The separated oil from the filtrate was combined with the ether washings and dried over solid sodium hydroxide. During this drying it was necessary to filter occasionally to remove precipitated salt. The ether was removed and the residue fractionated under reduced pressure. The fraction which boiled at 105–140° (corr.) at 3 mm. was redistilled and gave 266 g. of pure *1-diethylcarbamylpiperazine*, which distilled at 113.5–115.5° (corr.) (3 mm.).

Anal. Calc'd for $C_9H_{19}N_3O$: C, 58.4; H, 10.3.
Found: C, 58.2; H, 10.6.

The residue from the refractionation gave 154 g. of *1,4-bis(diethylcarbamyl)piperazine* which boiled at 174–178° (2 mm.). It melted at 55.7–56.0° (corr.) when recrystallized from mixed hexanes.

Anal. Calc'd for $C_{14}H_{28}N_4O_2$: C, 59.3; H, 9.9; N, 19.8.
Found: C, 59.2; H, 10.0; N, 19.9.

1-Diethylcarbamyl-4-carbethoxypiperazine (X). To 20 g. (0.13 mole) of 1-carbethoxypiperazine dissolved in 50 ml. chloroform was added slowly with stirring 8.5 g. (0.6 mole) of diethylcarbamyl chloride in 50 ml. of chloroform. From time to time more chloroform was added to maintain a clear solution. The reaction solution was then washed three times

with a saturated potassium carbonate solution and dried over magnesium sulfate and filtered. The chloroform was removed and the residue fractionated. The fraction boiling at 163–167° (3 mm.) was collected as the desired product, wt. 10.7 g.

Anal. Calc'd for $C_{12}H_{23}N_3O_3$: C, 56.0; H, 8.9; N, 16.3.
Found: C, 56.0; H, 9.4; N, 16.3.

1-Ethylcarbamyl-4-methylpiperazine hydrochloride (XX). To 5 g. (0.05 mole) of 1-methylpiperazine in 25 ml. of chloroform was added 2.7 g. (0.025 mole) of ethylcarbamyl chloride (9). The insoluble solids were dissolved in a small amount of water and extracted with ether after saturating the aqueous solution with potassium carbonate. The ethereal solution was dried with magnesium sulfate and the hydrochloride was precipitated as a solid with dry hydrogen chloride. It was recrystallized from alcohol-ether, m.p. 177°, wt. 1.7 g.

Anal. Calc'd for $C_8H_{18}ClN_3O$: N, 20.2. Found: N, 19.7.

1-Dialkylcarbamylpiperazine (XIII). To a solution of 0.2 mole of piperazine in 100 ml. of alcohol was added with stirring 0.2 mole of dialkylcarbamyl chloride (8, 10, 11, 12).[1] After standing overnight at room temperature the alcohol was removed and dilute hydrochloric acid was added to the residue. The 1,4-bis(dialkylcarbamyl)piperazine was extracted with ether and the potassium carbonate saturated aqueous phase was extracted with chloroform to obtain the 1-dialkylcarbamylpiperazine.

1-Diisopropylcarbamylpiperazine (XIII). B.p. 146° (9 mm.).

Anal. Calc'd for $C_{11}H_{23}N_3O$: C, 62.0; H, 10.8.
Found: C, 61.6; H, 10.4.

1-Dimethylcarbamylpiperazine (XI). B.p. 144–146° (15 mm.).

Anal. Calc'd for $C_7H_{15}N_3O$: C, 53.5; H, 9.5.
Found: C, 52.7; H, 9.6.

1-Dibutylcarbamylpiperazine (XIV). B.p. 158–162° (5 mm.).

Anal. Calc'd for $C_{13}H_{27}N_3O$: N, 17.4. Found: N, 17.5.

1-Diisoamylcarbamylpiperazine (XV). B.p. 200–202° (35 mm.).

Anal. Calc'd for $C_{15}H_{31}N_3O$: N, 15.6. Found: N, 15.5.

1-Diethylcarbamyl-4-methylpiperazine (XXI). A. To 400 ml. of 90% formic acid was slowly added with stirring 580.5 g. (3.13 moles) of 1-diethylcarbamylpiperazine or an equivalent of the hydrochloride salt. When the formic acid was added to the amine, a solid salt was formed. To this reaction mixture at 80° was slowly added 395 g. (4.74 moles; 50% excess) of 36% formalin, venting the evolved carbon dioxide through a reflux condenser. When the formaldehyde was added at room temperature and then heated, a sudden vigorous reaction took place at about 60°. Then after refluxing for one hour (105°) the mixture was distilled until the pot temperature reached 150°. The distillation residue was cooled to 30° and while stirring vigorously with strong cooling, 50% sodium hydroxide solution was slowly added until the reaction mixture was basic to phenolphthalein. The separated oil, after drying over solid sodium hydroxide, was distilled at 108.5–111° (corr.) (3 mm.); wt. 576 g., m.p. 47–49° (corr.).

B. To a cold solution of 1146 g. (6.0 moles) of 1-methylpiperazine dihydrochloride monohydrate in 1150 ml. of water was added with stirring and cooling 500 ml. of 50% sodium hydroxide solution to make the reaction mixture alkaline to Brilliant Yellow-red. While maintaining the temperature below 50°, 480 g. (12.0 moles) of sodium hydroxide pellets was dissolved while stirring and then with the temperature maintained at 35–40° with slight cooling 816 g. (6.0 moles) of diethylcarbamyl chloride was added during the course of one-half hour. After an additional hour of stirring at this temperature the oil which separated was dried over potassium hydroxide pellets and distilled, wt. 778 g.

C. To a stirred solution of 10 g. (0.1 mole) of 1-methylpiperazine in 100 ml. of chloro-

[1] Prepared by the same procedure as described by Lumiere for analogous derivatives; b.p. 90–93° (15 mm.).

form there was added dropwise during one hour 6.1 g. (0.045 mole) of diethylcarbamyl chloride. After standing at room temperature for fifteen to twenty minutes, the clear solution was cooled in an ice-bath and treated with an excess of dry hydrogen chloride. The precipitated 1-methylpiperazine dihydrochloride was removed and the filtrate was evacuated to a solid on the water-pump. It was again taken up in chloroform, filtered, and re-evacuated to a solid; wt. 8.5 g., m.p. 150–153°. After recrystallization from anhydrous acetone it melted at 156.5–157° (corr.).

Anal. Calc'd for $C_{10}H_{22}ClN_3O$: C, 51.0; H, 9.4; N, 17.8; Cl, 15.0.
Found: C, 50.6; H, 9.4; N, 18.2; Cl, 15.2.

1-Dimethylcarbamyl-4-methylpiperazine hydrochloride (XIX). The same procedure was used as described for the diethyl analog of part C above. From 10 g. of 1-methylpiperazine was obtained 3.5 g. of compound which melted after recrystallization from alcohol-ether at 180–181°.

Anal. Calc'd for $C_8H_{18}ClN_3O$: C, 46.2; H, 8.7; N, 20.2.
Found: C, 46.8; H, 9.0; N, 20.9.

1-Diisopropylcarbamyl-4-methylpiperazine hydrochloride (XXII). This compound was prepared in the same manner as part C of the diethyl analog. From 5 g. of 1-methylpiperazine and 4.1 g. of diisopropylcarbamyl chloride was obtained 4.0 g. of the desired product. After recrystallization from chloroform-ethyl acetate it melted at 200–203°.

Anal. Calc'd for $C_{12}H_{26}ClN_3O$: C, 54.7; H, 9.1; N, 15.9.
Found: C, 55.2; H, 10.6; N, 15.0.

1-Dibutylcarbamyl-4-methylpiperazine hydrochloride (XXIII). This was prepared in the same manner as those described above. It was recrystallized from alcohol-ether, m.p. 151–152°.

Anal. Calc'd for $C_{14}H_{30}ClN_3O$: C, 57.6; H, 10.3.
Found: C, 57.8; H, 10.0.

1-Diethylcarbamyl-4-isopropylpiperazine hydrochloride (XXVIII). To an ice-cold solution of 20.1 g. (0.1 mole) of 1-isopropylpiperazine dihydrochloride (1), 6.6 g. of 85% potassium hydroxide, and 100 ml. of water was slowly added simultaneously 8.1 g. (0.055 mole) of diethylcarbamyl chloride and 6.6 g. of 8.5% potassium hydroxide dissolved in 10 ml. of water. After saturating with potassium carbonate and extracting with ether, the dried ethereal solution was treated with an excess of anhydrous hydrogen chloride. The precipitated solid was recrystallized from alcohol-ether and a small sample was sublimed at 150° (0.002 mm.), it melted with decomposition at 206–208°.

Anal. Calc'd for $C_{12}H_{26}ClN_3O$: C, 54.8; H, 9.4; N, 16.0.
Found: C, 54.8; H, 8.8; N, 15.9.

SUMMARY

1. A number of mono and disubstituted piperazines have been prepared and characterized.

2. 1-Diethylcarbamyl-4-methylpiperazine and 1-dimethylcarbamyl-4-methylpiperazine have pronounced anti-filarial activity.

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REFERENCES

(1) STEWART, *et al.*, *J. Org. Chem.*, preceding article.
(2) HEWITT, *et al.*, *J. Lab. Clin. Med.*, in press.
(3) SANTIAGO-STEVENSON, *et al.*, in press.
(4) HEWITT, *et al.*, in press.

(5) MOORE, BOYLE, AND THORN, *J. Chem. Soc.*, 39 (1929).
(6) JAMES, *Am. Chem. J.*, **48**, 8 (1912).
(7) NEMETS AND KURLINA, *Trudy Leningrad Krasnozamen Khim. Tekh. Inst. im. Leningrad, Soveta*, **10**, 3 (1941); *Chem. Abstr.*, **38**, 1507 (1944).
(8) LUMIERE AND PERRIN, *Bull. soc. chim.*, (3) **31**, 689 (1904).
(9) GATTERMANN AND SCHMIDT, *Ann.*, **244**, 36 (1888).
(10) FRANCHEMONT AND RAUFFAER, *Rec. trav. chim.*, **13**, 333 (1893).
(11) WERNER, *J. Chem. Soc.*, **115**, 1013 (1914).
(12) ATKINSON, *J. Chem. Soc.*, **105**, 1296 (1914).
(13) BISCHOFF, *J. Biol. Chem.*, **80**, 345 (1928).