[Contribution from the Research Department, Calco Chemical Division, American Cyanamid Company]

PIPERAZINES. I. DERIVATIVES OF PIPERAZINE-1-CARBOXYLIC AND -1,4-DICARBOXYLIC ACID

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It has been reported (1, 2) that both 1-carbethoxy-4-methylpiperazine and 1-diethylcarbamyl-4-methylpiperazine (Hetrazan) show outstanding filaricidal activity in the cotton rat. The activity of the latter has since been repeatedly confirmed in human infestations. Because of this interesting biological action of several piperazine derivatives of this type and because some of them had also exhibited a depressant action on the central nervous system, the piperazine derivatives listed in Table I (3, 4) were synthesized for similar evaluation. Of the seventeen compounds listed, six are derived from piperazine itself, while the others are derivatives of *trans*-2,5-dimethylpiperazine. All are substituted with a carbethoxy, carbamyl, or guanyl group in the 1-position or the 1- and 4-positions.

In Table I, letters in the procedure column refer to procedures in the experimental part. Preparations of compounds not referred to by letter in the table are written separately after the general procedures.

The *trans*-2,5-dimethylpiperazine used in these preparations was purchased (5), labeled as 2,5-dimethylpiperazine. From results of its reaction with *p*-toluene sulfonyl chloride, it was found to contain at least 76% *trans*-isomer, 5% unreactive material, and 8% of some unidentified material isomeric with *trans*-2,5-dimethylpiperazine. No *cis*-isomer was definitely detected.

By Procedure A, the carbamyl derivatives were obtained by treatment of an aqueous solution of the hydrochloride of the corresponding piperazine with potassium cyanate. By this procedure, though Compound VIII was obtained, the monocarbamyl compound, *trans*-1-carbamyl-2,5-dimethylpiperazine, was never isolated in a pure state.

The 1-alkylthiocarbamyl-4-substituted piperazines VI, VII, XIII, and XIV were prepared by Procedure B which consisted of the interaction of the monosubstituted piperazine with an alkyl isothiocyanate in petroleum ether.

The guanyl piperazines XVI and XVII were prepared by Procedure C which is essentially that previously described (6) for 1,4-diguanylpiperazine.

Compounds I and II were prepared by a a method similar to that used by Moore, *et al.* (7) for 1-carbethoxy- and 1,4-dicarbethoxy-piperazine. An aqueous solution of *trans*-2,5-dimethylpiperazine was treated with ethyl chlorocarbonate while the reaction mixture was kept at *p*H 3.0 to 3.6. When benzene was used as a solvent, instead of water, with sodium carbonate present, or when either absolute or 91% aqueous ethanol was used with no alkaline agent, only *trans*-1,4-dicarbethoxy-2,5-dimethylpiperazine (II) could be isolated.

Compound IV was obtained from the reaction of 1-diethylcarbamylpiperazine

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with ethyl chloroacarbonate in benzene with sodium carbonate. Compound V was obtained similarly from XI except that sodium bicarbonate was used.

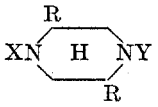
The distillation residue from the preparation of XI (8) yielded *trans*-1,4-bis (diethylcarbamyl)-2,5-dimethylpiperazine (XII).

1-Diethylcarbamyl-4-guanylpiperazine sulfate (XV) resulted from refluxing 1-diethylcarbamylpiperazine and S-methylisothiourea sulfate in ethanol.

None of these compounds showed antifilarial activity in the cotton rat at doses several times those effective for the most active previously described piperazines (1, 2).

TABLE I

SUBSTITUTED PIPERAZINES



COMPOUND	X	Y	R	PROCEDURE	LIT. REF.
I	$CO_2C_2H_5$	H	CH_3		3, 10
II	$CO_2C_2H_5$	$CO_2C_2H_5$	CH_3		10
III	$CO_2C_2H_5$	$CONH_2$	CH_3	A	3
IV	$CO_2C_2H_5$	$CON(C_2H_5)_2$	H		2, 3
V	$CO_2C_2H_5$	$CON(C_2H_5)_2$	CH_3		
VI	$CO_2C_2H_5$	$CSNHC_2H_5$	H	B	3
VII	$CO_2C_2H_5$	$CSNHC_2H_5$	CH_3	B	3
VIII	$CONH_2$	$CONH_2$	CH_3	A	
IX	$CONH_2$	$CON(C_2H_5)_2$	H	A	
X	$CONH_2$	$CON(C_2H_5)_2$	CH_3	A	
XI	$CON(C_2H_5)_2$	H	CH_3		8
XII	$CON(C_2H_5)_2$	$CON(C_2H_5)_2$	CH_3		
XIII	$CON(C_2H_5)_2$	$CSNHC_2H_5$	H	B	4
XIV	$CON(C_2H_5)_2$	$CSNHCH_2CH{=}CH_2$	H	B	4
XV	$CON(C_2H_5)_2$	$C(NH)NH_2$	H		4
XVI	$CON(C_2H_5)_2$	$C(NH)NH_2$	CH_3	C	4
XVII	$C(NH)NH_2$	$C(NH)NH_2$	CH_3	C	

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EXPERIMENTAL

IDENTIFICATION OF *trans*-2,5-DIMETHYLPIPERAZINE

One mole of 2,5-dimethylpiperazine (5), 114 g., was slurried in 400 cc. of absolute ether at 5°. On filtration there was obtained 107 g. (94%) of material which melted at 115.0–115.8°. Further crystallization from dry benzene gave a product which melted at 116.3–116.8°.

To a 500-cc. three-necked flask equipped with a stirrer and thermometer, there was added a solution of 11.4 g. (0.1 mole) of 2,5-dimethylpiperazine (5) in 50 cc. of water. This solution was stirred and kept at 45° with slight cooling while 76 g. (0.4 mole) of *p*-toluenesulfonyl chloride was added slowly. Then aqueous sodium hydroxide was slowly added until the reaction was alkaline to phenolphthalein. After stirring for one hour at 45°, the crude *trans-1,4-bis(p-toluenesulfonyl)-2,5-dimethylpiperazine* was isolated by filtration. The yield was 40.0 g.; 94.8%. It melted at 214–223°.

It was crystallized from nitromethane to a constant melting point of 227–228°. The yield after working the filtrates was 32.2 g.; 76%. Kipping and Pope (9) reported the melting point of the *trans* isomer to be 225° and of the *cis* isomer to be 146–147°.

Anal. Calc'd for $C_{20}H_{26}N_2O_4S_2$: C, 56.85; H, 6.20; N, 6.65; S, 15.16.

Found: C, 57.3; H, 6.28; N, 6.36; S, 15.2.

From the filtrates obtained in the purification of the *trans*-1,4-bis(*p*-toluenesulfonyl)-2,5-dimethylpiperazine, there was obtained 3.4 g. (8%) of an unidentified product which melted at 181–182°. The empirical formula was found to be $C_{20}H_{26}N_2O_4S_2$ indicating that it could be a derivative of a dimethylpiperazine.

Anal. Found: C, 57.4; H, 5.95; N, 6.47; S, 15.4.

In all of the following preparations, the 2,5-dimethylpiperazine (5), when used, was used without purification.

PROCEDURE A. CARBAMYLPIPERAZINES

One mole of the amine hydrochloride, or its equivalent of the base and hydrochloric acid, was dissolved in 200 cc. of water. To this there was added at room temperature a solution of one mole of potassium cyanate in 100 cc. of water (Compound VIII required two moles). Very little heat was evolved. After standing for several hours, the crude product which had precipitated was isolated by filtration, dried, and crystallized from the appropriate solvent.

trans-1-Carbamyl-4-carbethoxy-2,5-dimethylpiperazine (III). The yield was 92.5%. It was crystallized from carbon tetrachloride. Apparently it had solvated since it melted and solidified again when dried at 50°. The melting point was 118.5–119.0° (corr.). The approximate solubility was 6.4 g. per 100 cc. of distilled water at 29°. A 1% water solution had the same *p*H as that of the distilled water.

Anal. Calc'd for $C_{10}H_{19}N_3O_3$: C, 52.37; H, 8.35; N, 18.32.

Found: C, 52.3; H, 8.29; N, 18.4.

trans-1,4-Dicarbamyl-2,5-dimethylpiperazine (VIII). On crystallization from water the yield of pure material was 73%; m.p. 271–272° d. Less than 0.1 g. was soluble in 100 cc. of water at room temperature.

Anal. Calc'd for $C_8H_{16}N_4O_2$: C, 47.98; H, 8.06; N, 27.99.

Found: C, 48.0; H, 7.86; N, 27.7.

1-Carbamyl-4-diethylcarbamylpiperazine (IX) was isolated from the chilled reaction mixture. The yield of purified material from amyl alcohol, after using charcoal (Darco), was 78%; m.p. 164.4–164.5°.

Anal. Calc'd for $C_{10}H_{20}N_4O_2$: C, 52.61; H, 8.83; N, 24.55.

Found: C, 52.4; H, 8.73; N, 24.7.

trans-1-Carbamyl-4-diethylcarbamyl-2,5-dimethylpiperazine (X). The reaction mixture was evaporated to dryness, the residue was extracted with hot acetone, and the extract was crystallized from acetone-ether. The yields of crude and pure material were 82.5% and 68%, respectively. It melted at 140.5–141.5°. The approximate solubility was 13 g. per 100 cc. water at 25°; *p*H of a 1% water solution was 5.8.

Anal. Calc'd for $C_{12}H_{24}N_4O_2$: C, 56.23; H, 9.44; N, 21.86.

Found: C, 56.2; H, 9.35; N, 21.7.

PROCEDURE B. ALKYLTHIOCARBAMYLPIPERAZINES

To a solution of 0.15 mole of the amine in 200 cc. of petroleum ether, there was added over a period of ten minutes a solution of 0.15 mole of the appropriate isothiocyanate in 100 cc. of petroleum ether. During the addition, the reaction mixture was stirred and

cooled in an ice-bath. The white precipitate which formed was isolated by filtration, dried, and crystallized from the solvent mentioned below.

1-Carbethoxy-4-ethylthiocarbamylpiperazine (VI). The yield of crude material was 86%. It was purified by crystallization from isopropyl acetate and petroleum ether, m.p. 91.0–91.5°. The approximate solubility was 0.4 g. per 100 cc. of water at 27°. The *p*H of a saturated water solution was 7.3.

Anal. Calc'd for $C_{10}H_{19}N_3O_2S$: C, 48.96; H, 7.81; N, 17.13; S, 13.07.
Found: C, 49.1; H, 7.99; N, 17.3; S, 13.2.

trans-1-Carbethoxy-2,5-dimethyl-4-ethylthiocarbamylpiperazine (VII). The yield before purification was 73.8%. It was crystallized from isopropyl acetate and petroleum ether, m.p. 79.0–79.5°. The solubility in water was less than 1%; *p*H of a saturated solution was 6.6.

Anal. Calc'd for $C_{12}H_{23}N_3O_2S$: C, 52.71; H, 8.48; N, 15.37; S, 11.73.
Found: C, 52.4; H, 8.34; N, 15.3; S, 11.8.

1-Diethylcarbamyl-4-ethylthiocarbamylpiperazine (XIII). The yield of crude material was 90%. It was purified by crystallization from a mixture of isopropyl acetate and petroleum ether, m.p. 87.5–88.0°. The approximate solubility was 0.3 g. per 100 cc. of water at 25°; *p*H of a saturated water solution was 7.2.

Anal. Calc'd for $C_{12}H_{24}N_4OS$: C, 52.90; H, 8.88; N, 20.57; S, 11.77.
Found: C, 53.0; H, 8.69; N, 20.5; S, 11.7.

1-Allylthiocarbamyl-4-diethylcarbamylpiperazine (XIV). The yield of crude material was 78%. It was purified by crystallization from a mixture of isopropyl acetate and petroleum ether, m.p. 80.0–80.5°. The solubility was less than 1 g. per 100 cc. water; *p*H of a saturated water solution was 6.8.

Anal. Calc'd for $C_{13}H_{24}N_4OS$: C, 54.91; H, 8.51; N, 19.70; S, 11.27.
Found: C, 54.9; H, 8.59; N, 19.7; S, 11.2.

PROCEDURE C. GUANYLPIPERAZINES

To 250 g. of a 25% aqueous cyanamide solution containing 1.5 moles there was added 1.0 mole of the amine hydrochloride. If necessary, the *p*H of the reaction was adjusted with either hydrochloric acid or sodium hydroxide until the solution was just faintly acidic to Congo Red paper. The reaction was then heated at the refluxing temperature for seven hours.

trans-1-Diethylcarbamyl-2,5-dimethyl-4-guanylpiperazine acetate (XVI). On cooling, no crystals were isolated from the reaction. Potassium hydroxide pellets were slowly added keeping the temperature below 25° until the crude base separated as an oil. The oil was separated and dried with potassium hydroxide pellets. The dry solution was diluted with 200 cc. of absolute ethyl alcohol. A salt was precipitated by the addition of Dry Ice to this solution, giving a yield of 59%; m.p. 124–135° d. This salt was unstable and did not give the correct analysis. About 68 g. was treated with 25 g. of glacial acetic acid in 400 cc. of absolute diethyl ether. The solid was collected and dried at 50°. The yield of the pure *trans*-1-diethylcarbamyl-2,5-dimethyl-4-guanylpiperazine acetate was 62.0 g.; 49% (83% based on the carbonate salt). It melted at 209–209.5°. The approximate water solubility was 90 g. per 100 cc. at 25°; a 1% aqueous solution had *p*H 7.35.

Anal. Calc'd for $C_{12}H_{25}N_5O \cdot CH_3CO_2H$: C, 53.31; H, 9.27; N, 22.20.
Found: C, 53.2; H, 9.27; N, 21.9.

trans-1,4-Diguanyl-2,5-dimethylpiperazine dihydrochloride (XVII). Two times the amount of cyanamide liquor given in Procedure C was used. After the reaction, it was again made acidic to Congo Red paper with a small portion of aqueous hydrochloric acid and cooled to 10°. The crystals were isolated and were washed with acetone. A second crop of crystals was obtained as large as the first by concentrating the mother liquor to 300 cc. The total yield of crude material was 73.3%; it charred at 285°. Crystallizations from 60% aqueous acetone did not change the charring temperature. The approximate solubility was 25 g. per 100 cc. at 25°; a 1% aqueous solution had *p*H 6.3.

Anal. Calc'd for $C_8H_{18}N_6 \cdot 2HCl$: C, 35.46; H, 7.43; N, 30.99; Cl, 26.15.
Found: C, 35.2; H, 7.39; N, 30.8; Cl, 25.7.

trans-1,4-Dicarbethoxy-2,5-dimethylpiperazine (I) and *trans-1-carbethoxy-2,5-dimethylpiperazine* (II). This procedure was similar to that given by Moore, *et al.* (7) for the preparation of 1-carbethoxypiperazine and 1,4-dicarbethoxypiperazine.

To a solution of 561 g. of crude *trans*-2,5-dimethylpiperazine dihydrochloride (3.0 moles) in two liters of water there was added 1 cc. of a 5% Bromphenol Blue indicator solution. While keeping the temperature at 50–60° and the reaction mixture neutral to the indicator, there were slowly added simultaneously over a period of 1½ hours 424 g. of ethyl chloroformate (3.0 moles) and 600 g. of 50% aqueous sodium hydroxide (7.5 moles). The reaction was then allowed to stand overnight.

The insoluble, crude *trans*-1,4-dicarbethoxy-2,5-dimethylpiperazine was isolated by filtration and dried at room temperature. Yield 250 g.; theory 679 g.; 36.8% based on *trans*-2,5-dimethylpiperazine. It was crystallized from a concentrated solution of petroleum ether at −10°; m.p. 77.0–77.7°.

Anal. Calc'd for $C_{12}H_{22}N_2O_4$: C, 55.81; H, 8.59; N, 10.85.
Found: C, 55.8; H, 8.69; N, 10.8.

The aqueous filtrate from the above reaction was concentrated under reduced pressure until a large amount of inorganic salt had come out. Then it was made strongly alkaline with 50% aqueous sodium hydroxide, keeping the temperature at about room temperature. The oil which separated was dried over potassium hydroxide pellets and distilled at atmospheric pressure to remove the unreacted *trans*-2,5-dimethylpiperazine (b.p. 162°). The residue, *trans*-1-carbethoxy-2,5-dimethylpiperazine, was distilled under reduced pressure, b.p. 100–108° at 3 mm.; yield 160 g.; (0.86 mole), 28.6%. The crude *hydrochloride*, prepared from the base and anhydrous hydrogen chloride in acetone, was purified by extraction with boiling acetone and crystallization from the same solvent, using an atmosphere of nitrogen to prevent the formation of color. It melted at 130–131° and the approximate solubility was 100 g. per 100 cc. water at 25°. A 1% aqueous solution had *p*H 5.2.

Anal. Calc'd for $C_9H_{18}N_2O_2 \cdot HCl$: C, 48.53; H, 8.60; N, 12.58; Cl, 15.92.
Found: C, 48.6; H, 8.55; N, 12.7; Cl, 15.7.

1-Carbethoxy-4-diethylcarbamylpiperazine (IV). To 100 cc. of benzene containing 10.6 g. of sodium carbonate (0.1 mole), there were added 18.5 g. of 1-diethylcarbamylpiperazine (0.1 mole) and 10.8 g. of ethyl chlorocarbonate (0.1 mole). The reaction was stirred at the refluxing temperature for three hours. By filtration there was removed 11 g. of inorganic salts. The benzene was removed under reduced pressure and the residue distilled sharply at 179° at 7 mm. The yield was 22.7 g., 88%.

Anal. Calc'd for $C_{12}H_{23}N_3O_3$: C, 56.00; H, 9.01; N, 16.33.
Found: C, 56.2; H, 8.90; N, 16.1.

trans-1-Carbethoxy-4-diethylcarbamyl-2,5-dimethylpiperazine (V). To 100 cc. of benzene containing 56.0 g. of *trans*-1-carbethoxy-2,5-dimethylpiperazine (0.3 mole) (I) and 37.8 g. of sodium bicarbonate (0.45 mole) there was slowly added, with cooling, 40.7 g of diethylcarbamyl chloride (0.3 mole) at 40–45°. The reaction was stirred at the refluxing temperature for one hour and the inorganic salts were removed. The benzene was removed under reduced pressure and the residue was distilled sharply at 156–157° at 2.5 mm.; 78.4 g.; 91.5%. The approximate solubility was 2.8 g. per 100 cc. of water at 27°; a 1% water solution had *p*H 8.6 at 27°.

Anal. Calc'd for $C_{14}H_{27}N_3O_3$: C, 58.92; H, 9.54; N, 14.72.
Found: C, 58.7; H, 9.32; N, 14.5.

trans-1-Diethylcarbamyl-2,5-dimethylpiperazine (XI). This was prepared according to the procedure given in United States Patent 2,467,894 (8) for the preparation of 1-diethylcarbamyl-2,5-dimethylpiperazine. *trans*-2,5-Dimethylpiperazine (5) was used, 63% being recovered. The yield of the crude product after one distillation was 48 g. (22.5% based on the *trans*-2,5-dimethylpiperazine), b.p. 111–130° at 2 mm. After two more distillations the yield was 28 g., 13%; b.p. 103–106° at 1 mm. It was very soluble in water; a 1% aqueous solution had *p*H 10.5.

Anal. Calc'd for $C_{11}H_{23}N_3O$: C, 61.93; H, 10.86; N, 19.70.
Found: C, 62.1; H, 11.1; N, 19.50.

trans-1,4-Bis(diethylcarbamyl)-2,5-dimethylpiperazine (XII). The residue from the distillation of *trans*-1-diethylcarbamyl-2,5-dimethylpiperazine (XI) was distilled at a higher temperature. The yield was 30 g., 9.6%, b.p. 168–171° at 1.5 mm. It melted at 53.5–55.5°. The approximate solubility was 5.8 g. per 100 cc. of water at 25°; a 1% water solution had *p*H 8.4.

Anal. Calc'd for $C_{16}H_{32}N_4O_2$: C, 61.49; H, 10.29; N, 17.93.
Found: C, 61.5; H, 10.1; N, 17.8.

1-Diethylcarbamyl-4-guanylpiperazine sulfate (XV). To 200 cc. of ethyl alcohol there were added 74 g. of 1-diethylcarbamylpiperazine (0.4 mole) and 55.6 g. of S-methylisothiourea sulfate (0.2 mole). The reaction was stirred at the refluxing temperature for 14 hours. On cooling there was isolated by filtration 1.2 g. of a white solid which was discarded. The filtrate was concentrated to a viscous syrup and the residue was dissolved in 250 cc. of amyl alcohol. The solution was treated with Darco and clarified and diluted while hot with acetone. After two crystallizations from amyl alcohol and acetone the yield was 65.1 g., 59%; m.p. 239.5–240.5° d. It was hygroscopic.

Anal. Calc'd for $C_{10}H_{21}N_5O \cdot \frac{1}{2}H_2SO_4$: C, 43.46; H, 8.02; N, 25.35; S, 5.80.
Found: C, 43.2; H, 7.87; N, 25.2; S, 6.08.

SUMMARY

Several new 1-, and 1,4-carboxylic acid derivatives of piperazine and of *trans*-2,5-dimethylpiperazine have been prepared and described. None of these compounds had any antifilarial activity.

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