[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

PIPERAZINES. III. 1-HETEROCYCLIC-4- GUANYL-, CARBAMYL-, AND THIOCARBAMYL-PIPERAZINES

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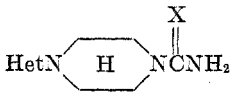
Received March 26, 1953

The clinically established utility of 1-methyl-4-diethylcarbamylpiperazine (Hetrazan) and the reported analgesic and anticonvulsant activities of certain 1,4-diheterocyclicpiperazines (1) have led us to prepare the eleven 1-heterocyclic-4- guanyl-, carbamyl-, and thiocarbamyl-piperazines in Table I for similar evaluation. All of these compounds were prepared from 1-heterocyclicpiperazines described in paper II (2) of this series.

TABLE I

HETEROCYCLIC PIPERAZINES



NUMBER	Het	X
I	2-Pyridyl	NH
V	2-Pyridyl	O
IX	2-Pyridyl	S
II	2-Pyrimidyl	NH
VI	2-Pyrimidyl	O
X	2-Pyrimidyl	S
III	2-Pyrazinyl	NH
VII	2-Pyrazinyl	O
XI	2-Pyrazinyl	S
IV	2-Thiazolyl	NH
VIII	2-Thiazolyl	O

The 1-heterocyclic-4-guanylpiperazines (I, II, III, and IV) were obtained from the reaction of S-methylisothiourea sulfate with the corresponding 1-heterocyclicpiperazine in aqueous alcohol.

The 1-heterocyclic-4-carbamylpiperazines (V, VI, VII, and VIII) were prepared from the appropriate 1-heterocyclicpiperazine and potassium cyanate in aqueous solution.

The 1-heterocyclic-4-thiocarbamylpiperazines (IX, X, and XI) were obtained by the fusion of the corresponding 1-heterocyclicpiperazine thiocyanate salt. The 1-heterocyclicpiperazine thiocyanates (XII, XIII, and XIV) were prepared from the appropriate 1-heterocyclicpiperazine and potassium thiocyanate in aqueous solution.

None of these compounds showed outstanding anticonvulsant action when tested against audiogenic seizures in the rat, and none of these tested exhibited antifilarial action.

Acknowledgment. The authors are indebted to Mr. O. E. Sundberg, Mrs. M. E. Nielson, and Miss I. H. Prokul for the microchemical analyses.

EXPERIMENTAL

1-(2-Pyridyl)-4-guanylpiperazine benzoate (I). In 400 ml. of 50% aqueous ethanol was dissolved 82 g. (0.50 mole) of 1-(2-pyridyl)piperazine and 73 g. (0.25 mole) of S-methylisothiourea sulfate and the solution was refluxed for six hours. The solvent was then removed on the steam-bath under reduced pressure and the residue was dissolved in 100 ml. of water. This solution was made strongly basic with 50 ml. of 50% aqueous sodium hydroxide whereupon the free base of the product separated as a viscous yellow oil. This oil, which weighed 67 g., was removed and dissolved in 100 ml. of 95% ethanol. To this solution was added a solution of an equivalent quantity, 40 g., of benzoic acid in 100 ml. of 95% ethanol. The white precipitate which formed was removed and recrystallized, first from 100 ml. of water and then from 200 ml. of 95% ethanol. After drying, there was obtained 22 g. (13% yield) of the *benzoate salt*, m.p. 268° with decomposition.

Anal. Calc'd for $C_{17}H_{21}N_5O_2$: C, 62.4; H, 6.42; N, 21.4.
Found: C, 62.5; H, 6.42; N, 21.6.

1-(2-Pyrimidyl)-4-guanylpiperazine benzoate (II) was prepared in the same manner as compound I in 23% yield with the corresponding use of 1-(2-pyrimidyl)piperazine; m.p. 252° with decomposition.

Anal. Calc'd for $C_{16}H_{20}N_6O_2$: C, 58.5; H, 6.10; N, 25.6.
Found: C, 58.5; H, 5.96; N, 25.5.

1-(2-Pyrazinyl)-4-guanylpiperazine benzoate (III) was prepared in the same manner as compound I in 25% yield with the corresponding use of 1-(2-pyrazinyl)piperazine; m.p. 278° with decomposition.

Anal. Calc'd for $C_{16}H_{20}N_6O_2$: C, 58.5; H, 6.10; N, 25.6.
Found: C, 58.6; H, 6.23; N, 25.5.

1-(2-Thiazolyl)-4-guanylpiperazine benzoate (IV) was prepared in the same manner as compound I in 19% yield with the corresponding use of 1-(2-thiazolyl)piperazine; m.p. 267° with decomposition.

Anal. Calc'd for $C_{15}H_{19}N_5O_2S$: C, 54.1; H, 5.71; N, 21.0; S, 9.61.
Found: C, 54.3; H, 5.74; N, 21.3; S, 9.75.

1-(2-Pyridyl)-4-carbamylpiperazine (V). In 150 ml. of water was dissolved 82 g. (0.5 mole) of 1-(2-pyridyl) piperazine and the solution was acidified to Congo Red with 80 ml. of concentrated hydrochloric acid and cooled to 5°. Then a solution of 40 g. (0.5 mole) of potassium cyanate in 50 ml. of water was added at 5–10°. The reaction mixture was kept at 5–10° for half an hour and then made ammoniacal with concentrated ammonia solution. The resulting white precipitate was removed and recrystallized, first from 250 ml. of water and then from 400 ml. of 50% acetone—*n*-hexane. After drying, there was obtained 21 g. (20% yield) of 1-(2-pyridyl)-4-carbamylpiperazine as white crystals, m.p. 179.5–180.5°.

Anal. Calc'd for $C_{10}H_{14}N_4O$: C, 58.2; H, 6.83; N, 27.1.
Found: C, 58.4; H, 6.71; N, 27.3.

1-(2-Pyrimidyl)-4-carbamylpiperazine (VI). This was prepared similarly to compound V with the corresponding use of 1-(2-pyrimidyl)piperazine in 32% yield; m.p. 207.0–208.5° after recrystallization from ethanol.

Anal. Calc'd for $C_9H_{13}N_5O$: C, 52.2; H, 6.33; N, 33.8.
Found: C, 52.5; H, 6.44; N, 34.0.

1-(2-Pyrazinyl)-4-carbamylpiperazine (VII). This was prepared similarly to compound V with the corresponding use of 1-(2-pyrazinyl)piperazine in 27% yield; m.p. 197.5–198.0° after recrystallization from ethanol.

Anal. Calc'd for $C_9H_{13}N_5O$: C, 52.2; H, 6.33; N, 33.8.
Found: C, 52.1; H, 6.47; N, 33.7.

1-(2-Thiazolyl)-4-carbamylpiperazine (VIII) was prepared similarly to compound V with

the corresponding use of 1-(2-thiazolyl)piperazine in 19% yield; m.p. 219.0–220.0° after recrystallization from isopropyl alcohol.

Anal. Calc'd for $C_8H_{12}N_4OS$: C, 45.2; H, 5.70; N, 26.4; S, 15.1.
Found: C, 45.1; H, 5.75; N, 26.4; S, 15.0.

1-(2-Pyridyl)piperazine thiocyanate (XII). In 300 ml. of water was dissolved 246 g. (1.5 moles) of 1-(2-pyridyl)piperazine and to this solution was added 125 ml. of concentrated hydrochloric acid. Then a solution of 150 g. (1.5 moles) of potassium thiocyanate in 150 ml. of water was added. Crystals started to separate from the solution almost immediately and the suspension was kept at 5–10° for half an hour. The white precipitate was then removed and recrystallized from 600 ml. of water. After drying, there was obtained 175 g. (52% yield) of 1-(2-pyridyl)piperazine thiocyanate as white crystals, m.p. 138–140°.

Anal. Calc'd for $C_{10}H_{14}N_4S$: C, 54.1; H, 6.31; N, 25.2; S, 14.4.
Found: C, 53.9; H, 6.36; N, 25.3; S, 14.4.

1-(2-Pyrimidyl)piperazine thiocyanate (XIII) was prepared in the same manner as compound XII in 40% yield with corresponding use of 1-(2-pyrimidyl)piperazine; m.p. 147–149° after recrystallization from 95% ethanol.

Anal. Calc'd for $C_9H_{12}N_5S$: C, 48.4; H, 5.83; N, 31.4; S, 14.4.
Found: C, 48.4; H, 5.86; N, 31.6; S, 14.4.

1-(2-Pyrazinyl)piperazine thiocyanate (XIV) was prepared in the same manner as compound XII in 40% yield with corresponding use of 1-(2-pyrazinyl)piperazine; m.p. 177–179° after recrystallization from 95% ethanol.

Anal. Calc'd for $C_9H_{12}N_5S$: C, 48.4; H, 5.83; N, 31.4; S, 14.4.
Found: C, 48.3; H, 5.81; N, 31.5; S, 14.6.

1-(2-Pyridyl)-4-thiocarbamylpiperazine (IX). In an Erlenmeyer flask set in an oil-bath was placed 111.2 g. (0.5 mole) of 1-(2-pyridyl)piperazine thiocyanate. This was fused and the melt was held at about 150° for seven hours. At the end of this time, the melt was dissolved in 300 ml. of boiling absolute ethanol. The yellow precipitate which formed upon cooling was removed and recrystallized first from 500 ml. of water and finally from 500 ml. of absolute ethanol. After drying, there was obtained 20 g. (18% yield) of 1-(2-pyridyl)-4-thiocarbamylpiperazine as light tan crystals, m.p. 171.0–171.5°.

Anal. Calc'd for $C_{10}H_{14}N_4S$: C, 54.1; H, 6.31; N, 25.2; S, 14.4.
Found: C, 54.3; H, 6.33; N, 25.2; S, 14.5.

1-(2-Pyrimidyl)-4-thiocarbamylpiperazine (X) was prepared similarly to compound IX in 6% yield with corresponding use of 1-(2-pyrimidyl)piperazine thiocyanate; m.p. 178.0–178.5° after recrystallization first from water and finally from isopropyl acetate.

Anal. Calc'd for $C_9H_{12}N_5S$: C, 48.4; H, 5.83; N, 31.4; S, 14.4.
Found: C, 48.5; H, 5.99; N, 31.3; S, 14.5.

1-(2-Pyrazinyl)-4-thiocarbamylpiperazine (XI) was prepared in the same manner as compound IX except that a fusion temperature of 180° was required. After recrystallization first from water and finally from absolute ethanol, a 12% yield of product as light yellow crystals, m.p. 196.0–196.5°, was obtained.

Anal. Calc'd for $C_9H_{12}N_5S$: C, 48.4; H, 5.83; N, 31.4; S, 14.4.
Found: C, 48.3; H, 5.90; N, 31.3; S, 14.6.

SUMMARY

Several new 1-heterocyclic-4- guanyl-, carbamyl-, and thiocarbamyl-piperazines have been prepared and described. None of these compounds exhibited useful anticonvulsant or antifilarial activity.

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REFERENCES

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(2) HOWARD, *et al.*, *J. Org. Chem.*, **18**, preceding paper (1953).