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

PIPERAZINES. II. 1-HETEROCYCLICPIPERAZINES AND 1-HETEROCYCLIC-4-CARBETHOXYPIPERAZINES

K. L. HOWARD,[1] H. W. STEWART, E. A. CONROY, AND J. J. DENTON

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It has been reported (1) that 1,4-bis(2-pyrimidyl)piperazine shows anticonvulsant activity and that the 1,4-bis(2-pyrazinyl)piperazine is active as an analgesic. The outstanding antifilarial activity of certain 1-carbethoxypiperazines has also been established (2). Because of these interesting biological actions, the piperazine derivatives listed in Table I were synthesized for similar evaluation. Of the twelve compounds listed, ten are derived from piperazine itself, while the other two are derivatives of *trans*-2,5-dimethylpiperazine. All are substituted with a heterocyclic group in the 1-position.

Several quinolylpiperazines (3–6) and an acridylpiperazine (7) have been reported, but only one monocyclic heterocyclic piperazine, 1-(2-pyridyl)piperazine (VIII), has been previously described (8). It has been prepared from the reaction of 2-bromopyridine and piperazine in an autoclave (8) and from the acid hydrolysis of 1-(2-pyridyl)-4-carbethoxypiperazine by the present authors according to the method of Moore, Boyle, and Thorn (9) for the acid hydrolysis of 1-ethyl-4-carbethoxypiperazine. However, a procedure involving the reaction of 2-bromopyridine and piperazine under reflux in Pentasol has been found preferable (10). A similar procedure has been used in preparing 1-(2-pyrimidyl) piperazine (X), 1-(2-pyrazinyl)piperazine (XI), and 1-(2-thiazolyl)piperazine (XII).

All of the 1-heterocyclic-4-carbethoxypiperazines except 1-(2-thiazolyl)-4-carbethoxypiperazine (VII) were prepared from 1-carbethoxypiperazine (2) and the appropriate heterocyclic halide. Compound VII was prepared from 1-(2-thiazolyl)piperazine and ethyl chlorocarbonate.

The reaction of 1-carbethoxypiperazine with 2,4-dichloropyrimidine resulted in a 57% yield of pure crystalline 1-[2(or 4)-chloro-4(or 2)-pyrimidyl]-4-carbethoxypiperazine. In order to prove the structure of this product by removing the 2(or 4)-chloro substituent, it was reduced catalytically in aqueous alkali by a procedure similar to that used by English, *et al.* (11) for the preparation of 2-orthanilamidopyrimidine. In addition to a 45% recovery of starting material, there was obtained a 36% yield of 1-[4(or 2)-pyrimidyl]piperazine which was not identical with the known 1-(2-pyrimidyl)piperazine and must therefore be the 1-(4-pyrimidyl)piperazine. The product obtained from the reaction of 1-carbethoxypiperazine with 2,4-dichloropyrimidine must therefore be the 1-(2-chloro-4-pyrimidyl)-4-carbethoxypiperazine.

English, *et al.* (11) have shown that 2,5-dichloropyrimidine and methylamine gave only the 2-methylamino-5-chloropyrimidine. From this it is concluded

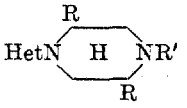
[1] Present Address: Wallerstein Laboratories, 180 Madison Avenue, New York, New York.

that the product obtained from the reaction of 1-carbethoxypiperazine with 2,5-dichloropyrimidine must be the 1-(5-chloro-2-pyrimidyl)-4-carbethoxypiperazine.

Compounds IV, VI, and XII exhibited some analgesic activity in animal tests, but none of the compounds described herein showed useful antifilarial activity.

TABLE I

HETEROCYCLIC PIPERAZINES



No.	Het	R	R′
I	2-Pyridyl	H	$CO_2C_2H_5$
II	2-Pyridyl	CH_3	$CO_2C_2H_5$
III	2-Pyrimidyl	H	$CO_2C_2H_5$
IV	2-Chloro-4-pyrimidyl	H	$CO_2C_2H_5$
V	5-Chloro-2-pyrimidyl	H	$CO_2C_2H_5$
VI	2-Pyrazinyl	H	$CO_2C_2H_5$
VII	2-Thiazolyl	H	$CO_2C_2H_5$
VIII	2-Pyridyl	H	H
IX	2-Pyridyl	CH_3	H
X	2-Pyrimidyl	H	H
XI	2-Pyrazinyl	H	H
XII	2-Thiazolyl	H	H

EXPERIMENTAL[2]

1-(2-Pyridyl)-4-carbethoxypiperazine (I). In a glass-lined autoclave was placed a mixture of 120 g. (1.43 moles) of sodium bicarbonate, 100 g. (0.63 mole) of 2-bromopyridine, and a suspension previously prepared from 139 g. (0.71 mole) of 1-carbethoxypiperazine hydrochloride, 56 g. of 50% aqueous sodium hydroxide, and 60 ml. of water, and the reactants were heated for five hours at 150°. The contents were removed and acidified with concentrated hydrochloric acid. This solution was heated to expel carbon dioxide, cooled, and made alkaline with 50% aqueous sodium hydroxide. The white solid which separated was extracted with ether, and the ether extract was evaporated to give 122 g. (81% yield) of the free base as a white solid, m.p. 66–67°. A portion of the base was dissolved in ether and the hydrochloride salt was precipitated with gaseous hydrogen chloride. After recrystallizing from acetone, 1-(2-pyridyl)-4-carbethoxypiperazine hydrochloride was obtained as white crystals, m.p. 204–205°.

Anal. Calc'd for $C_{12}H_{17}N_3O_2 \cdot HCl$: C, 53.0; H, 6.67; N, 15.5; Cl, 13.1.

Found: C, 53.3; H, 6.46; N, 15.8; Cl, 13.1.

trans-1-(2-Pyridyl)-4-carbethoxy-2,5-dimethylpiperazine (II). To a suspension of 74 g. (0.70 mole) of anhydrous sodium carbonate in 175 ml. of *o*-dichlorobenzene was added 139 g. (0.75 mole) of *trans*-1-carbethoxy-2,5-dimethylpiperazine and 120 g. (0.75 mole) of 2-bromopyridine, and the reaction mixture was refluxed for seven hours, cooled, and fil-

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

tered. The filter cake was washed with benzene and the combined filtrate and washings were distilled. The fraction boiling at 175–183° at 3.5 mm. was collected as an oil. There was obtained 44 g. (22% yield) of *trans*-1-(2-pyridyl)-4-carbethoxy-2,5-dimethylpiperazine which crystallized upon standing to give a solid, m.p. 49.4–51.0°.

Anal. Calc'd for $C_{14}H_{21}N_3O_2$: C, 63.9; H, 8.04; N, 16.0.

Found: C, 63.8; H, 8.24; N, 15.9.

1-(2-Pyrimidyl)-4-carbethoxypiperazine (III). A stirred suspension of 101 g. (1.2 moles) of sodium bicarbonate, 78 g. (0.4 mole) of 1-carbethoxypiperazine hydrochloride, and 46 g. (0.4 mole) of 2-chloropyrimidine in 250 ml. of absolute ethanol was refluxed for one hour. The reaction mixture was filtered, and the filter cake was washed with 100 ml. of absolute ethanol. The combined filtrate and washings were diluted with a large volume of water till no further precipitation of an oil was obtained. This oil solidified on standing and melted at 67.5–69.0°. The yield was 84.5 g. (90%) of the base. A portion of the base was dissolved in ether, poured into alcoholic hydrogen chloride, and allowed to stand overnight. The 1-(2-pyrimidyl)-4-carbethoxypiperazine hydrochloride which precipitated melted at 177–178°.

Anal. Calc'd for $C_{11}H_{16}N_4O_2 \cdot HCl$: C, 48.4; H, 6.28; N, 20.6; Cl, 13.0.

Found: C, 48.7; H, 6.07; N, 20.8; Cl, 13.2.

1-(2-Chloro-4-pyrimidyl)-4-carbethoxypiperazine (IV). This was prepared in the same manner as compound III, with the corresponding use of 2,4-dichloropyrimidine. The yield of crude base, which melted at 111–119°, was 89%. After five crystallizations from aqueous ethyl alcohol the yield was 57% of pure material which melted at 123.5–124.0°.

Anal. Calc'd for $C_{11}H_{15}ClN_4O_2$: C, 48.8; H, 5.59; Cl, 13.1; N, 20.7.

Found: C, 48.8; H, 5.60; Cl, 13.2; N, 20.7.

Reduction of compound IV. A suspension consisting of 25 ml. of water, 1 ml. of 50% sodium hydroxide, 1.08 g. (0.004 mole) of 1-(2-chloro-4-pyrimidyl)-4-carbethoxypiperazine, 0.1 g. of 10% palladium oxide on charcoal, and 0.01 g. of platinum oxide was shaken with 45 lbs. of hydrogen at room temperature for six hours. The aqueous reaction slurry was filtered and the filter cake was extracted with 10 ml. of boiling ethyl alcohol. This alcohol solution, on evaporation, gave 0.48 g. of the starting material which was identified by its melting point 121.5–123.0°, and a mixture melting point which gave no depression. The original aqueous filtrate was alkaline to Clayton Yellow paper and was made just neutral to phenolphthalein paper with acetic acid and evaporated to dryness. The residue was extracted with two 20-ml. portions of boiling acetone. On evaporation of the acetone an oil was obtained which was dissolved in 10 ml. of ethyl alcohol. The solution was filtered to remove some inorganic salt and after the addition of 10 ml. of diethyl ether 0.34 g. of white crystals was precipitated with an excess of anhydrous hydrogen chloride. Upon crystallization from methanol and diethyl ether, pure 1-(4-pyrimidyl)piperazine dihydrochloride was obtained which melted at 272.5–274.5° d. (corr.) with darkening.

Anal. Calc'd for $C_8H_{12}N_4 \cdot 2HCl$: C, 40.52; H, 5.95; N, 23.63; Cl, 29.90.

Found: C, 40.4; H, 6.11; N, 23.4; Cl, 29.7 (Volhard).

A mixture melting point of this compound with 1-(2-pyrimidyl)piperazine dihydrochloride (X), m.p. 252.5–253.0° d., gave a depression (221–223° d.).

Attempts at reduction of 1-(2-chloro-4-pyrimidyl)-4-carbethoxypiperazine with zinc dust, sodium bicarbonate, and charcoal (Darco) in boiling water gave only unreacted starting material.

1-(5-Chloro-2-pyrimidyl)-4-carbethoxypiperazine[8] (V) was prepared in the same manner as compound III with the corresponding use of 2,5-dichloropyrimidine. The yield of crude base was 93% and it melted at 87.5–88.0°. When purified by crystallization from aqueous ethyl alcohol the yield was 85%; m.p. 88.0–88.3°.

Anal. Calc'd for $C_{11}H_{15}ClN_4O_2$: C, 48.8; H, 5.59; Cl, 13.1; N, 20.7.

Found: C, 48.8; H, 5.50; Cl, 13.0; N, 20.8.

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[8] This compound, SN 14802, appears in *A Survey of Antimalarial Drugs, 1941–1945*, Vol. II, 1403.

1-(2-Pyrazinyl)-4-carbethoxypiperazine (VI) was prepared in the same manner as compound II, with the corresponding use of 2-chloropyrazine and 1-carbethoxypiperazine hydrochloride, in 70% yield; b.p. 190–191° at 3.0 mm. A portion of the base was converted to the hydrochloride salt by precipitation from an alcoholic solution of hydrogen chloride with ether. The 1-(2-pyrazinyl)-4-carbethoxypiperazine hydrochloride melted at 152–153°.

Anal. Calc'd for $C_{11}H_{16}N_4O_2 \cdot HCl$: C, 48.4; H, 6.28; N, 20.5; Cl, 13.0.

Found: C, 48.5; H, 6.20; N, 20.2; Cl, 13.1.

1-(2-Thiazolyl)-4-carbethoxypiperazine (VII). In a solution of 50.8 g. (0.3 mole) of 1-(2-thiazolyl)piperazine in 600 ml. of benzene was suspended 42.0 g. (0.4 mole) of anhydrous sodium carbonate. To the suspension was added, with stirring, 32.6 g. (0.3 mole) of ethyl chlorocarbonate over a period of five minutes at room temperature. The reaction mixture was then refluxed for one hour and filtered. The filtrate was concentrated on the steam-bath under reduced pressure to a red oil which solidified upon cooling to a white crystalline cake. This material was crystallized three times from 500-ml. portions of *n*-hexane and dried. There was obtained 25.5 g. (35% yield) of 1-(2-thiazolyl)-4-carbethoxypiperazine as a white crystalline material, m.p. 58.5–60.0°.

Anal. Calc'd for $C_{10}H_{15}N_3O_2S$: C, 49.8; H, 6.27; N, 17.4; S, 13.3.

Found: C, 49.8; H, 5.98; N, 17.4; S, 13.2.

1-(2-Pyridyl)piperazine (VIII). *Procedure* (*A*). A suspension of 114 g. of anhydrous sodium carbonate in a solution of 210 g. (2.5 moles) of anhydrous piperazine and 194 g. (1.25 moles) of 2-bromopyridine in 300 ml. of Pentasol was stirred and refluxed, with continual removal of water formed, for five hours. The reaction mixture was filtered and the filter cake was washed with *n*-butanol. The combined filtrate and washings were concentrated on the steam-bath under reduced pressure to give a dark oil. This oil was distilled under reduced pressure and the fraction boiling at 120–122° at 2.0 mm. was collected as a light yellow oil. There was obtained 137 g. (70% yield) of 1-(2-pyridyl)piperazine which formed a *dihydrochloride*, m.p. 267–269.5°.

Procedure (*B*). A mixture of 58.5 g. (0.25 mole) of 1-(2-pyridyl)-4-carbethoxypiperazine and 150 ml. of concentrated hydrochloric acid was refluxed for 72 hours. The reaction mixture was poured into a mixture of 120 g. of 50% aqueous sodium hydroxide and 300 g. of ice. The resulting solution was extracted with ethyl acetate and the extract was dried over sodium sulfate. The precipitate which formed upon adding alcoholic hydrogen chloride to the extract was removed and dried. There was obtained 35.4 g. (60% yield) of 1-(2-pyridyl)-piperazine dihydrochloride, m.p. 260–262°. After recrystallizing from methanol, the salt melted at 267–268.5°.

Anal. Calc'd for $C_9H_{13}N_3 \cdot 2HCl$: C, 45.8; H, 6.40; N, 17.8; Cl, 30.0.

Found: C, 45.5; H, 6.21; N, 17.8; Cl, 29.6.

trans-1-(2-Pyridyl)-2,5-dimethylpiperazine (IX) was prepared in the same manner as compound VIII, Procedure (*B*), with the corresponding use of *trans*-1-(2-pyridyl)-4-carbethoxy-2,5-dimethylpiperazine, in 85% yield; b.p. 123–133° at 2.5 mm. A portion of the base was converted to the *hemisulfate salt* with 98% sulfuric acid in methanol, and the salt was precipitated by the addition of ether. After drying, the *trans*-1-(2-pyridyl)-2,5-dimethylpiperazine hemisulfate melted at 188.5–189.5°.

Anal. Calc'd for $C_{11}H_{17}N_3 \cdot \frac{1}{2}H_2SO_4$: C, 55.0; H, 7.55; N, 17.5; S, 6.67.

Found: C, 54.9; H, 7.54; N, 17.4; S, 6.64.

1-(2-Pyrimidyl)piperazine (X). A solution of 100 g. (1.2 moles) of anhydrous piperazine and 50 g. (0.6 mole) of 2-chloropyrimidine in 400 ml. of 95% ethanol was refluxed for half an hour, made ammoniacal with concentrated aqueous ammonia, and concentrated on the steam-bath under reduced pressure to yield a dark semi-crystalline mass. This was dissolved in 200 ml. of water, extracted with chloroform, and the extract was evaporated to a red oil. This oil was distilled under reduced pressure and the fraction boiling at 118–120° at 2.0 mm. was collected as a yellow oil. There was obtained 43 g. (60% yield) of 1-(2-pyrimidyl)piperazine. The *dihydrochloride* was obtained from an ether solution of the base and excess anhydrous hydrogen chloride. After crystallization from methanol and diethyl ether, it melted at 252.5–253.0° d. (corr.).

Anal. Calc'd for $C_8H_{12}N_4 \cdot 2HCl$: C, 40.52; H, 5.95; N, 23.63; Cl, 29.90.
Found: C, 40.8; H, 5.94; N, 23.9; Cl, 29.6 (Volhard).

When a stoichiometric amount of anhydrous hydrogen chloride was used, the *monohydrochloride* was obtained. It melted at 289–289.5° d.

Anal. Calc'd for $C_8H_{12}N_4 \cdot HCl$: C, 47.6; H, 7.00; N, 27.8; Cl, 17.6.
Found: C, 47.5; H, 6.85; N, 27.9; Cl, 17.6.

1-(2-Pyrazinyl)piperazine (XI). This was prepared similarly to compound VIII, Procedure (*A*), with the corresponding use of 2-chloropyrazine, in 70% yield; b.p. 138–143° at 2.0 mm. The free base forms a monohydrochloride, m.p. 250–251.5° with decomposition.

Anal. Calc'd for $C_8H_{12}N_4 \cdot HCl$: C, 47.9; H, 6.52; N, 27.9; Cl, 17.7.
Found: C, 48.0; H, 6.75; N, 28.2; Cl, 17.5.

1-(2-Thiazolyl)piperazine (XII). This was prepared in the same manner as compound VIII, Procedure (*A*), with the corresponding use of 2-chlorothiazole, in 70% yield, b.p. 120–125° at 2.0 mm. The base forms a *monohydrogen citrate*, m.p. 187–188.5°.

Anal. Calc'd for $(C_7H_{11}N_3S)_2 \cdot C_6H_8O_7$: C, 45.3; H, 5.70; N, 15.8; S, 12.1.
Found: C, 45.0; H, 6.14; N, 16.4; S, 11.7.

SUMMARY

Several new 1-heterocyclicpiperazines and 1-heterocyclic-4-carbethoxypiperazines have been prepared and described. None of these compounds exhibited useful analgesic or antifilarial activity.

BOUND BROOK, NEW JERSEY

REFERENCES

(1) DENTON AND HOWARD, U. S. Patent 2,459,367.
(2) STEWART, *et al.*, *J. Org. Chem.*, **13**, 134 (1948); U. S. Patent 2,472,496.
(3) KRAHLER AND BURGER, *J. Am. Chem. Soc.*, **63**, 2367 (1941).
(4) FOURNEAU AND BARRELET, *Bull. soc. chim.*, [4], **45**, 1172 (1929).
(5) KERMACK AND SMITH, *J. Chem. Soc.*, 1356 (1930).
(6) CERKOVNIKOV AND PRELOG, *Ber.*, **74**, 1661 (1941).
(7) HATA, MATSUMURA, AND ISHIHARA, U. S. Patent 2,083,908.
(8) HAMLIN, *et al.*, *J. Am. Chem. Soc.*, **71**, 2731 (1949).
(9) MOORE, BOYLE, AND THORN, *J. Chem. Soc.*, 39 (1929).
(10) HULTQUIST AND HOWARD, U. S. Patent 2,606,905.
(11) ENGLISH, *et al.*, *J. Am. Chem. Soc.*, **68**, 1047 (1946).