[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Derivatives of 1-Piperazinecarboxylic Acid as Sedatives[1]

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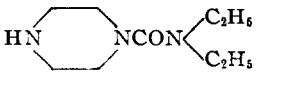
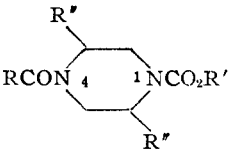
A series of esters of 4-acyl- and 4-aroyl-1-piperazinecarboxylic acid represented by formula II has been synthesized and characterized. Several have been found to possess sedative properties.

In studying the pharmacological properties of various derivatives of piperazine it has been noted[2] that some possess sedative properties when tested in animals; Nonas[3] has reported that N,N-diethyl-1-piperazinecarboxamide[4] (I) has possible clinical usefulness as a daytime sedative. Since various amides and urethans exhibit sedative and hypnotic properties,[5] it was decided to synthesize derivatives of piperazine represented by formula II in which N^4 is substituted with an acyl or aroyl group and N^1 is substituted with a carbalkoxy or carbaralkoxy group.

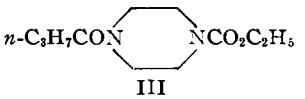


I



II, R = alkyl or aryl
R′ = alkyl or aralkyl
R″ = H or methyl

Among the 4-acyl and aroyl derivatives of ethyl 1-piperazinecarboxylate listed in Table I, a number were found to be active as sedatives when tested with the asymptomatic dose in rats in activity cages. In the normal acyl series there is a narrow range of activity with the peak (4+) reached at C_4–C_5 in ethyl 4-*n*-butyryl-1-piperazinecarboxylate (III) and in ethyl 4-*n*-valeryl-1-piperazinecarboxylate (XIII). In the branched-chain acyl series there is a wider range of activity with the peak



III

(4+) at isovaleryl[6] (XIV), and 3+ activity for the 2-methylbutyryl (XV), 3-methylvaleryl (XVIII) and 2-ethylcaproyl (XXII) derivatives. The isocaproyl derivative (XVII) is much more toxic than the previously mentioned compounds and at the asymptomatic dose level (30 mg./kg. orally) the compound is inactive. The aroyl derivatives (XXV, XXVI, XXVII, XXVIII) are inactive.

A comparison of the methyl, ethyl, *n*-butyl and benzyl esters (IX, III, X, XI) of 4-*n*-butyryl-1-piperazinecarboxylic acid reveals that the peak sedative activity is reached in the ethyl ester III.

The compounds listed in Table I were synthesized by reaction of an alkyl or aralkyl ester of 1-piperazinecarboxylic acid with an anhydride (procedures A, B and C) or with an acyl or aroyl halide under Schotten–Baumann conditions in the presence of sodium hydroxide (procedure D) or sodium bicarbonate (procedure E); or with a molar excess of the ester of 1-piperazinecarboxylic acid in an anhydrous solvent (procedures F, G, H and I).

Experimental[8]

The intermediate methyl, ethyl, *n*-butyl and benzyl esters of 1-piperazinecarboxylic acid were prepared by the methods of Moore, *et al.*,[7] Stewart, *et al.*,[9] and Goldman, *et al.*[10] Ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate was prepared as described previously.[11] 2-Methylbutyryl chloride was obtained in 92% yield as previously described.[12]

2-Ethyl-*n*-caproyl Chloride.—*n*-Butylethylmalonic acid was decarboxylated to 2-ethyl-*n*-caproic acid in 96% yield according to the method of Raper.[13] Reaction with thionyl chloride according to Levene and Kuna[14] for the (−)-isomer gave 2-ethyl-*n*-caproyl chloride, b.p. 73° (17 mm.), in 87% yield. Tiffeneau[15] reports b.p. 85–90° (20 mm.); Levene and Kuna[14] report b.p. 62–64° (10 mm.) for the (−)-isomer.

3-Methylvaleryl Chloride.—*sec*-Butylmalonic acid,[16] obtained in 76% yield by saponification of the ethyl ester,[16] was decarboxylated[17] to give a 93% yield of 3-methylvaleric acid,[18] which reacted with thionyl chloride according to Colonge[19] to give a 65% yield of 3-methylvaleryl chloride, b.p. 73–75° (80 mm.); Hommelen[18] gives b.p. 142.5–143.0° (749 mm.).

***n*-Caprylyl Chloride.**—Obtained in 96% yield by reaction of *n*-caprylic acid with phosphorus pentachloride. Averill, *et al.*,[20] had synthesized this compound by the reaction of *n*-caprylic acid with oxalyl chloride (method of Adams and Ulich[21]).

Procedure A. Ethyl 4-Acetyl-1-piperazinecarboxylate (IV).—A solution of 31.6 g. (0.2 mole) of ethyl 1-piperazinecarboxylate[7] in 100 ml. of glacial acetic acid was treated, with cooling, with 20.4 g. (0.2 mole) of 97% acetic anhydride. The resulting solution was heated for 1 hour on a steam-bath and then evaporated *in vacuo* to remove the acetic acid. Distillation *in vacuo* of the residual sirup gave 33.7 g. (84%) of colorless liquid, b.p. 143–145° (0.3 mm.), $n^{25}D$ 1.4865.

(1) Presented before the Division of Medicinal Chemistry, 126th National Meeting of the American Chemical Society, New York, N. Y., September 12–17, 1954.

(2) R. W. Cunningham, *et al.*, private communication.

(3) G. Nonas, *N. Y. State J. Med.*, **50**, 1257 (1950).

(4) S. Kushner, L. M. Brancone, R. I. Hewitt, W. L. McEwen and Y. SubbaRow; H. W. Stewart, R. J. Turner and J. J. Denton, *J. Org. Chem.*, **13**, 144 (1948).

(5) S. Fränkel, "Die Arzneimittel-Synthese," Julius Springer, Berlin, 1927, p. 522.

(6) During the course of this investigation R. B. Keller and R. A. LaForge, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 301 (1952), reported the synthesis of XIV and found that it does not show promise as a sedative.

(8) All boiling points and melting points are uncorrected.

(9) H. W. Stewart, R. J. Turner and J. J. Denton; S. Kushner, L. M. Brancone, W. L. McEwen, R. I. Hewitt and Y. SubbaRow, *J. Org. Chem.*, **13**, 134 (1948).

(10) L. Goldman and J. H. Williams, *ibid.*, **18**, 815 (1953).

(11) (a) H. W. Stewart, N. Q. Quinones, E. G. Lee and J. J. Denton, *ibid.*, **18**, 1478 (1953); (b) K. M. Beck, K. E. Hamlin and A. W. Weston, THIS JOURNAL, **74**, 605 (1952), not identified as *trans* isomer.

(12) R. Leimu, *Ber.*, **70B**, 1040 (1937).

(13) H. S. Raper, *J. Chem. Soc.*, **91**, 1831 (1907).

(14) P. A. Levene and M. Kuna, *J. Biol. Chem.*, **140**, 259 (1941).

(15) M. M. Tiffeneau, *Bull. soc. chim.*, [4], **33**, 183 (1923).

(16) F. Ehrlich, *Ber.*, **41**, 1153 (1908).

(17) P. van Rumburgh, *Rec. trav. chim.*, **6**, 150 (1887).

(18) M. Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933).

(19) J. Colonge, *Bull. soc. chim.*, [4], **49**, 411 (1931).

(20) H. P. Averill, J. N. Roche and C. G. King, THIS JOURNAL, **51**, 866 (1929).

(21) R. Adams and L. H. Ulich, *ibid.*, **42**, 603 (1920).

TABLE I. RCON(R″)CH₂CH₂NCO₂R′

Cmpd.	R	R′	R″	Procedure	B.p. °C.	B.p. Mm.	M.p., °C.	$n^{25}D$	Yield, %	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sedative rating[a]	(mg./kg. in rat)[b]
IV	CH_3	C_2H_5	H	A	143–145	0.3		1.4865	84	$C_9H_{16}N_2O_3$	54.0	53.7	8.1	8.4	14.0	14.1	+	500
V	CH_3	C_2H_5	CH_3	B	163	5			22	$C_{11}H_{20}N_2O_3$	57.9	57.5	8.8	8.9	12.3	12.1	0	125 ip[c]
VI	CH_3	$CH_2C_6H_5$	H	A[d]	198–203	0.3	42.5–43[e]		87	$C_{14}H_{18}N_2O_3$	64.1	64.1	6.9	6.9	10.7	10.5	0	500
VII	C_2H_5	C_2H_5	H	A[f]	145–149	.3		1.4867	61	$C_{10}H_{18}N_2O_3$	56.0	56.0	8.5	8.5	13.1	12.7	0	500
VIII	C_2H_5	$CH_2C_6H_5$	H	C[g]	184–188	.3	50–50.5[e]		65	$C_{15}H_{20}N_2O_3$	65.2	65.4	7.3	7.1	10.1	10.1	0	85 ip
IX	*n*-C_3H_7	CH_3	H	C	154–156	.7	35–37		77	$C_{10}H_{18}N_2O_3$	56.0	56.1	8.5	8.6	13.1	12.9	+	200 ip
III	*n*-C_3H_7	C_2H_5	H	D[h]	150–153	1.2		1.4849	84	$C_{11}H_{20}N_2O_3$	57.9	57.5	8.8	8.8	12.3	12.3	4+	400
				G[i]	136–138.5	0.6			76			57.6		9.0		12.1		
X	*n*-C_3H_7	*n*-C_4H_9	H	C	155–156	.4		1.4820	80	$C_{13}H_{24}N_2O_3$	60.9	60.9	9.4	9.7	10.9	10.6	0	50 ip
XI	*n*-C_3H_7	$CH_2C_6H_5$	H	D	197–203	.3		1.5353	75	$C_{16}H_{22}N_2O_3$	66.2	66.0	7.6	7.8	9.6	9.5	0	200
XII	iso-C_3H_7	C_2H_5	H	F	130–131	.5		1.4840	97	$C_{11}H_{20}N_2O_3$	57.9	57.7	8.8	8.8	12.3	12.0	2+	500
XIII	*n*-C_4H_9	C_2H_5	H	C[j]	157–158	.6		1.4840	87	$C_{12}H_{22}N_2O_3$	59.5	59.2	9.2	9.2	11.6	11.7	4+	400
XIV	iso-C_4H_9[k]	C_2H_5	H	G	121–122[k]	.15		1.4839	71	$C_{12}H_{22}N_2O_3$	59.5	59.2	9.2	9.0	11.6	11.2	4+	500
XV	$C_2H_5CH(CH_3)$	C_2H_5	H	G	128–132	.08–0.1		1.4835	77	$C_{12}H_{22}N_2O_3$	59.5	59.3	9.2	8.8	11.6	11.4	3+	500
XVI	*n*-C_5H_{11}	C_2H_5	H	I	130–136	.05–0.08		1.4835[l]	90	$C_{13}H_{24}N_2O_3$	60.9	61.0	9.4	9.7	10.9	10.6	+	125
XVII	iso-C_5H_{11}	C_2H_5	H	F[m]	163–165	1.1		1.4823	92	$C_{13}H_{24}N_2O_3$	60.9	60.3	9.4	9.8	10.9	10.9	0	30
XVIII	$C_2H_5CH(CH_3)CH_2$	C_2H_5	H	G	137–140	0.04		1.4840	87	$C_{13}H_{24}N_2O_3$	60.9	60.7	9.4	9.3	10.9	10.9	3+	500
XIX	$(C_2H_5)_2CH$	C_2H_5	H	F[n]	149–151	.8		1.4811	87	$C_{13}H_{24}N_2O_3$	60.9	60.5	9.4	9.7	10.9	10.7	+	50
XX	*n*-C_6H_{13}	C_2H_5	H	I	136–141	.05		1.4828[o]	98	$C_{14}H_{26}N_2O_3$	62.2	61.8	9.7	9.8	10.4	10.3	0	125
XXI	*n*-C_7H_{15}	C_2H_5	H	G[p]	168–172	.3–0.4	23–24.5	1.4810	82	$C_{15}H_{28}N_2O_3$	63.4	63.4	9.9	9.6	9.8	9.8	0	500
XXII	$C_4H_9CH(C_2H_5)$	C_2H_5	H	G[q]	138–143	.03–0.04		1.4791	89	$C_{15}H_{28}N_2O_3$	63.4	62.9	9.9	9.5	9.8	9.6	3+	75
XXIII	*n*-$C_{11}H_{23}$	C_2H_5	H	H[p]			27–29		97	$C_{19}H_{36}N_2O_3$	67.0	66.8	10.7	10.8	8.2	8.0	0	1000
XXIV	*n*-$C_{13}H_{27}$	C_2H_5	H	H			36.5–38[r]		96	$C_{21}H_{40}N_2O_3$	68.4	68.3	10.9	10.8	7.6	7.5	0	500
XXV	C_6H_5[s]	C_2H_5	H	F[m]	186–187	0.9	80.5–82[t]		67	$C_{14}H_{18}N_2O_3$	64.1	64.0	6.9	6.8	10.7	10.4	0	500
				F[m]			82.5–83.5[s]		94			64.4		7.1		10.4		
XXVI	*p*-$C_6H_4NO_2$	C_2H_5	H	E			91.5–92.5[t]		45	$C_{14}H_{17}N_3O_5$	54.7	54.9	5.6	5.9	13.7	14.0	0	500
XXVII	*o*-C_6H_4Cl	C_2H_5	H	F[m]	181–184	0.2	71–73, 77–78[u]		79	$C_{14}H_{17}ClN_2O_3$	56.7	56.3	5.8	5.8	9.4	9.2		
															Cl, 11.9	11.5	0	500
XXVIII	2,6-$C_6H_4Cl_2$	C_2H_5	H	F[m]			89.5–91[v]		98	$C_{14}H_{16}Cl_2N_2O_3$	50.8	51.0	4.9	5.0	8.5	8.2	0	500
															Cl, 21.4	21.4		

[a] Tested in rats in activity cages. [b] Asymptomatic dose administered orally unless otherwise indicated. [c] ip is intraperitoneally. [d] Reaction run in benzene at room temperature for 2 hours. [e] From ether. [f] Reaction run in benzene on a steam-bath for 3.5 hours. [g] Reaction time 3 hours. [h] Run at −5 to −10° (when run at +2 to −5° the yield was 35%), product extracted into benzene. [i] Reaction mixture refluxed 3 hours. [j] Reaction time 2 hours. [k] Keller and LaForge[6] give b.p. 168–170° (4 mm.). [l] Temperature 24°. [m] Reaction mixture allowed to stand overnight at room temperature. [n] Reaction mixture heated to boiling, cooled, and worked up as for XII. [o] Reaction mixture allowed to stand at room temperature for 2 days. [p] Reaction mixture allowed to stand at room temperature for 3 days. [q] From hexane. [r] Moore, *et al.*,[7] give m.p. 82° (from light petroleum). [s] From benzene–hexane. [t] From ethanol. [u] The compound melts at 71–73°, and when the temperature is raised it solidifies and remelts at 77–78°. [v] Obtained by triturating the undistilled crude product with 5% sodium bicarbonate and recrystallizing from heptane and from aqueous ethanol.

(7) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).

Procedure B. Ethyl *trans*-4-Acetyl-2,5-dimethyl-1-piperazinecarboxylate (V).—A mixture of 18.6 g. (0.1 mole) of ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate[11] and 25 ml. of acetic anhydride was refluxed for 8 hours. The resulting solution was distilled *in vacuo*. After removal of acetic acid and acetic anhydride two fractions were obtained: (a) 7.2 g. of colorless liquid, b.p. 128–143° (15 mm.) (mainly ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate); (b) 10.2 g. of nearly colorless viscous liquid, b.p. 120–163° (5 mm.) (mainly b.p. 163°). Fraction b was redistilled and after removal of 3.0 g. of forerun, b.p. 113–163° (5 mm.), 5.1 g. (22%) of V was obtained as a viscous yellow liquid, b.p. 163° (5 mm.). After standing for a long time the material solidified.

Procedure C. *n*-Butyl 4-*n*-Butyryl-1-piperazinecarboxylate (X).—To 37.2 g. (0.2 mole) of *n*-butyl 1-piperazinecarboxylate,[9] 31.6 g. (0.2 mole) of *n*-butyric anhydride was added with mixing and cooling. The resulting solution was heated on a steam-bath for 1 hour and then distilled through a Vigreux column. After removal of the *n*-butyric acid, 40.8 g. (80%) of X was obtained as a colorless liquid, b.p. 155–156° (0.4 mm.), $n^{25}D$ 1.4820.

Procedure D. Benzyl 4-*n*-Butyryl-1-piperazinecarboxylate (XI).—To a stirred mixture of 44 g. (0.2 mole) of benzyl 1-piperazinecarboxylate[10] and ice were added simultaneously and dropwise 32 g. (0.3 mole) of *n*-butyryl chloride and 100 ml. of 4 *N* sodium hydroxide; ice was added as required to maintain an excess. A colorless oil separated. The mixture was kept cold by means of an ice-bath and stirring was continued for 3 hours. The oil was extracted into chloroform and the chloroform extract was washed with 0.5 *N* hydrochloric acid and then with water and dried over magnesium sulfate. The dried extract was evaporated *in vacuo* to remove the chloroform and the residual liquid was distilled *in vacuo* to yield 43.2 g. (75%) of nearly colorless liquid, b.p. 197–203° (0.3 mm.), $n^{25}D$ 1.5353.

Procedure E. Ethyl 4-*p*-Nitrobenozyl-1-piperazinecarboxylate (XXVI).—A mixture of 31.6 g. (0.2 mole) of ethyl 1-piperazinecarboxylate, 37.1 g. (0.2 mole) of *p*-nitrobenzoyl chloride and 33.6 g. (0.4 mole) of sodium bicarbonate in 300 ml. of water was stirred at room temperature for 7.5 hours and then heated on a steam-bath for 30 minutes. The resulting precipitate was removed by filtration and crystallized twice from absolute ethanol (using Norit), yielding 27.5 g. (45%) of very pale yellow crystals, m.p. 91–92°. When recrystallized from absolute ethanol the product had m.p. 91.5–92.5°.

Procedure F. Ethyl 4-Isobutyryl-1-piperazinecarboxylate (XII).—To a cold stirred solution of 150 g. (0.95 mole) of ethyl 1-piperazinecarboxylate in 1 l. of ethyl acetate, 50 g. (0.47 mole) of isobutyryl chloride was added dropwise. After standing for 1.5 hours at room temperature the mixture was filtered to remove 91.9 g. (100%) of colorless crystals of ethyl 1-piperazinecarboxylate hydrochloride.[22] The filtrate was distilled to remove the ethyl acetate and the residual red-brown liquid was distilled *in vacuo*. The product, 89 g. (97%), was obtained as a colorless liquid, b.p. 130–131° (0.5 mm.), $n^{25}D$ 1.4840.

Procedure G. Ethyl 4-(3-Methylvaleryl)-1-piperazinecarboxylate (XVIII).—3-Methylvaleryl chloride (13.5 g., 0.1 mole) was added dropwise to 34.8 g. (0.22 mole) of ethyl 1-piperazinecarboxylate in 250 ml. of ether with cooling. After standing overnight at room temperature the reaction mixture was filtered to remove 19.6 g. (100%) of ethyl 1-piperazinecarboxylate hydrochloride. The filtrate was washed with 1 *N* hydrochloric acid, water and 5% sodium bicarbonate, and dried over magnesium sulfate. The ether was removed on a steam-bath and the residual liquid was distilled *in vacuo* to yield 22.3 g. (87%) of XVIII as a colorless liquid, b.p. 137–140° (0.04 mm.), $n^{25}D$ 1.4840.

Procedure H. Ethyl 4-Myristoyl-1-piperazinecarboxylate (XXIV).—To a solution of 63.3 g. (0.4 mole) of ethyl 1-piperazinecarboxylate in 350 ml. of ether, 49.4 g. (0.2 mole) of myristoyl chloride was added in portions with shaking and cooling. After standing overnight at room temperature the mixture was filtered to remove 38.4 g. (99%) of ethyl 1-piperazinecarboxylate hydrochloride. The filtrate was washed with 5% sodium bicarbonate and dried over Drierite. The dried solution was heated on a steam-bath to remove the ether, leaving 71.1 g. (96%) of XXIV, m.p. 35–36.5°. Recrystallization from hexane gave colorless crystals, m.p. 36.5–38°.

Procedure I. Ethyl 4-*n*-Caproyl-1-piperazinecarboxylate (XVI).—To a cold solution of 63.3 g. (0.4 mole) of ethyl 1-piperazinecarboxylate in 350 ml. of ether, 26.9 g. (0.2 mole) of *n*-caproyl chloride was added carefully, immediately producing a precipitate of ethyl 1-piperazinecarboxylate hydrochloride. After standing at room temperature for 2 hours 100 ml. of water was added to dissolve the precipitate. The layers were separated and the ether layer was washed successively with 5% hydrochloric acid, water and 5% sodium bicarbonate, and dried over magnesium sulfate. The ether was removed on a steam-bath and the residual pale yellow liquid, 46.1 g. (90%), was distilled *in vacuo*. The product was obtained as a nearly colorless liquid, b.p. 130–136° (0.05–0.08 mm.), $n^{23.8}D$ 1.4835.

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(22) K.-R. Jacobi, *Ber.*, **66B**, 113 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF HARVARD UNIVERSITY AND THE DIVISION OF NUTRITION AND PHYSIOLOGY OF THE PUBLIC HEALTH RESEARCH INSTITUTE OF NEW YORK CITY]

The Synthesis of 4-Amino-2(3H)-oxo-5-imidazolecarboxamide

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4-Amino-2(3H)-oxo-5-imidazolecarboxamide has been synthesized by the action of base on carboxamidoaminocyanoacetamide. Its structure has been proved by hydrolytic degradation to 2,4-dioxo-5-imidazolecarboxamide and to hydantoin. Biological testing of C^{13}-labeled material gave no evidence of its being a precursor of uric acid.

Introduction

In 1945, Stetten and Fox[3] discovered a new diazotizable amine in cultures of *E. coli* whose growth was inhibited by sulfadiazine or sulfapyridine. The amine was subsequently identified by Shive, *et al.*,[4] as 4-amino-5-imidazolecarboxamide (I). Isotopic studies have demonstrated this compound to be a purine precursor in a number of biological systems including yeast,[5] the pigeon,[6] the rat[7] and man.[8] In man, with a ureotelic nitrogen metabolism, uric

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(3) M. R. Stetten and C. L. Fox, *J. Biol. Chem.*, **161**, 333 (1945).

(4) W. Shive, W. W. Ackermann, M. Gordon, M. E. Getzendaner and R. E. Eakin, THIS JOURNAL, **69**, 725 (1947).

(5) W. J. Williams, *Federation Proc.*, **10**, 270 (1951).

(6) W. P. Schulman, J. M. Buchanan and C. S. Miller, *ibid.*, **9**, 225 (1950).

(7) C. S. Miller, S. Gurin and D. W. Wilson, *Science*, **112**, 654 (1950).

(8) J. E. Seegmiller, personal communication.