[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of Some 3,3-Dialkyl-2,6-piperazinediones

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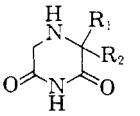
A group of 3,3-dialkyl-2,6-piperazinediones (Ic) has been prepared. These compounds are obtained by treating N-(1-cyanoalkyl)-glycine esters (III) or the corresponding amide acids V or amide esters VI with polyphosphoric acid. Some of these piperazinediones have hypnotic activity.

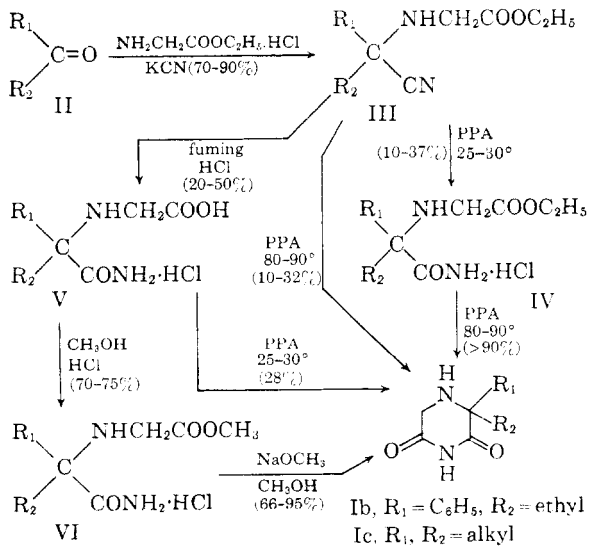
Appropriately substituted heterocyclic compounds of the 2,4-piperidinedione,[1] hydantoin,[2] succinimide[3] and barbiturate types are well known for their ability to depress the central nervous system. Such compounds have found wide use in medicine as sedatives, hypnotics and anticonvulsants. The 2,6-piperazinedione system (Ia), which combines some of the structural features of the aforementioned types, appeared to be an appropriate nucleus for investigation. Previous work[4] had, in fact, shown that 3-ethyl-3-phenyl-2,6-piperazinedione (Ib) possessed depressant properties. A systematic



Ia, $R_1 = R_2 = H$
Ib, R_1 = phenyl, R_2 = ethyl
Ic, R_1, R_2 = alkyl

study of the 3,3-dialkyl-2,6-piperazinediones (Ic) offered the possibility that useful substances with hypnotic or anticonvulsant properties might be found. The synthesis of a group of compounds of type Ic is the subject of this paper.

The previously reported[4] synthesis of derivatives of Ib required four steps from the starting ketone (II → III → V → VI → Ib). In the present investigation it was found possible to carry out certain simplifications, and, by making use of polyphosphoric acid (PPA), to shorten the synthesis to two steps (II → III → Ic). The various transformations leading to Ic are (yields in parentheses).



The ordinary Strecker procedure,[5] in which the starting aliphatic ketones were condensed with glycine ethyl ester hydrochloride and potassium cyanide, was found to proceed more smoothly and to give more satisfactory yields of III than the procedure using liquid hydrogen cyanide. The aliphatic imino nitriles III were isolated as colorless, oily liquids which were used in subsequent steps without further purification.[6] Treatment of the crude imino nitriles III with polyphosphoric acid on a steam-bath for about 45 minutes gave the 2,6-piperazinediones (Ic) directly, but in only fair to poor yields. Alternatively, treatment of III with polyphosphoric acid at room temperature yielded the intermediate amide esters IV, isolated as the hydrochlorides (see Table III). Cyclization of the latter was then accomplished smoothly with polyphosphoric acid at 80-90° in one instance to give Ic ($R_1 = R_2$ = ethyl). An additional route to Ic was provided by hydrolysis of the imino nitriles III with fuming hydrochloric acid to the amide acid salts V (see Table II) followed by treatment with polyphosphoric acid at 25-30°.

In summary, a substantial shortening of the synthesis of 3,3-dialkyl-2,6-piperazinediones was achieved through the use of polyphosphoric acid, but the over-all yields remained comparable to those obtained by the longer route.

A limitation of the reaction scheme was encountered while attempting to carry out the indicated sequences with several ketones containing methyl groups on the α-carbon atom. Thus, while ethyl 1-methylbutyl ketone and ethyl isopropyl ketone appeared to yield the presumed nitriles on treatment with glycine ethyl ester and cyanide, these products were not characterized and failed to give identifiable products on hydrolysis with fuming hydrochloric acid. Cyclohexyl ethyl ketone also gave a presumed imino nitrile. However, from treatment with polyphosphoric acid at 80-90°, the only definite product isolated was a small quantity of a colorless solid, which, from analytical, infrared and chemical data appeared to be α-cyclohexylcrotonamide. This substance presumably arose from the elimination of the glycine ester moiety from the initially formed amide ester (IV, R_1 = cyclohexyl, R_2 = ethyl).

A comparison of the hypnotic ratings shown in Table I reveals that the highest activity is associ-

(1) B. Pellmont, A. Studer and R. Jürgens, *Schweiz. med. Wochschr.*, **85**, 350 (1955).

(2) A. Burger, "Medicinal Chemistry," Interscience Publishers, Inc., New York, N. Y., 1951, Vol. I, p. 144.

(3) C. A. Miller and L. M. Long, THIS JOURNAL, **75**, 373 (1953).

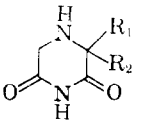
(4) S. R. Safir and J. J. Hlavka, U. S. Patent 2,762,805 (1956); see also U. S. Patent 2,763,652 (1956) and U. S. Patent 2,762,804 (1956).

(5) R. E. Steiger, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. III, p. 66.

(6) Attempts to distil resulted in elimination of hydrogen cyanide.

TABLE I

3,3-DIALKYL-2,6-PIPERAZINEDIONES



R_1	R_2	M.p., °C.[a]	Recrystd.[b] from	Method[c] of synthesis	Yield,[d] %	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen % Calcd.	Nitrogen % Found	Hypnotic[e] activity
Methyl	Methyl	142–144	E	II-C	13	$C_6H_{10}N_2O_2$	50.69	51.03	7.09	7.17	19.71	19.63	0
Methyl	Pentyl	68–71	L	II-C	20	$C_{10}H_{18}N_2O_2$	60.58	60.53	9.15	8.97	14.13	13.97	+1
Methyl	Hexyl	74–75	L	II-C	33	$C_{11}H_{20}N_2O_2$	62.23	62.52	9.50	9.51	13.20	13.54	+1
Methyl	Heptyl	87–88	L	II-C	32	$C_{12}H_{22}N_2O_2$	63.68	63.80	9.80	9.86	12.38	12.13	0
Ethyl	Ethyl	119–120	E–L	II-A II-B I	33 12 23	$C_8H_{14}N_2O_2$	56.45	56.47	8.29	8.34	16.46	16.28	0
Ethyl	Propyl	81–82[f]	B–P	I II-C	22 18	$C_9H_{16}N_2O_2$	58.67	59.08	8.75	8.62	15.21	14.88	+1
Ethyl	Butyl	66–67	B–P	I	17	$C_{10}H_{18}N_2O_2$	60.58	60.81	9.15	9.22	14.13	14.17	+1
Ethyl	Pentyl[g]	38–40	P	I	19	$C_{11}H_{20}N_2O_2$	62.23	62.24	9.50	9.30	13.20	13.17	+2
Ethyl	Isopentyl[h]	53–55	P	I	22	$C_{11}H_{20}N_2O_2$	62.23	62.57	9.50	9.63	13.20	13.13	+2
Ethyl	Hexyl	55–56	P	I	13	$C_{12}H_{22}N_2O_2$	63.68	63.82	9.80	9.86	12.38	12.61	+2
Ethyl	Heptyl	.....[i]	..	II-C	8	$C_{13}H_{24}N_2O_2 \cdot HCl$	...	...	..	..	...	...	+1
Propyl	Propyl	73–74	L	II-C	32	$C_{10}H_{18}N_2O_2$	60.58	60.30	9.15	9.20	14.13	14.30	0
Propyl	Pentyl	.....[j]	..	II-C	9	$C_{12}H_{22}N_2O_2 \cdot HCl$	...	...	..	..	...	...	+1
Butyl	Butyl	.....[k]	..	II-C	11	$C_{12}H_{22}N_2O_2 \cdot HCl$	...	...	..	..	...	...	0
Pentamethylene		183–185	E	II-C	66	$C_9H_{14}N_2O_2$	59.32	59.53	7.74	7.99	15.37	15.08	0

[a] Uncor. [b] E = ethanol; L = ligroin; B = benzene; P = petroleum ether (b.p. 30–60°). [c] See titles in Experimental. [d] Based on the N-(1-cyanoalkyl)-glycine ethyl esters (III). [e] The hypnotic activity is measured by the loss of righting reflex (LRR) of at least five minutes duration in a group of six mice following oral administration of the test substance at a dose of 600 mg./kg. A +2 rating corresponds to a LRR for 5–6 of the test group; a +1 rating corresponds to a LRR for 1–4 of the test group; a 0 rating corresponds to no LRR by any of the test group. [f] Hydrochloride, m.p. 202–205° dec. [g] The hydrochloride, recrystallized from methanol–ether, melted at 192–198° dec. [h] The hydrochloride, recrystallized from methanol–ether, melted at 195–210° dec. [i] Obtained as an oil. The hydrochloride, recrystallized from methanol, melted at 193–199° dec. *Anal.* Calcd. for $C_{13}H_{24}N_2O_2 \cdot HCl$: C, 56.40; H, 9.10; N, 10.12. Found: C, 56.63; H, 9.36; N, 10.04. [j] Obtained as an oil. The hydrochloride, recrystallized from methanol–ether, melted at 187–198°, dec. *Anal.* Calcd. for $C_{12}H_{22}H_2O_2 \cdot HCl$: C, 54.83; H, 8.83; N, 10.64. Found: C, 54.56; H, 9.13; N, 10.58. [k] Obtained as an oil. The hydrochloride, recrystallized from ethanol, melted at 213–218° dec. *Anal.* Calcd. for $C_{12}H_{22}N_2O_2 \cdot HCl$: C, 54.83; H, 8.83; N, 10.64. Found: C, 54.92; H, 9.13; N, 10.17.

ated with those compounds whose alkyl groups have the features: (1) a total of 7 or 8 carbon atoms in the two alkyl groups, (2) dissimilar alkyl substituents, and (3) one of the alkyl groups an ethyl group.

Experimental[7]

I. 3,3-Dialkyl-2,6-piperazinediones (Ic) *via* III → V → VI. N-(1-Cyanoalkyl)-glycine Ethyl Esters (III).—To 0.5 mole of potassium cyanide dissolved in 50 ml. of water was added a solution of 0.5 mole of glycine ethyl ester hydrochloride in 70 ml. of water. The mixture was cooled under running water and stirred mechanically while a solution of 0.5 mole of the required ketone in 80 ml. of methanol was added. Vigorous stirring at room temperature was continued for 4 hours and the heterogeneous mixture was then allowed to stand overnight. The organic phase was separated and the aqueous phase extracted with 100 ml. of ether. The ether extract was added to the organic phase and the solution was dried with sodium sulfate. Evaporation of the solvent at reduced pressure gave the imino nitriles generally as colorless oils in 70–90% yield. Attempts to distil these compounds caused the evolution of large amounts of hydrogen cyanide, even at 60°. They were, therefore, used without further purification in the synthesis of the piperazinediones.

The liquid hydrogen cyanide procedure was used in two instances (III, R_1 = ethyl, R_2 = pentyl; R_1 = ethyl, R_2 = isopentyl). To a well-stirred and heated suspension of 0.78 mole of glycine ethyl ester hydrochloride in 120 ml. of absolute alcohol was added a solution composed of 0.78 mole of sodium methoxide and 100 ml. of absolute alcohol. After a few minutes, the salt was filtered and the filtrate cooled. The solution was then added in portions to a well-stirred, cooled solution composed of 0.78 mole of the required ketone and 200 ml. (5 moles) of liquid hydrogen cyanide. The resulting solution was stirred at 0–5° for 3 hours, and then allowed to remain at room temperature for 2 days. The alcohol and excess hydrogen cyanide were then carefully evaporated at reduced pressure, leaving a brown liquid residue. This material was dissolved in 200 ml. of ether and the ethereal solution was washed successively with 10% sodium bicarbonate solution and with water and then dried. Evaporation of the ether at reduced pressure left a dark colored liquid in 50–70% yield. In the case of III (R_1 = ethyl, R_2 = pentyl) a small sample was cautiously distilled by slow evaporation at 60–65° (0.03 mm.) to give a pale yellow oil.

Anal. Calcd. for $C_{13}H_{24}N_2O_2$: C, 64.96; H, 10.07; N, 11.66. Found: C, 64.41; H, 10.37; N, 11.22.

N-(1-Carbamoylalkyl)-glycine Hydrochlorides (V).—A 0.12-mole sample of N-(1-cyanoalkyl)-glycine ethyl ester was dissolved in 250 ml. of cold fuming hydrochloric acid prepared by bubbling hydrogen chloride gas through concentrated hydrochloric acid at 5° for 30 minutes. The resulting solution was allowed to remain at room temperature for 24 hours. Then it was evaporated at reduced pressure and at temperatures not exceeding 45°. The residue was usually a clear colorless sirup which on further drying in a vacuum desiccator solidified to a crystalline mass. Table II summarizes the pertinent data.

N-(1-Carbamoylalkyl)-glycine Methyl Ester Hydrochlorides (VI).—A 0.04-mole sample of N-(1-carbamoylalkyl)-glycine hydrochloride was dissolved in 650 ml. of anhydrous methanol containing 20 g. of anhydrous hydrogen chloride (3% solution). The solution was allowed to remain at room temperature for 24 hours and then evaporated at reduced pressure to a crystalline residue. The analytically pure products, obtained in 70–75% yields, are listed in Table II.

3,3-Dialkyl-2,6-piperazinediones (Ic).—A 0.035-mole sample of N-(1-carbamoylalkyl)-glycine methyl ester hy-

(7) Infrared spectra were taken as mineral oil mulls with a Perkin-Elmer Infracord.

TABLE II

N-(1-CARBAMOYLALKYL)-GLYCINE HYDROCHLORIDES[a] $R_1R_2C(NHCH_2COOH)(CONH_2)\cdot HCl$

R_1	R_2	M.p., °C.[b] (dec.)	Recrystd.[c] from	Yield, %	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Methyl ester hydrochloride m.p., °C. (dec.)
Ethyl	Ethyl	175–177	M–E	44	$C_9H_{16}N_2O_3\cdot HCl$	42.76	42.56	7.63	7.64	12.47	12.24	177–178.5[d]
Ethyl	Propyl	158–159	M–ET	50	$C_{9}H_{18}N_2O_3\cdot HCl$	45.28	44.22[e]	8.02	8.58	11.74	10.73	168–169[f]
Ethyl	Butyl	124–128	A–M	36	$C_{10}H_{20}N_2O_3\cdot HCl$	47.52	46.91[g]	8.37	8.70	11.08	10.77	165–167[h]
Ethyl	Pentyl	101–103	E	47	$C_{11}H_{22}N_2O_3\cdot HCl$	49.51	49.58	8.70	8.81	10.50	10.36	164–165[i]
Ethyl	Isopentyl	95–100	E	32	$C_{11}H_{22}N_2O_3\cdot HCl$	49.51	49.27	8.70	8.52	10.50	10.24	165[j]
Ethyl	Hexyl	88–93	M–Et	21	$C_{12}H_{24}N_2O_3\cdot HCl$	51.32	50.05[k]	8.97	9.38	9.98	10.14	122–125[l]

[a] Prepared by hydrolysis of imino nitriles (III) with fuming hydrochloric acid. [b] Uncor. [c] M = methanol; ET = ether; A = acetone; E = ethanol. [d] Recrystallized from methanol–ether. [e] Contained water of crystallization. [f] Recrystallized from methanol–acetone. *Anal.* Calcd. for $C_{10}H_{20}N_2O_3\cdot HCl$: C, 47.52; H, 8.37; N, 11.08. Found: C, 47.40; H, 8.60; N, 10.94. [g] Contained water of crystallization. [h] Recrystallized from methanol–ether. *Anal.* Calcd. for $C_{11}H_{22}N_2O_3\cdot HCl$: C, 49.51; H, 8.62; N, 10.50. Found: C, 49.29; H, 8.86; N, 10.50. [i] Recrystallized from acetone–methanol. [j] Recrystallized from methanol–ether. [k] Contained water of crystallization. [l] Recrystallized from acetone. *Anal.* Calcd. for $C_{13}H_{26}N_2O_3\cdot HCl$: C, 52.95; H, 9.23; N, 9.50. Found: C, 52.69; H, 9.31; N, 9.62.

TABLE III

N-(1-CARBAMOYLALKYL)-GLYCINE ETHYL ESTER HYDROCHLORIDES[a] $R_1R_2C(NHCH_2COOC_2H_5)(CONH_2)\cdot HCl$

R_1	R_2	M.p., °C.[b] (dec.)	Recrystd.[c] from	Yield, %	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	Methyl	188–190	E	15	$C_8H_{16}N_2O_3\cdot HCl$	42.76	42.69	7.63	7.65	12.47	12.84
Ethyl	Propyl	162–163	M–A	37	$C_{11}H_{22}N_2O_3\cdot HCl$	49.51	49.65	8.62	8.91	10.50	10.48
Butyl	Butyl	182–184	E	10	$C_{14}H_{28}N_2O_3\cdot HCl$	54.50	54.17	9.35	9.16	9.08	9.18

[a] Prepared by the treatment of the corresponding N-(1-cyanoalkyl)-glycine ethyl ester (III) with PPA at 25–30°. [b] Uncor. [c] E = ethanol; M = methanol; A = acetone.

drochloride was dissolved in 350 ml. of absolute methanol. To this solution was added a solution of 0.07 mole of sodium methoxide in 35 ml. of absolute methanol. The resulting solution was allowed to remain at 22° for 1 hour. At the end of this time, the solvent was evaporated at reduced pressure and 31 ml. of 1 *N* hydrochloric acid was added. This was quickly followed by extraction with small portions of chloroform. Evaporation of the solvent at reduced pressure gave the piperazinedione base usually as a colorless solid. The yields of purified products ranged from 66–95%. The pertinent data including over-all yields are summarized in Table I. The hydrochlorides were prepared by dissolving the bases in 3% methanolic hydrogen chloride and adding ether to crystallization.

II. 3,3-Dialkyl-2,6-piperazinediones (Ic) by Means of Polyphosphoric Acid (PPA). A. From N-(1-Carbamoylalkyl)-glycine Methyl Ester Hydrochlorides (VI).—A slurry of 0.015 mole of N-(1-carbamoylalkyl)-glycine methyl ester hydrochloride in 35 g. of PPA was stirred on the steam-bath for 30 minutes. When the mixture became clear and homogeneous it was cooled in an ice-bath, and 100 g. of ice was added. To the well-stirred solution was slowly added 6 *N* sodium hydroxide until the *p*H was about 6. The solution was extracted twice with chloroform, the extract was dried with sodium sulfate and evaporated at reduced pressure to give the product.

B. From N-(1-Carbamoylalkyl)-glycine Hydrochlorides (V).—A slurry of 0.015 mole of N-(1-carbamoylalkyl)-glycine hydrochloride in 35 g. of PPA was stirred at 25° for 30 minutes, stored for 18 hours and worked up in the manner described in part IIA.

C. From N-(1-Cyanoalkyl)-glycine Ethyl Esters (III).—A mixture of 0.05 mole of N-(1-cyanoalkyl)-glycine ethyl ester and 160 g. of PPA was stirred while heating on a steam-bath for 45 minutes. The heat was then withdrawn and stirring was continued for another 1.5 hours. The mixture was then worked up as described in part IIA.

N-(1-Carbamoylalkyl)-glycine Ethyl Ester Hydrochlorides (IV).—A mixture of 0.03 mole of N-(1-cyanoalkyl)-glycine ethyl ester and 75 g. of PPA was stirred for 2 hours and then allowed to remain at room temperature for 3 days. At the end of this time, ice was added and the mixture was slowly neutralized with 6 *N* sodium hydroxide solution while stirring efficiently. The solution was then extracted several times with small portions of ether, the extract was dried and evaporated *in vacuo* to an oil. The oil was redissolved in 50 ml. of ether and anhydrous hydrogen chloride was passed through the solution. The white, crystalline precipitate was filtered and dried. Table III summarizes the data.

α-Cyclohexylcrotonamide.—A mixture of 12.6 g. (0.05 mole) of N-(1-cyano-1-cyclohexylpropyl)-glycine ethyl ester and 175 g. of PPA was heated with stirring at 80–90° for 45 minutes. Work-up in the manner described for the N-(1-carbamoylalkyl)-glycine ethyl ester hydrochlorides gave 200 mg. of a crystalline product which after recrystallization from 10 ml. of a mixture of equal volumes of ligroin and alcohol melted at 168–169°. This compound slowly decolorized a permanganate solution, but appeared inert to bromine in carbon tetrachloride. The following pertinent infrared bands were noted: 2.90, 3.10, 6.02, 6.10 (weak) and 6.2 μ. Analysis showed agreement with the values calculated for α-cyclohexylcrotonamide.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.54; H, 10.41; N, 8.53.

A 45-mg. sample of this compound was dissolved in 10 ml. of ethanol and hydrogenated in the presence of PtO_2. The compound rapidly absorbed the quantity of hydrogen calculated for 1 double bond. The catalyst was filtered and the filtrate on concentration to a small volume yielded a crystalline product which melted at 176–177°. A mixed m.p. with unhydrogenated material was depressed. The product was characterized by the disappearance of the 6.2 μ band in the infrared spectrum. The saturated product, therefore, appeared to be **α-cyclohexylbutyramide.**

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 71.12; H, 11.40; N, 8.03.

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