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ANTICONVULSANTS. BENZYL 4-CARBAMYL-1-PIPERAZINE-CARBOXYLATE AND RELATED COMPOUNDS

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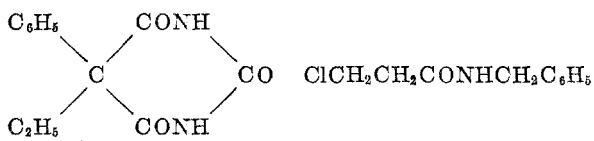
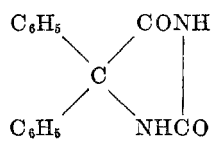
Phenobarbital (I) has long been known to possess anticonvulsant properties and finds wide use in the treatment of epilepsy. A number of N-benzylamides (1) have been found to be effective against electrically-induced convulsions (2) and audiogenic-metrazol shock in the rat; Hibicon[1] (N-benzyl-β-chloropropionamide, II) has been found useful in grand mal epilepsy (3, 4). Putnam and Merritt (5, 6) have shown that Dilantin[2] (5,5-diphenylhydantoin, III) has the ability to suppress electroshock and is effective against grand mal epilepsy (7). Tridione[3] (3,5,5-trimethyloxazolidine-2,4-dione, IV), a compound which is particularly effective against the convulsions induced by metrazol (8), has been widely used in the treatment of petit mal epilepsy (,9 10), but there are certain undesirable side-effects. Recently, it has been reported (11) that Milontin[4] (N-methyl-α-phenylsuccinimide, V), effective against both metrazol and electrically-induced convulsions, controls petit mal attacks.



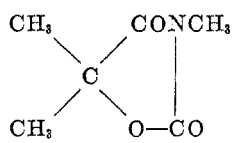
I

$ClCH_2CH_2CONHCH_2C_6H_5$

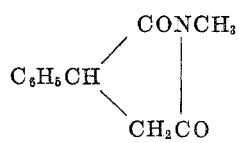
II



III



IV



V

In the present work routine screening of compounds by means of the audiogenic-metrazol test in rats has revealed that benzyl esters of certain 4-carbamyl-1-piperazinecarboxylates (VI) are active. Hibital[5] (benzyl 4-carbamyl-1-piperazinecarboxylate, XI) protects animals against convulsive seizures induced by audiogenic-metrazol, electroshock, and intravenous metrazol.

When one hydrogen of the carbamyl group of XI is replaced by methyl, ethyl, or *n*-propyl, activity is retained but diminished; however when the unbranched alkyl group is larger than *n*-propyl, activity is lost. The isopropyl, *sec*-butyl, and

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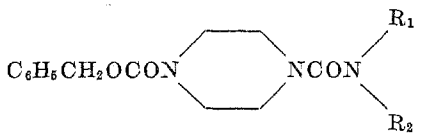
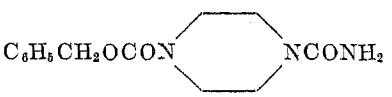
[2] Trademark registered by Parke, Davis and Co.
[3] Trademark registered by Abbott Laboratories.
[4] Trademark registered by Parke, Davis and Co.
[5] Trademark registered by American Cyanamid Co.

cyclohexyl analogs still retain some activity. Substitution of one hydrogen by benzyl or an aryl group causes complete loss of activity. Substitution of both hydrogen atoms of the carbamyl group of XI by lower alkyl or dicarbethoxymethyl gives compounds with no anticonvulsant activity. Replacement of the oxygen of the carbamyl group by imino produces an inactive compound. Benzyl 4,4′-carbonylbis-(1-piperazinecarboxylate) has no anticonvulsant activity.



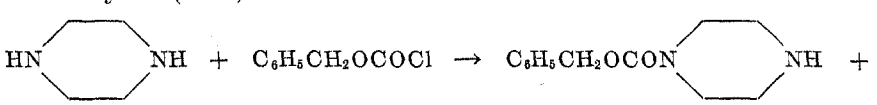
Where R_1 = hydrogen or alkyl
R_2 = hydrogen, alkyl or cyclohexyl

VI

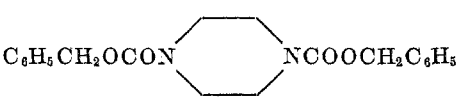


XI

The intermediate required for the synthesis of the compounds listed in Table I, benzyl 1-piperazinecarboxylate (VII), was prepared by using the conditions described by Moore, Boyle, and Thorn (12) for the monocarbethoxylation of piperazine. Thus, carbobenzyloxy chloride was allowed to react with piperazine in aqueous solution at *p*H 3–4.5 to produce VII in 87 % yield based on the carbobenzyloxy chloride. In addition, a small quantity of benzyl 1,4-piperazinedicarboxylate (VIII) was formed.



VII



VIII

Reaction of VII with nitrourea produced the 4-carbamyl derivative XI, which was also prepared by reaction of benzyl 1-piperazinecarboxylate hydrochloride (IX) with potassium cyanate.

The 4-arylcarbamyl derivatives were synthesized by reaction of VII with the appropriate aryl isocyanate (Procedure A). The 4-benzylcarbamyl group was introduced by reaction of VII with phenylacetohydroxamic acid benzoate by the method of Kushner, *et al.* (13) for the synthesis of 1-benzylcarbamyl-4-methylpiperazine hydrochloride. The 4-dimethylcarbamyl derivative was obtained by reaction of VII with dimethylcarbamyl chloride. The 4-guanyl derivative was synthesized by reaction of VII with S-methyl isothiourea sulfate.

When VII was reacted with phosgene in toluene, 4-carbobenzyloxy-1-piperazinecarbonyl chloride (X) was formed. Various benzyl 4-(substituted carbamyl)-1-piperazinecarboxylates were prepared by the reaction of X with the appropri-

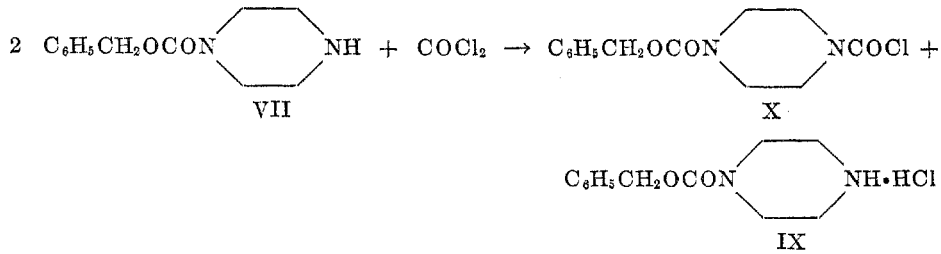
TABLE I

BENZYL 4-SUBSTITUTED-1-PIPERAZINECARBOXYLATES $C_6H_5CH_2OCON$ NR

	R	PROCEDURE	YIELD, %	M.P., °C.	B.P., °C./MM.	FORMULA	ANALYSES						ANTICONVULSANT RATING[j] AUDIOGENIC METRAZOLE (mg./kg. in rat)
							Calc'd			Found			
							C	H	N	C	H	N	
XI	$CONH_2$		72	140.5–141.5[b]		$C_{13}H_{17}N_3O_3$	59.3	6.5	16.0	59.4	6.7	15.8	4+ (500 oral)
			89	140.5–141.5[b]			59.3	6.5	16.0	59.4	6.5	15.7	
XII	$CONHCH_3$	B	90	120 –120.5[c]		$C_{14}H_{19}N_3O_3$	60.6	6.9	15.2	60.4	7.2	15.2	2+ (70 ip)[k]
XIII	$CONHC_2H_5$	B	90	126 –126.5[d]		$C_{15}H_{21}N_3O_3$	61.9	7.3	14.4	62.1	7.4	14.4	3+ (100 ip)
XIV	$CONHC_3H_7$-*n*	C	91	112.5–113.5[c]		$C_{16}H_{23}N_3O_3$	62.6	7.6	13.8	62.8	7.8	14.2	2+ (100 ip)
XV	$CONHCH(CH_3)_2$	C	92	118 –119[d]		$C_{16}H_{23}N_3O_3$	62.6	7.6	13.8	62.9	7.9	13.7	2+ (75 ip)
XVI	$CONHC_4H_9$-*n*	C	97	94 –95.5[e]		$C_{17}H_{25}N_3O_3$	64.0	7.9	13.2	63.9	8.2	13.2	0 (80 ip)
XVII	$CONHCH(CH_3)C_2H_5$	C	83	58 –59[f]		$C_{17}H_{25}N_3O_3$	64.0	7.9	13.2	64.0	7.9	13.3	2+ (75 ip)
XVIII	$CONHC_5H_{11}$-*n*	C	69	93 –94[g]		$C_{18}H_{22}N_3O_3$	64.8	8.2	12.6	65.0	8.3	12.3	0 (1000 oral)
XIX	$CONHC_6H_{11}$[a]	C	98	118 –119[c]		$C_{19}H_{27}N_3O_3$	66.2	7.9	12.2	66.0	8.0	12.1	2+ (750 oral)
XX	$CONHCH_2C_6H_5$		76	134 –135[b]		$C_{20}H_{23}N_3O_3$	68.0	6.6	11.9	68.2	6.8	12.0	0 (750 oral)
XXI	$CONHC_6H_5$	A	95	139.5–140[b]		$C_{19}H_{21}N_3O_3$	67.4	6.2	12.4	67.4	6.5	12.8	0 (500 oral)
		D	80	139 –140[h]									
XXII	$CONHC_6H_4$-*o*-Cl	A	95	118.5–119.5		$C_{19}H_{20}ClN_3O_3$	61.1	5.4	11.2	61.3	5.6	11.4	0 (750 oral)
							9.5*			9.5*			
XXIII	$CONHC_6H_4$-*p*-OC_2H_5	A	76	147 –148[b]		$C_{21}H_{25}N_3O_4$	65.9	6.6	11.0	65.6	6.7	11.3	0 (750 oral)
XXIV	$CONHC_6H_4$-*m*-CH_3	A	99	136–136.5[b]		$C_{20}H_{23}N_3O_3$	68.1	6.6	11.9	68.0	6.9	11.8	0 (750 oral)
XXV	$CON(CH_3)_2$		55		206–207/1.1	$C_{15}H_{21}N_3O_3$	61.9	7.3	14.4	61.9	7.3	13.9	0 (50 ip)
XXVI	$CON(C_2H_5)_2$	C	95		188–192/0.4	$C_{17}H_{26}N_3O_3$	63.9	7.9	13.2	63.8	7.9	13.0	1+ (175 oral)
XXVII	$CON(C_3H_7$-*n*$)_2$	C	94		183–188/ 0.07–0.2	$C_{19}H_{29}N_3O_3$	65.7	8.4	12.1	65.8	8.6	12.0	0 (200 oral)
XXVIII	$CON(C_4H_9$-iso$)_2$	C	95	62.5–64.5	212–216/1	$C_{21}H_{33}N_3O_3$	67.2	8.9	11.2	67.0	9.0	11.0	0 (175 oral)
XXIX	$CON(C_5H_{11}$-*n*$)_2$	C	97		[i]	$C_{23}H_{37}N_3O_3$	68.5	9.3	10.4	68.2	9.3	10.4	0 (1000 oral)
XXX	$CONHCH(COOC_2H_5)_2$	C	77	95.5–97[b]		$C_{20}H_{27}N_3O_7$	57.0	6.5	10.0	56.8	6.3	9.9	0 (500 ip)
XXXI	CON NCOOCH$_2$C$_6$H$_5$	C	100	137.5–139[c]		$C_{25}H_{30}N_4O_5$	64.5	6.5	12.0	64.8	6.5	11.8	0 (500 oral)
XXXII	$C(=NH)NH_2]_2 \cdot H_2SO_4$		35	227 (dec.)[d]		$C_{26}H_{38}N_8O_8S$	50.2	6.2	18.0	50.1	6.3	18.4	0 (50 ip)
							5.2†			5.3†			

* Chlorine analysis. † Sulfur analysis. [a] C_6H_{11} = cyclohexyl. [b] From absolute ethanol. [c] From ethyl acetate. [d] From ethanol-water. [e] From absolute ethanol-ether. [f] From ether. [g] From ethyl acetate-hexane. [h] From benzene. [i] Undistillable syrup. [j] Highest rating possible is 4+; compounds were tested at the asymptomatic dose level. [k] ip is intraperitoneally.

ate amine using, as the acid binding agent, a second equivalent of amine in aqueous medium (Procedure B), a second equivalent of amine in ethyl acetate (Procedure C), or one equivalent of aqueous sodium hydroxide (Procedure D).



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EXPERIMENTAL

All melting points and boiling points are uncorrected.

Benzyl 1-piperazinecarboxylate (VII) *and benzyl 1,4-piperazinedicarboxylate* (VIII). A mixture of 194 g. (1 mole) of piperazine hexahydrate, 250 ml. of water, 500 ml. of methanol, and 30 ml. of 0.04% Bromphenol Blue solution was acidified to *p*H 3 (yellow color) with 163 ml. of conc'd hydrochloric acid. The resulting solution was cooled to 25° and while being vigorously stirred 0.59 mole (190 g. of a 53% toluene solution) of carbobenzyloxy chloride (14) was added in 20-ml. portions, and 344 ml. of 4 *N* sodium hydroxide was added as required to maintain the solution at *p*H 3.0–4.5 (addition time, 1¼ hours).

The solvents were removed by distillation *in vacuo* and the residue was taken up in 500 ml. of water and acidified to Congo red with 1.5 ml. of conc'd hydrochloric acid. The oily precipitate which appeared was dissolved in benzene, removal of which by distillation yielded an oil. Addition of absolute ethanol produced 19 g. of crystals of benzyl 1,4-piperazinedicarboxylate, m.p. 109–112°. When recrystallized from absolute ethanol colorless crystals of VIII were obtained, m.p. 112–113°.

Anal. Calc'd for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9.
Found: C, 67.9; H, 6.6; N, 8.2.

The aqueous solution from the benzene extraction was chilled and brought to *p*H 13 by adding 115 ml. of 12.5 *N* sodium hydroxide. The oil which separated was extracted into benzene, and the benzene extract was dried over potassium carbonate and then distilled to remove the benzene. The residual oil was distilled *in vacuo* to yield 113 g. (87%) of benzyl 1-piperazinecarboxylate (VII), which distilled as a colorless liquid at 158–161°/1.4 mm.

Anal. Calc'd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3; N, 12.7.
Found: C, 65.1; H, 7.3; N, 12.5.

Benzyl 1-piperazinecarboxylate hydrochloride (IX). Reaction of VII with excess ethanolic hydrogen chloride yielded colorless crystals of the hydrochloride, IX, which, purified by crystallization from absolute ethanol, melted at 155–156.5°.

Anal. Calc'd for $C_{12}H_{17}ClN_2O$: C, 56.1; H, 6.7; N, 10.9; Cl, 13.8.
Found: C, 55.9; H, 6.8; N, 10.9; Cl, 13.7.

4-Carbobenzyloxy-1-piperazinecarbonyl chloride (X). To a stirred solution of 29.8 g. (0.302 mole) of phosgene in 150 ml. of anhydrous toluene, surrounded by an ice-bath, there was added during one hour a solution of 113 g. (0.512 mole) of VII in 100 ml. of anhydrous benzene. After 1½ hours at 0°, 64.4 g. (98%) of colorless crystals of benzyl 1-piperazinecarboxylate hydrochloride (IX) were obtained by filtration.

The filtrate was distilled *in vacuo*, and after removal of the solvents the 4-carbobenzyloxy-1-piperazinecarbonyl chloride (X) distilled as a colorless liquid, b.p. 203–208°/1.3–1.5 mm., with some decomposition.

Anal. Calc'd for $C_{13}H_{15}ClN_2O_3$: C, 55.2; H, 5.4; N, 9.9; Cl, 12.6.

Found: C, 55.4; H, 5.8; N, 9.2; Cl, 14.7.

For Procedures B, C, and D, the filtrate from the hydrochloride (IX) was concentrated *in vacuo* to remove the excess phosgene and part of the toluene. The residual concentrated solution of X was used for reaction with the amines.

Benzyl 4-carbamyl-1-piperazinecarboxylate (XI). (*a.*) *By reaction of benzyl 1-piperazinecarboxylate* (VII) *with nitrourea.* A mixture of 70.2 g. (0.319 mole) of VII and 34.7 g. (0.33 mole) of nitrourea (15) in 300 ml. of water was heated on a steam-bath for 20 minutes. After cooling, the colorless crystals which formed were removed and pressed dry on the funnel. The crude product was crystallized once from absolute ethanol, yielding 60.5 g. (72%) of colorless crystals of XI, m.p. 140.5–141.5°.

(*b.*) *By reaction of benzyl 1-piperazinecarboxylate hydrochloride* (IX) *with potassium cyanate.* A solution of 113 g. (1.4 moles) of potassium cyanate in 200 ml. of water was added to a chilled solution of 305 g. (1.19 moles) of benzyl 1-piperazinecarboxylate hydrochloride (IX) in 400 ml. of water. Within several minutes a heavy crystalline precipitate formed. The mixture was diluted with 600 ml. of water and let stand overnight.

The colorless crystals of XI were removed, washed with iced water, and dried at 100°. The product (280 g., 89%), m.p. 140–141°, was crystallized from absolute ethanol to yield colorless shiny plates, m.p. 140.5–141.5°.

PROCEDURE A

Benzyl 4-o-chlorophenylcarbamyl-1-piperazinecarboxylate (XXII). To a chilled solution of 22.0 g. (0.1 mole) of VII in 125 ml. of anhydrous benzene, 15.4 g. (0.1 mole) of *o*-chlorophenyl isocyanate was added. After standing overnight at room temperature the reaction was filtered to yield 35.4 g. (95%) of colorless crystals of XXII, m.p. 118–119°. Recrystallization from benzene and from absolute ethanol gave m.p. 118.5–119.5°.

PROCEDURE B

(*a.*) *Benzyl 4-methylcarbamyl-1-piperazinecarboxylate* (XII). A toluene solution of 0.12 mole of X was added, dropwise, to a stirred mixture of 50 ml. of 25% aqueous methylamine and ice. After the addition was complete the mixture was stirred at 0° for one hour and then concentrated *in vacuo* to remove the benzene and excess methylamine. The residue was cooled, acidified, and filtered to yield 29.8 g. (90%) of colorless crystals of XII, m.p. 115–117°. Crystallization from ethyl acetate gave colorless crystals, m.p. 120–120.5°.

(*b.*) *Benzyl 4-ethylcarbamyl-1-piperazinecarboxylate* (XIII). A solution of 31.1 g. (0.11 mole) of X in 76 ml. of toluene was added to a stirred solution of 25 ml. of 33% aqueous methylamine at 0°, and then stirred at room temperature for two hours. Filtration of the reaction mixture yielded 22.3 g. (70%) of colorless crystals of XIII, m.p. 120–123°. An additional 6.6 g., giving a total yield of 90%, was obtained from the filtrate by concentration *in vacuo*. Recrystallization from aqueous ethanol and then from ethyl acetate produced colorless crystals, m.p. 126–126.5°.

PROCEDURE C

(*a.*) *Benzyl 4-n-propylcarbamyl-1-piperazinecarboxylate* (XIV). To a cold solution of 73.5 g. (0.26 mole) of X in 155 ml. of toluene and 100 ml. of ethyl acetate, 32.2 g. (0.542 mole) of *n*-propylamine was added dropwise with stirring. After standing at 5° the solid was removed, triturated with dilute hydrochloric acid, and washed with water, to yield 43.3 g. of colorless crystals of XIV, m.p. 111–113°. Concentration of the mother liquor yielded an additional 27.8 g., bringing the crude yield to 72.1 g. (91%). When recrystallized from ethyl acetate, colorless crystals were obtained, m.p. 112.5–113.5°.

(*b.*) *Benzyl 4-n-butylcarbamyl-1-piperazinecarboxylate* (XVI). A solution of 31.1 g. (0.11 mole) of X in 67 ml. of toluene and 250 ml. of ethyl acetate was chilled in an ice-bath and 18.3 g. (0.25 mole) of *n*-butylamine was added in small portions with shaking. After standing at room temperature overnight the reaction was filtered to remove 11.2 g. (93%) of *n*-butylamine hydrochloride. The filtrate was concentrated to dryness *in vacuo* and the residue was crystallized from ethyl acetate to yield 34.1 g. (97%) of XVI, m.p. 83–91°. When recrystallized from ethyl acetate-ether, colorless crystals were obtained, m.p. 94–95.5°.

(*c.*) *Ethyl 4-carbobenzyloxy-1-piperazinecarbonylaminomalonate* (XVII). Reaction of 70.6 g. (0.25 mole) of X with 87.6 g. (0.5 mole) of ethyl aminomalonate (16) under conditions used for preparing XVI yielded 41 g. (0.19 mole) of ethyl aminomalonate hydrochloride (17) and 80.5 g. (77%) of XVII, which, purified by crystallization from absolute ethanol, melted at 94–97°. Recrystallization from absolute ethanol gave colorless crystals, m.p. 95.5–97°.

(*d.*) *Benzyl 4-diethylcarbamyl-1-piperazinecarboxylate* (XXVI). A solution of 31.1 g. (0.11 mole) of X in 19.1 g. of toluene was added to 16.5 g. (0.225 mole) of diethylamine in 250 ml. of ethyl acetate at 5°. After standing overnight at room temperature the reaction mixture was filtered to yield 11.8 g. (98%) of diethylamine hydrochloride. The filtrate was concentrated *in vacuo* to remove the solvents and the residual syrup was dissolved in ether and washed with 1 *N* hydrochloric acid, water, and 5% sodium bicarbonate. The ether solution was then dried over Drierite and distilled to remove the ether, leaving 33.4 g. (95%) of crude XXVI as a syrup. The syrup was distilled *in vacuo*, and XXVI was obtained as a colorless liquid, b.p. 188–192°/0.4 mm.

(*e.*) *Benzyl 4,4'-carbonylbis(1-piperazinecarboxylate)* (XXXI). A mixture of 31.1 g. (0.11 mole) of X in 67 ml. of toluene and 58.5 g. (0.27 mole) of VII in 350 ml. of anhydrous ethyl acetate was allowed to stand for five days at room temperature. The residue, obtained by concentrating the reaction mixture to dryness, was triturated with 90–100° ligroin and then with water, yielding 51.2 g. (100%) of nearly colorless XXXI, m.p. 136–138°. When recrystallized from absolute ethanol and from ethyl acetate, colorless crystals were obtained, m.p. 137.5–139°.

PROCEDURE D

(*a.*) *Benzyl 4-phenylcarbamyl-1-piperazinecarboxylate* (XXI). A mixture of 9.3 g. (0.1 mole) of aniline, a solution of 28.3 g. (0.1 mole) of X in 15.5 ml. of toluene, and 25 ml. of 4 *N* sodium hydroxide was shaken in a stoppered flask for 22 hours. The reaction mixture was then acidified, the aqueous layer decanted, and the organic layer diluted with 20–40° petroleum ether. Filtration yielded 27.2 g. (80%) of colorless XXI, m.p. 127–136°. Recrystallization from ethanol and from benzene gave colorless crystals, m.p. 139–140°.

Benzyl 4-benzylcarbamyl-1-piperazinecarboxylate (XX). A mixture of 45.2 g. (0.205 mole) of VII, 20 g. (0.0785 mole) of phenylacetohydroxamic acid benzoate (18), and 100 ml. of water was heated for ten minutes on a steam-bath. The mixture became cloudy and an oil separated. The mixture was diluted with 225 ml. of water, chilled, acidified with concentrated hydrochloric acid, and filtered to remove a colorless precipitate. The precipitate was warmed with aqueous sodium bicarbonate, washed with water, and dried at 100°. The yield of crude XX, m.p. 120–129°, was 21 g. (76%). Recrystallization from absolute ethanol, using Norit, gave colorless crystals, m.p. 134–135.°

Benzyl 4-dimethylcarbamyl-1-piperazinecarboxylate (XXV). A solution of 10.8 g. (0.1 mole) of dimethylcarbamyl chloride (19) in 10 ml. of ethyl acetate was added with shaking and cooling to 44.0 g. (0.2 mole) of VII in 250 ml. of ethyl acetate. After one-half hour at 0°, the reaction mixture was allowed to stand at room temperature overnight.

Filtration of the reaction mixture yielded 21.5 g. (85%) of colorless crystals of benzyl 1-piperazinecarboxylate hydrochloride (IX), m.p. 155–156°. The filtrate was concentrated on a steam-bath, the residual yellow oil was dissolved in chloroform, and the chloroform solution was washed with 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and then with water, and dried over magnesium sulfate.

The chloroform was removed by distillation and the residual pale amber syrup was distilled *in vacuo*. The product (XXV) distilled as a colorless viscous liquid, b.p. 206–207°/1.1 mm., and weighed 16.1 g. (55%).

Benzyl 4-guanyl-1-piperazinecarboxylate sulfate (XXXII). A mixture of 26.4 g. (0.12 mole) of VII, 13.9 g. (0.05 mole) of S-methyl isothiourea sulfate, and 50 ml. of 65% ethanol was refluxed for nine hours, at which time the evolution of methyl mercaptan had ceased. The resulting solution, containing a small amount of crystalline precipitate, was concentrated *in vacuo*, and the residual glassy resin was crystallized by trituration with ether. Recrystallization from aqueous ethanol yielded 10.7 g. (35%) of colorless crystals of XXXIII, m.p. 227° (dec.).

SUMMARY

Benzyl 4-carbamyl-1-piperazinecarboxylate and related compounds have been synthesized from benzyl 1-piperazinecarboxylate and from 4-carbobenzyloxy-1-piperazinecarbonyl chloride. A number of these compounds have been demonstrated to possess anticonvulsant activity.

PEARL RIVER, NEW YORK.

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