Centrally Active 2-(Substituted phenyl)-γ-aminobutyric Acids

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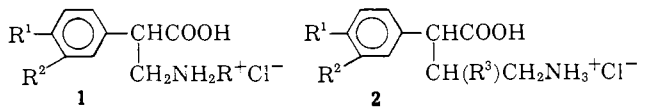
Alkylation of several arylmalonates with chloroalkylcyanides gave cyanoalkylmalonates (**4**) which were hydrogenated to aminoalkylmalonates (**5**). The latter were hydrolyzed to α-aryl-γ-aminobutyric acids (**6**) which in turn were converted to ethyl esters (**7**). Preliminary pharmacological data demonstrate that **5**, **6**, and **7** are weak central stimulants.

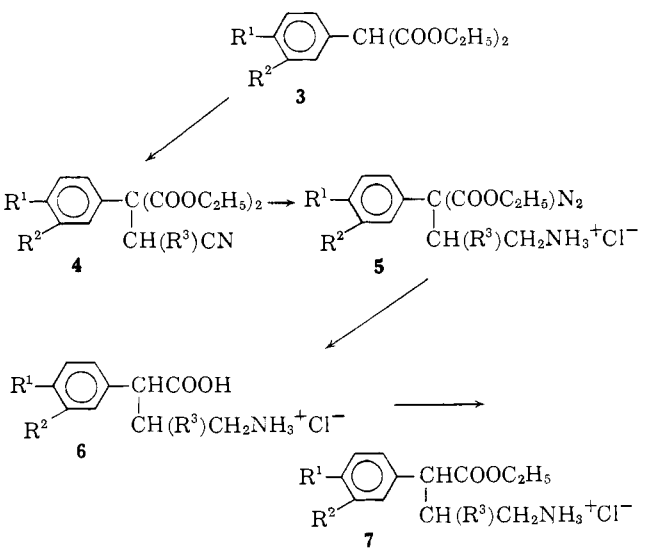
The possibility that γ-aminobutyric acid (GABA) may participate in the control of neurophysiological activity[1] provided a biological rationale for the synthesis of a number of its homologs and analogs for biological evaluation.[2-4] The program on the synthesis of GABA homologs in these laboratories encompassed the synthesis of α-aryl-β-alanines (**1**), α-aryl-γ-aminobutyric acids (**2**), and the related esters. Our findings on the



1 **2**

alanines (**1**) were reported in a previous publication on GABA analogs.[3] The synthesis and pharmacological effects of several of the related derivatives of γ-aminobutyric acid are described in this communication.

Alkylation of the diethyl (substituted phenyl)-malonates (**3**) with either chloroacetonitrile or α-chloroproponitrile gave the diethyl cyanoalkyl-(substituted phenyl)-malonates (**4**). This reaction proceeded in yields of 30–40% and in several instances gave products which could not be obtained analytically pure. Hydrogenation of these compounds over platinum catalyst in acid solution, however, gave the desired aminoalkylmalonates (**5**), thus obviating extensive purification and concomitant loss of material. Hydrolysis and decarboxylation of the aminoalkylmalonates (**5**) gave the GABA analogs (**6**) which on Fisher esterification yielded the esters (**7**) (Table I).



3 **4** **5** **6** **7**

The new aminoalkylmalonates (**5**), γ-aminobutyric acids (**6**), and γ-aminobutyrates (**7**) were screened in the Department of Pharmacology of these Laboratories for central effects and toxicity by conventional methods. The γ-aminobutyric acids (**6**), like the β-alanines previously described,[3] are less toxic and less potent than the corresponding esters (**7**). All but one of the compounds were found to be short acting central stimulants in high doses (Table II). None were regarded of sufficient interest to justify a detailed pharmacological study.

Experimental[5]

p-Chloro- and *p*-methoxyphenylacetonitrile were purchased from the Aldrich Chemical Co. 3,4-Methylenedioxyphenylacetonitrile was prepared by the method which we previously described.[3]

3,4-Xylylacetonitrile.—*o*-Xylene (212 g., 2.0 moles) was mixed with 167 g. of 37% formaldehyde and 1060 ml. of concentrated hydrochloric acid. The mixture was treated with gaseous hydrogen chloride for 7 hr. at 60–70° with constant stirring and then let stand overnight. The oil was extracted with benzene. The benzene extracts were washed with water, dried over anhydrous calcium chloride, and distilled. 3,4-Xylylmethyl chloride distilled at 100–106° (15 mm.); yield, 194 g. (63%).

Anal. Calcd. for $C_9H_{11}Cl$: C, 69.90; H, 7.17. Found: C, 69.83; H, 7.23.

Sodium cyanide (98 g., 2.0 moles) and sodium iodide (8 g.) were added to a solution of 3,4-xylylmethyl chloride (154 g., 1.0 moles) dissolved in dry acetone (550 ml.). The mixture was stirred and refluxed for 20 hr., cooled, and filtered. The filtrate was combined with the acetone washings from the precipitate and evaporated *in vacuo*. The residual oil was dissolved in ether, washed with water, dried over anhydrous calcium chloride, and fractionated at 1.5 mm. The fraction which distilled at 101–103° crystallized and melted at 51.5–53° after recrystallization from a mixture of benzene and petroleum ether; yield, 24.2 g. (16.5%).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 83.38; H, 7.71; N, 9.72.

The nitriles were converted to the corresponding ethyl esters when refluxed in ethanolic sulfuric acid solution. New boiling point data were recorded on the known esters as follows: (1) ethyl *p*-methoxyphenylacetate: b.p. found 102–103° (0.6 mm.); Cain, *et al.*[6] reported b.p. 138–140° (7 mm.); (2) ethyl *p*-chlorophenylacetate: b.p. found 107–108° (1.4 mm.); Curtius[7] re-

(1) A. Bazemore, K. A. C. Elliott, and E. Florey, *Nature*, **178**, 1052 (1956); D. P. Purpura, M. Girado, and H. Grundfest, *Proc. Soc. Exptl. Biol. Med.*, **95**, 791 (1957).

(2) M. E. Farquharson and J. A. R. Maclean, *J. Med. Pharm. Chem.*, **4**, 31 (1961).

(3) F. Leonard, A. Wajngurt, M. Klein, and G. M. Smith, *J. Org. Chem.*, **26**, 4062 (1961).

(4) E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. Da Vanzo, and M. E. Greig, *J. Med. Pharm. Chem.*, **5**, 464 (1962).

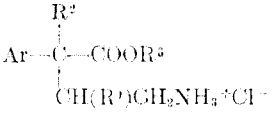
(5) Microanalysis were performed by Mr. J. Deonorine of these Laboratories. All melting points were taken in a Herschberg melting point apparatus and are corrected.

(6) J. C. Cain, J. L. Simonson, and C. Smith, *J. Chem. Soc.*, **103**, 1036 (1913).

(7) T. Curtius, *J. prakt. Chem.*, [2] **89**, 527 (1914).

TABLE I

ARYLAMINOALKYLMALONATES, γ-AMINOBUTYRIC ACIDS, AND γ-AMINOBUTYRATES



No.	Ar	R¹	R²	R³	M.p., °C.[a]	Molecular Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	H	$COOC_2H_5$	C_2H_5	112–114	$C_{15}H_{22}ClNO_4$	57.04	7.02	4.44	57.41	7.30	4.66
2	C_6H_5	H	H	H	196–198	$C_{10}H_{14}ClNO_2$	55.68	6.54	6.50	55.44	6.60	6.67
3	C_6H_5	H	H	C_2H_5	131–132	$C_{12}H_{18}ClNO_2$	59.14	7.44	5.75	58.96	7.34	5.85
4	C_6H_5	CH_3	$COOC_2H_5$	C_2H_5	124–125	$C_{16}H_{24}ClNO_4$	58.27	7.33	4.25	58.60	8.15	4.67
5	C_6H_5	CH_3	H	H	177–178	$C_{11}H_{16}ClNO_2$	57.50	7.02	6.10	57.16	7.91	6.03
6	4-$CH_3OC_6H_4$	H	$COOC_2H_5$	C_2H_5	91–96	$C_{16}H_{24}ClNO_5$	55.56	7.00	4.05	55.71	7.41	4.26
7	4-$CH_3OC_6H_4$	H	H	C_2H_5	93–95	$C_{13}H_{20}ClNO_3$	57.02	7.36	5.12	56.75	7.26	5.30
8	4-ClC_6H_4	H	$COOC_2H_5$	C_2H_5	157–158	$C_{15}H_{21}Cl_2NO_4$	51.43	6.04		51.19	5.84	
9	4-ClC_6H_4	H	H	H	201–202	$C_{10}H_{13}Cl_2NO_2$	48.02	5.24	5.60	48.12	4.99	5.62
10	4-ClC_6H_4	H	H	C_2H_5	161–162	$C_{12}H_{17}Cl_2NO_2$	51.81	6.16	5.04	52.12	6.50	5.08
11	3,4-$(CH_3)_2C_6H_3$	H	$COOC_2H_5$	C_2H_5	105–107	$C_{17}H_{26}ClNO_4$	59.38	7.62	4.07	59.22	7.69	4.30
12	3,4-$(CH_3)_2C_6H_3$	H	H	C_2H_5	103–104	$C_{14}H_{22}ClNO_2$	61.87	8.16	5.15	61.54	7.78	4.91
13	3,4-$(CH_2O_2)C_6H_3$	H	$COOC_2H_5$	C_2H_5	91–93	$C_{16}H_{22}ClNO_6$	53.41	6.16	3.89	53.31	6.31	4.24
14	3,4-$(CH_2O_2)C_6H_3$	H	H	H	213–214	$C_{11}H_{14}ClNO_4$	50.86	5.43	5.39	50.74	5.88	5.11
15	3,4-$(CH_2O_2)C_6H_3$	H	H	C_2H_5	105–106	$C_{13}H_{18}ClNO_4$	54.16	5.96	4.98	54.12	6.22	4.69

[a] Recrystallization solvents: 1,4,11: benzene–petroleum ether; 2,8,15: ethanol–ether; 3,10,14: ethanol; 5: benzene; 6,13: benzene–ether; 7: ethylacetate–hexane; 9: isopropyl alcohol–ether; 12: ethyl acetate–petroleum ether.

TABLE II

PRELIMINARY PHARMACOLOGICAL OBSERVATIONS

No.	Mouse LD_{50}, intraperitoneal mg./kg.	Symptomatology in mice[a]: Dose, mg./kg., intraperitoneal	Symptomatology in mice[a]: Symptoms
1	160	100	Weak stimulant
2	2000	1000	Weak stimulant (tremors)
3	160	150	Stimulant (convulsions)
4	138	100+	Stimulant (tremors)
5	1700	100+	Stimulant (convulsions)
6	260	100+	Stimulant (tremors, 24 hr.)
7	235	200	Weak stimulant (tremors)
8	170	150	Stimulant (convulsions)
9	1200	100-400	Stimulant (convulsions)
10	160	50+	Stimulant (tremors, convulsions)
11	130	50–125	Stimulant (convulsions)
12	135	100	Weak stimulant (tremors)
13	270	100+	Weak stimulant (tremors)
14	1000	.....	.....
15	270	100	Stimulant (tremors, convulsions)

[a] Determined by intraperitoneal administration of aqueous solutions of compounds 1–15 to groups of six mice each. The mice were kept under observation and indications of CNS stimulation such as increased and spontaneous locomotor activity accompanied by piloerection, twitching, and ultimately convulsions were noted.

ported b.p. 253–254° (749 mm.); (3) ethyl 3,4-methylenedioxyphenylacetate: b.p. found 120–121° (0.5 mm.); Tieman[8] reported b.p. 291° (760 mm.).

The preparation of ethyl 3,4-xylylacetate is illustrative of the method used for the conversion of the nitriles to esters.

Ethyl 3,4-Xylylacetate.—3,4-Xylylacetonitrile (20 g., 0.138 mole) was dissolved in a solution of 14.6 ml. of concentrated sulfuric acid in 33.6 ml. of commercial 2B ethanol. The mixture was stirred and refluxed for 6 hr., cooled, and diluted with water. The oily layer was extracted with ether and the extract was washed with water and dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was fractionated, 105–107° (2 mm.); yield 15 g. (56.7%)

(8) F. Tieman, *Ber.*, **24**, 2855 (1891).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.96; H, 8.39. Found: C, 74.77; H, 8.32.

The new diethyl arylmalonates described in Table III were prepared by carbethoxylation of the appropriate arylacetates by the method of Wallingford, *et al.*,[9] as modified by Blicke and Leonard.[10] Diethyl phenylmalonate was purchased from Distillation Products, Inc.

The following examples illustrate the methods employed for the preparation of the cyanoalkymalonates (4, Table III), aminoalkylmalonates (5, Table I), δ-aminobutyric acids (6, Table I), and ethyl δ-aminobutyrates (7, Table I).

Diethyl Cyanomethyl-(3,4-methylenedioxyphenyl)-malonate.—A solution of 85 g. (0.304 mole) of diethyl 3,4-methylenedioxyphenylmalonate in 175 ml. of diethyl carbonate was added to a cool solution of sodium ethoxide prepared by dissolution of 7.0 g. (0.304 g.-atom) of sodium in absolute ethanol. The mixture was stirred for 10 min. at 60°, treated with 23 g. (0.307 mole) of chloroacetonitrile dissolved in 30 ml. of diethyl carbonate, stirred for 5 hr., poured into cold water, and neutralized with dilute acetic acid. The crude reaction product was extracted with ether, dried over anhydrous sodium sulfate, and fractionated *in vacuo*. The material which distilled from 140–180° (0.3 mm.) was collected and redistilled to yield 31 g. (32%) of product, b.p. 157–160° (0.1 mm.).

Diethyl 2-Aminoethyl-(*p*-methoxyphenyl)-malonate Hydrochloride.—Diethyl 2-cyanomethyl-2-(*p*-methoxyphenyl)-malonate (7.25 g., 0.025 mole) was dissolved in a solution of 100 ml. of alcohol and 2.25 ml. of concentrated hydrochloric acid. Platinum oxide (0.05 g.) was added and the mixture was hydrogenated at an initial hydrogen pressure of 2.8 kg./cm.². Absorption of hydrogen stopped in 3 hr.; the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The sirupy residue was triturated with ether at ice bath temperature to cause crystallization. Recrystallization from benzene gave 6.5 g. of pure material.

4-Amino-2-(*p*-chlorophenyl)butyric Acid Hydrochloride.—Diethyl 2-aminoethyl-(*p*-chlorophenyl)malonate (19 g., 0.054 mole) was refluxed overnight with 50 ml. of 6 *N* hydrochloric acid. The reaction mixture was concentrated *in vacuo*, alcohol was added to the residue, and the resulting solution was concentrated *in vacuo* to dryness. The white crude crystalline residue melted at 196–198°, and at 198–199° after recrystallization from a mixture of isopropyl alcohol and ether; yield, 11 g. (81.5%).

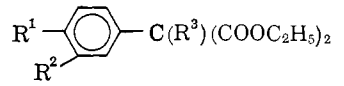
Ethyl 4-Amino-2-(*p*-chlorophenyl)-butyrate Hydrochloride.—A solution of 8 g. (0.032 mole) of 4-amino-2-(*p*-chlorophenyl)-

(9) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Am. Chem. Soc.*, **63**, 2056 (1941).

(10) F. F. Blicke and F. Leonard, *ibid.*, **68**, 1934 (1946).

TABLE III

DIETHYL ARYLMALONATES AND ARYLCYANOALKYLMALONATES



R¹	R²	R³	B.p., ° C. (mm.)	Yield, %	Molecular formula	Calcd., % C	H	N	Found, % C	H	N
H	H	CH_2CN	115–116 (0.4)	63.5	$C_{15}H_{17}NO_4$	65.52	6.23	..	66.59	6.03	..
H	H	$CH(CH_3)CN$	140–142 (2)	34.6	$C_{16}H_{19}NO_4$	66.43	6.57	..	68.35	6.70	..
CH_3O	H	H	146–147 (1.0)	72	$C_{14}H_{18}O_5$	63.16	6.81	..	62.12	6.42	..
CH_3O	H	CH_2CN	160–170 (1.2)	39.2	$C_{16}H_{19}NO_5$	62.94	6.27	4.59	63.33	6.28	4.70
Cl	H	H	140–142 (1.0)	73	$C_{13}H_{15}ClO_4$	57.59	5.54	..	57.51	5.61	..
Cl	H	CH_2CN	155–160 (0.4)	42.2	$C_{15}H_{16}ClNO_4$	58.15	5.21	4.52	59.20	4.96	3.91
CH_3	CH_3	H	150–152 (2.2)	39.0	$C_{15}H_{20}O_4$	68.16	7.63	..	67.92	8.16	..
CH_3	CH_3	CH_2CN	150–170 (2.2)	43.0	$C_{17}H_{21}NO_4$	67.53	6.97	4.63	67.57	7.11	5.00
OCH_2O		H	174–175 (0.6)	81	$C_{14}H_{16}O_6$	59.98	5.75	..	59.74	5.31	..
OCH_2O		CH_2CN	157–160 (0.1)	32.0	$C_{16}H_{17}NO_6$	60.20	5.37	4.39	60.57	5.40	4.10

butyrate hydrochloride in 150 ml. of absolute ethanol was saturated at ice bath temperature with gaseous hydrogen chloride and then was stored at room temperature for 4 days. The crude crystalline precipitate, m.p. 158–159°, was isolated and recrystallized from ethanol to give 8 g. (90%) of product, m.p. 159–160°.

Synthesis and Pharmacological Study of New Piperazine Derivatives. I. Benzylpiperazines

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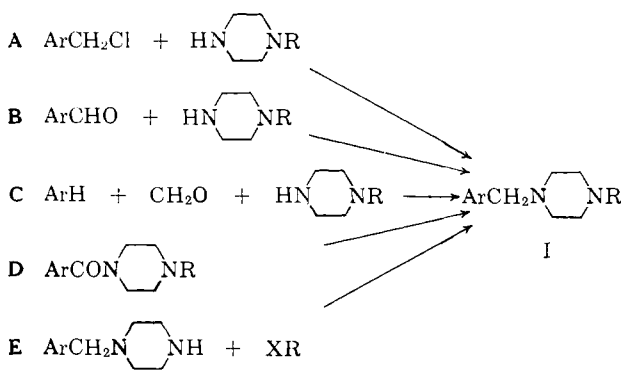
Twenty-three 1,4-disubstituted piperazines have been prepared, in which the 1-substituents are benzyl or its mono- or polyalkoxy-, or alkoxyhydroxy- derivatives, and the 4-substituents are phenyl, chloro- or methoxyphenyl, pyridyl, methylpyrazinyl, chloro- or methoxypyridazinyl. They have been studied systematically for potency against epinephrine and histamine on the isolated guinea pig seminal vesicle, in comparison with ergotamine and promethazine. Some compounds show potent activity against epinephrine, and all present very weak histaminolytic effects. The adrenergic blocking action observed *in vitro* was verified in anesthetized dogs.

Adrenolytic, sympatholytic, and antihistaminic properties have been described in 1-phenylpiperazine[1] and derivatives[2]: hypotensive, vasodilatator, and neuroleptic effects have also been reported in series of 1-aralkyl piperazines.[3]

A series of new benzyl piperazines (Table I) of type I has been prepared where Ar = phenyl, mono- or polyalkoxyphenyl, or alkoxyhydroxyphenyl and R = phenyl, chlorophenyl, methoxyphenyl, pyridyl, methylpyrazinyl, chloro- or methoxypyridazinyl.

These piperazine derivatives were obtained by five general methods according to the scheme



In method A, benzyl chlorides (whether isolated or not) were condensed with twice the theoretical amount

(1) (a) D. Bovet and F. Bovet-Nitti, "Médicaments du système nerveux végétatif," S. Karger, S. A., Bâle, 1948, p. 247; (b) L. W. Roth, *J. Pharmacol. Exptl. Therap.*, **110**, 157 (1954); (c) V. Prelog and G. J. Driza, *Collection Trav. Chim. Tchecoslov.*, **5**, 497 (1933).

(2) (a) E. Cerkovnikov and P. Stern, *Arkhiv. Kem.*, **18**, 12 (1946); (b) B. B. Morphis, L. W. Roth, and R. K. Richards, *Proc. Soc. Exptl. Biol. Med.*, **101**, 174 (1959); (c) D. F. Marsh and J. F. O'Leary, *Federation Proc.*, **12**, 348 (1953); (d) J. F. O'Leary, *Federation Proc.*, **12**, 355 (1953); (e) J. F. O'Leary, *Am. J. Med. Sci.*, **226**, 111 (1953); (f) J. E. Owen and T. Verhave, *J. Pharmacol. Exptl. Therap.*, **122**, 59A (1958); (g) I. H. Page, R. W. Wolford, and A. C. Corcoran, *Arch. Intern. Pharmacodyn.*, **119**, 214 (1959); (h) A. P. Swain and S. K. Naegele, *J. Am. Chem. Soc.*, **76**, 5091 (1954).

(3) (a) J. R. Boissier, C. Dumont, R. Ratouis, and J. Pagny, *Arch. Intern. Pharmacodyn.*, **133**, 29 (1961); (b) J. Mills, M. M. Boren, and N. R. Easton, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., 1957, p. 11-O; (c) R. L. Moffitt and R. K. S. Lim, *Federation Proc.*, **15**, 461 (1956); (d) G. Quesnel, R. Chalaust, H. Schmitt, G. Kroneberg, and H. Schmitt, *Arch. Intern. Pharmacodyn.*, **128**, 17 (1960); (e) N. H. Schimmel and J. R. Beerm, *Antibiot. Med. Clin. Therapy*, **6**, 25 (1958); (f) G. Stille, W. Braun, and M. Walter, *Arzneimittel-Forsch.*, **7**, 225 (1957).