gradually became yellow. Stirring was continued for 30 min, then the Celite–chloromercuri-2-ethylthio-6-methylaminopurine mixture was filtered, washed with ethanol, and dried *in vacuo* (yield 39.28 g, 99%). The product was further dried and treated with 43.5 mmoles of **3** as described for **1a**. The condensation product was deblocked with methanolic NH_3 as described for **1a,** and **1d** (6.2 g) crystallized during the chloroform extraction of the final aqueous solution. Two recrystallizations from ethanol gave white plates (4.4 g, 30%), mp 206–207.5°.

Anal. Calcd for $C_{13}H_{19}N_5O_4S$: C, 45.73; H, 5.61; N, 20.51. Found: C, 45.79; H, 5.81; N, 20.00.

2-Trifluoromethyl-N^6-methyladenosine (1e).—Chloromercuri-2-trifluoromethyl-6-methylaminopurine on Celite was prepared from 4.12 g (19 mmoles) of the purine, 10 g of Celite, 5.18 g (19 mmoles) of $HgCl_2$, and 0.765 g (19 mmoles) of NaOH as described for **2d**; 17.2 g of the chloromercuri-2-trifluoromethyl-6-methylaminopurine–Celite mixture was obtained and treated with 19 mmoles of **3** (from 9.65 g, 19 mmoles, of **5**). The procedure and work-up were as described for **1d**, and **1e** separated from water as a light brown crystalline solid (2.85 g, 43%), mp 203–205°, which crystallized from water as white needles (2.4 g, 36%), mp 203.5–206°. A second recrystallization gave pure **1e**, mp 204–206°.

Anal. Calcd for $C_{12}H_{14}F_3N_5O_4 \cdot 0.5H_2O$: C, 40.19; H, 4.19; N, 19.54. Found: C, 40.15; H, 4.20; N, 19.49.

2-Chloro-N^6-dimethyladenosine (1f).—A chloromercuri-2-chloro-6-dimethylaminopurine–Celite mixture was prepared in 84% yield, as described for **2d** from 6.0 g (30.4 mmoles) of 2-chloro-6-dimethylaminopurine,[17] Celite (12.0 g), $HgCl_2$ (8.25 g, 30.4 mmoles), and NaOH (1.22 g, 30.4 mmoles). The dried product (21.6 g) was treated with 30.4 mmoles of **3** (from 15.3 g, 30.4 mmoles, of **5**) as described for **1d**. Evaporation of methanolic NH_3 after the deblocking step left a dark oil. Trituration with $CHCl_3$–water gave crystals (4.55 g, 46%) which were recrystallized twice from aqueous ethanol to give **1f** as needles (3.5 g), mp 214–215°. Two recrystallizations from methanol gave analytically pure **1f**, mp 218–220°.

Anal. Calcd for $C_{12}H_{10}ClN_5O_4$: C, 43.69; H, 4.89; N, 21.24. Found: C, 44.02; H, 5.08; N, 21.27.

2-Methoxy-N^6-methyladenosine (1c).—Sodium methoxide (2 *N*, 8 ml) was added to a solution of **1a** (1.0 g) in dry methanol (100 ml), and the solution was heated under reflux for 50 hr. Paper chromatography showed that only a trace of **1a** remained. The solution was cooled, neutralized with dilute HCl, and evaporated to a white residue. This was extracted with dry ethanol (50 ml), NaCl was filtered off, and the filtrate was evaporated leaving a colorless gum. This was dissolved in water (50 ml), and the solution was filtered from some insoluble material, concentrated to 10 ml, and refrigerated. Crystals of **1c** (0.75 g) separated. The product was chromatographically pure and two recrystallizations from 50% aqueous ethanol gave pure **1c**, clusters of needles, mp 106–108°.

Anal. Calcd for $C_{12}H_{17}N_5O_5 \cdot H_2O$: C, 43.77; H, 5.82; N, 21.27. Found: C, 43.93; H, 6.21; N, 21.22.

Acknowledgment.—The authors are indebted to Mr. D. Nobbs for his expert preparation of chemical intermediates.

Unnatural Amino Acids. II. Congeners of DL-3-Carboxy-4-methoxyphenylalanine

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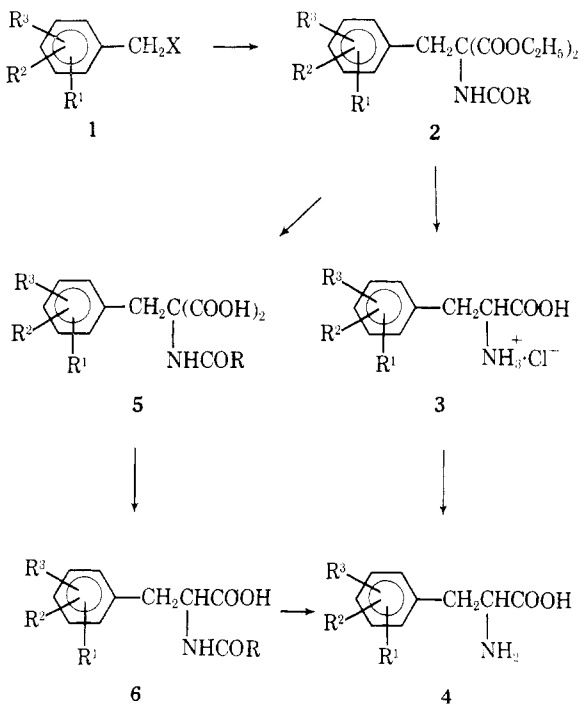
Received January 29, 1966

Several studies on the use of amino acid residues to transport biologically active groups across cell membranes have been reported.[2–6] In the main, however, the possibility that an amino acid derivative of a pharmacologically active moiety would penetrate to sites not reached by the parent compound has not been explored. In the first paper of this series,[6] the preparation and some of the biological properties were described of three new amino acids related both to tyrosine and aspirin. One of the compounds, DL-3-carboxy-4-methoxyphenylalanine (CMPA; **4**, R^1 = 3-COOH; R^2 = 4-CH_3O; R^3 = H) was found to be an orally effective analgetic agent in animals and man but was poorly and erratically absorbed. It served, however, as a reference compound in the search for compounds which are better absorbed and at least as potent. The congeners of DL-3-carboxy-4-methoxyphenylalanine which were prepared and evaluated (Tables I and II) include isomers, homologs, and analogs. All were synthesized from acylamidomalonates as shown in Scheme I.

SCHEME I



The pharmacological data in Table I show that small structural changes in DL-3-carboxy-4-methoxyphenylalanine (CMPA) are accompanied by increased toxicity and attenuation or loss of analgetic activity. Replacement of the methoxy group by ethoxy or chloro and of the carboxy group by formyl or carboxamido results in considerable loss of analgetic activity. Substitution of the benzene nucleus of CMPA with a methyl group does not seem to have a markedly deleterious effect on analgetic activity but causes a great increase in toxicity. One of the isomers of CMPA, DL-3-carboxy-2-methoxyphenylalanine, shows analgetic activity in the same range as CMPA but is more toxic.

(1) Deceased.

(2) E. F. Elliot, A. T. Fuller, and C. R. Harington, *J. Chem. Soc.*, 85 (1948).

(3) J. H. Burckhalter and V. C. Stevens, *J. Am. Chem. Soc.*, **73**, 56 (1951).

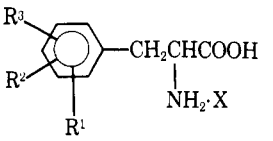
(4) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954); F. Bergel, V. C. E. Burnop, and J. A. Stock, *ibid.*, 1223 (1955).

(5) L. F. Larionov, E. M. Shkodinskaya, V. I. Troosheikina, A. S. Khokhlov, O. S. Vasina, and M. A. Movikova, *Lancet*, **269**, 169 (1959).

(6) F. Leonard, A. Wajngurt, W. Tschannen, and F. B. Block, *J. Med. Chem.*, **8**, 812 (1965).

TABLE I

ANALGETIC ACTIVITY AND ACUTE TOXICITY

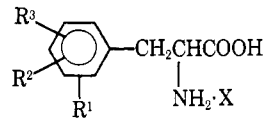


No.	R^1	R^2	R^3	X	Mouse LD_{50} ip, mg/kg	Mouse tail flick test: Dose, Route	Mouse tail flick test: Dose, mg/kg	Mouse tail flick test: Av % increase in reaction time[a]
1	3-COOH	4-CH_3O	H	HCl	5000	Ip	150	+22
							300	+81
2	3-COOH	4-HO	H	HCl	1000	Ip	300	+13, +15
3	3-COOH	4-HO	5-CH_3	...	75	Ip	70	+18
4	3-COOH	4-CH_3O	5-CH_3	...	...	Ip	80	+24
5	3-CHO	4-CH_3O	H	HCl	400	Sc	200	0
6	3-$CONH_2$	4-CH_3O	H	HCl	1500	Sc	300	+10
7	3-$CONH_2$	4-CH_3O	H	...	4000	Sc	300	+2.7
8	3-COOH	4-C_2H_5O	H	HCl	3000	Ip	1000	+4
9	3-COOH	4-Cl	H	HCl	...	Ip	300	+20
10	3-COOH	4-Cl	H	...	3000	..	...	...
11	4-COOH	3-HO	H	...	1500	Sc	300	+2.6
12	3-COOH	2-CH_3O	H	HCl	3500	Ip	150	+16

[a] Average of reaction times determined at 15, 30, 45, and 60 min after administration of compounds. See ref 6 for a description of the test method.

TABLE II

PHENYLALANINE DERIVATIVES



No.	R^1	R^2	R^3	X	Mp, °C	Recrystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	3-COOH	4-OH	5-CH_3		271–272	W–E	$C_{11}H_{13}NO_5$	55.13	5.48	5.84	54.67	6.28	5.61
2	3-COOH	4-OH	5-CH_3	HCl	255–256	E	$C_{11}H_{13}NO_5 \cdot HCl$	47.85	5.06	5.06	47.85	5.07	4.81
3	3-COOH	4-CH_3O	5-CH_3	H_2O	291–292	R	$C_{12}H_{15}NO_5 \cdot H_2O$	53.50	6.25	5.16	53.55	6.36	4.80
4	3-CHO	4-CH_3O	H	HCl	349–350	I–EA	$C_{11}H_{13}NO_4 \cdot HCl$	50.80	5.46	5.46	50.46	5.57	5.33
5	3-$CONH_2$	4-CH_3O	H	HCl	246–247	E	$C_{11}H_{14}N_2O_4 \cdot HCl$	48.01	5.49	10.18	47.74	5.49	9.80
6	3-$CONH_2$	4-CH_3O	H		270	E	$C_{11}H_{14}N_2O_4$	55.61	5.91	11.74	55.64	5.77	11.39
7	3-COOH	4-C_2H_5O	H	HCl	206–207	I–EA	$C_{12}H_{16}NO_5 \cdot HCl$	49.65	5.55	4.79	49.36	5.52	4.85
8	3-COOH	4-Cl	H	HCl	255	I	$C_{10}H_{10}ClNO_4 \cdot HCl$	42.88	3.96	5.00	42.62	3.99	4.97
9	3-COOH	4-Cl	H		292–293	R	$C_{10}H_{10}ClNO_4$	49.29	4.14	5.75	49.10	4.38	5.53
10	4-COOH	3-OH	H	H_2O	305	R	$C_{10}H_{11}NO_5 \cdot H_2O$	49.42	5.38	5.74	49.62	5.61	5.66
11	4-COOH	3-CH_3O	H		158–160	W	$C_{11}H_{13}NO_5$	55.22	5.48	5.86	55.43	5.69	5.62
12	3-COOH	2-CH_3O	H	HCl	200	I	$C_{11}H_{13}NO_5 \cdot HCl$	47.92	5.08	5.38	47.80	5.19	5.28

[a] E, ethanol; EA, ethyl acetate; I, isopropyl alcohol; R, reprecipitated from 0.1 *N* $NaHCO_3$ with 0.1 *N* HCl; W, water.

The carboxaldehyde (**5**, Table I) was prepared as a potential biological precursor of CMPA. Its considerably greater toxicity than that of CMPA but complete lack of analgetic activity suggests that while it is probably much better absorbed, it is very slowly, if at all, converted to CMPA *in vivo*. The amide analog of CMPA (**7**, Table I) was prepared on the basis of the similarity of its relationship with CMPA to that of glutamine and glutamic acid. It was hoped that, like glutamine, it would be better absorbed than the related dicarboxylic acid[7] and would provide higher blood and brain levels of an analgetically active species. The poor analgetic activity of this compound could be directly correlated with its very poor gastrointestinal absorption[8] determined by the method of Hogben, *et al.*[9] It is noteworthy that ring methylation in this series markedly enhances toxicity and analgetic activity. It would seem that ring methylation may have the effect of forming a lipophilic center which facilitates absorption by passive diffusion. The situation we envision for compounds of this type parallels that of soaps which also have lipophilic and ionic centers and are able to partition both between fat and aqueous phases.

Experimental Section[10]

o-Methoxybenzoic acid, *o*-ethoxybenzoic acid, 2-hydroxy-*m*-toluic acid, *o*-methoxybenzaldehyde, and *p*-chlorotoluene were obtained from Distillation Products Industries, Inc. 2-Hydroxy-*p*-toluic acid was purchased from K & K Laboratories, Inc. The toluic acids were esterified and methylated by standard reactions and gave products with physical constants in agreement with the published data: methyl 2-methoxy-*m*-toluate, bp 95° (1.2 mm), lit.[11] 114–116 (14 mm); methyl 2-

(7) P. Schwerin, S. P. Bessman, and H. Waelsch, *J. Biol. Chem.*, **184**, 37 (1950).

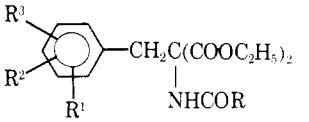
(8) Private communication from Dr. P. Greengard.

(9) C. A. Hogben, D. J. Tocco, B. B. Brodie, and L. M. Schanker, *J. Pharmacol. Exptl. Therap.*, **125**, 279 (1955).

(10) Microanalyses were performed by Mr. J. Deonorine of these laboratories. Melting points (corrected) were taken on a Thomas–Hoover melting point apparatus.

(11) R. Anschütz, H. Aschenberg, H. Keuhert, F. Krone, K. Riepenkroger, and V. Zerbe, *Ann.*, **442**, 18 (1925).

TABLE III
INTERMEDIATE ACYLAMIDOMALONIC ACID ESTERS



No.	R	R¹	R²	R³	Mp, °C	Recrystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H	3-HOOC	4-CH_3O	H	152–153	B	$C_{17}H_{21}NO_8$	55.58	5.72	3.81	55.88	6.01	3.65
2	H	3-HOOC	4-CH_3O	5-CH_3	...	EA–P	$C_{18}H_{23}NO_8$	56.58	6.05	3.69	56.32	6.39	3.75
3	CH_3	3-HOOC	4-CH_3O	5-CH_3	225–226	E	$C_{19}H_{25}NO_8$	57.43	6.53	3.53	57.27	6.01	3.55
4	H	3-CHO	4-CH_3O	H	86–87	I–P	$C_{17}H_{21}NO_7$	58.11	6.00	4.00	58.53	6.53	4.08
5	CH_3	3-HCO	4-CH_3O	H	...	B	$C_{18}H_{23}NO_7$	59.13	6.30	3.80	59.16	6.26	4.12
6	H	3-H_2NCO	4-CH_3O	H	130–131	EA–P	$C_{17}H_{22}N_2O_7$	...	...	7.95	...	...	7.95
7	CH_3	3-H_2NCO	4-CH_3O	H	165	EA–P	$C_{18}H_{24}N_2O_7$	56.84	6.31	7.40	56.68	6.65	7.75
8	CH_3	3-HOOC	4-C_2H_5O	H	133–134	B	$C_{19}H_{25}NO_8$	57.71	6.37	3.56	57.38	6.69	4.01
9	CH_3	3-CH_3COO	4-Cl	H	112–114	I	$C_{18}H_{22}ClNO_7$	54.07	5.55	3.50	54.43	6.03	3.18
10	CH_3	4-CH_3OOO	3-CH_3O	H	Oil	...	$C_{19}H_{25}NO_8$	57.85	6.37	3.55	58.13	6.35	3.54
11	CH_3	3-CH_3OOO	2-CH_3O	H	Oil	...	$C_{19}H_{25}NO_8$	57.85	6.37	3.55	58.20	6.40	3.36

[a] B, benzene; E, ethanol; EA, ethyl acetate; I, isopropyl alcohol; P, petroleum ether.

methoxy-*p*-toluate, bp 108–110° (1.4 mm), lit.[11] 137–139° (14 mm). *p*-Chlorotoluene was converted to 2-chloro-5-methylacetophenone, bp 108–109° (7 mm), $n^{25}D$ 1.5420; lit.[12] bp 239–240°, $n^{25}D$ 1.5419. The latter gave, when oxidized with NaOBr[13] instead of with $KMnO_4$ as described in the literature,[14] an 87.5% yield of 6-chloro-*m*-toluic acid (mp 157–158°, lit.[14] mp 167°) which was esterified by the method of Clinton and Laskowski[15] to methyl 6-chloro-*m*-toluate, yield 84%, bp 79–80° (0.8 mm), $n^{22}D$ 1.5338.

Anal. Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91. Found: C, 58.20; H, 4.89.

o-Ethoxybenzoic acid, *o*-methoxy-*m*-toluic acid and *o*-methoxybenzaldehyde were chloromethylated with a mixture of formaldehyde, concentrated HCl, and gaseous HCl utilizing the procedure described in the first article of this series.[6] The products had physical constants and analytical data as follows: 5-chloromethyl-2-methoxy-*m*-toluic acid, mp 186–187° (*Anal.* Calcd for $C_{10}H_{11}ClO_3$: C, 55.97; H, 5.15. Found: C, 55.80; H, 4.70); 5-chloromethyl-2-ethoxybenzoic acid, mp 51–52° (*Anal.* Calcd for $C_{10}H_{11}ClO_3$: C, 55.97; H, 5.15. Found: C, 55.90; H, 5.58); 5-chloromethyl-2-methoxybenzaldehyde, mp 75–76°, lit.[16] mp 76°.

The chloro- and methoxytoluates were brominated with N-bromosuccinimide as described below for methyl 6-chloro-*m*-toluate. The bromination products decomposed when distilled and were therefore used without purification in the subsequent alkylation reactions.

Methyl 5-Bromomethyl-2-chlorobenzoate.—N-Bromosuccinimide (17.8 g, 0.1 mole) and 4 g of benzoyl peroxide were added to a solution of 18.5 g (0.1 mole) of methyl 6-chloro-*m*-toluate in 250 ml of CCl_4. The reaction mixture was stirred and refluxed for 1 hr and filtered. The filtrate was concentrated *in vacuo*, and the residual syrup was dissolved in 300 ml of benzene and chromatographed on a column of neutral alumina. The column was washed with benzene, the combined eluate and benzene washings were concentrated *in vacuo*, and the syrupy residue was freed of traces of solvent by prolonged warming *in vacuo;* yield 20 g (75%).

Alkylations of diethyl acetamidomalonate with 5-chloromethyl-2-methoxy-*m*-toluic acid and 5-chloromethyl-2-ethoxybenzoic acid were carried out in absolute ethanol in the presence of 2 equiv of sodium ethoxide as described previously for alkylations with 5-chloromethyl-2-methoxybenzoic acid.[6] The preparation of diethyl acetamido(3-carbomethoxy-4-chlorobenzyl)malonate illustrates the method utilized for alkylations with the bromomethyl esters and 5-chloromethyl-2-methoxybenzaldehyde. The carboxamidomalonates were prepared from carboxymalonates as illustrated by the preparation of diethyl formamido(3-carboxamido-4-methoxybenzyl)malonate. Physical data on the new malonates are reported in Table III.

Diethyl Acetamido(3-carbomethoxy-4-chlorobenzyl)malonate.—Diethyl acetamidomalonate (15.7 g, 0.072 mole) and 18.7 g (0.071 mole) of methyl 5-bromomethyl-2-chlorobenzoate were added to a cool solution of NaOEt prepared from 1.7 g (0.074 g-atom) of Na and 100 ml of ethanol. The resultant mixture was refluxed with stirring for 5 hr, filtered, and concentrated *in vacuo*. The solid residue was recrystallized from a benzene–hexane mixture, cyclohexane, and finally from 2-propanol to yield 12.5 g (44%) of product, mp 112–114°.

Diethyl Formamido(3-carboxamido-4-methoxybenzyl)malonate.—Thionyl chloride (3.3 g, 10% excess) was added to a solution of 9.2 g (0.025 mole) of diethyl formamido(3-carboxy-4-methoxybenzyl)malonate. The mixture was refluxed for 10 hr and concentrated *in vacuo* to remove excess $SOCl_2$. The residue was taken up in benzene and the solution was saturated with gaseous NH_3. The product crystallized and was filtered off. The filter cake was washed with water and recrystallized from a mixture of ethyl acetate and hexane. The product melted at 130–131°, yield 7.0 g (80%).

The following examples illustrate the methods employed for the preparation of the acylamidomalonic acids, acylamido acids and amino acids (Table II).

Formamido(3-carboxy-4-methoxy-5-methylbenzyl)malonic Acid.—Diethyl formamido(3-carboxy-4-methoxy-5-methylbenzyl)malonate[17] (12.0 g, 0.0315 mole) was refluxed for 4 hr with 50 ml of 10% NaOH. The reaction mixture was cooled and acidified to pH 3 with dilute HCl. The precipitate was filtered off and was recrystallized from a mixture of water and isopropyl alcohol: mp 175–177°, yield 4.65 g (45%).

Anal. Calcd for $C_{14}H_{15}NO_8$: C, 51.70; H, 4.61; N, 4.30. Found: C, 51.65; H, 5.16; N, 4.01.

Formamido(3-carboxamido-4-methoxybenzyl)malonic Acid.—Diethyl formamido(3-carboxamido-4-methoxybenzyl)malonate[18] (14.0 g, 0.04 mole) was added to 32 ml of 2.5 *N* (0.08 mole) of NaOH. The mixture was warmed in a boiling-water bath for 20 min to dissolve the malonate, cooled, and acidified to congo red with concentrated HCl. The crystalline precipitate melted at 184–185° after recrystallization from water; yield 6.1 g (60%).

Anal. Calcd for $C_{13}H_{14}N_2O_7$: C, 50.25; H, 4.52; N, 9.03. Found: C, 49.90; H, 4.96; N, 8.86.

(12) F. Mayer and W. Freund, *Ber.*, **55**, 1049 (1922).

(13) The method employed for this oxidation was the same as that which was used for the preparation of β-naphthoic acid described by "Organic Synthesis," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 428.

(14) A. Claus, *J. Prakt. Chem.*, [2] **46**, 20 (1892).

(15) R. D. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(16) W. Beck and I. A. Kaye, *J. Org. Chem.*, **16**, 1434 (1951).

(17) Diethyl acetamido(3-carboxy-4-methoxy-5-methylbenzyl)malonate was recovered unchanged after 70 hr of reflux with 2 *N* HCl. When, however, it was refluxed with concentrated HCl for 70 hr, not only ester hydrolysis but decarboxylation and ether cleavage occurred with the formation of DL-3-carboxy-5-methyltyrosine hydrochloride (**2**, Table II).

(18) Several unsuccessful attempts were made to selectively hydrolyze the ester and acetamido groups of diethyl acetamido(3-carboxamido-4-methoxybenzyl)malonate with dilute HCl or NaOH. Mixtures of amido- and aminomonocarboxylic and dicarboxylic acids were obtained as shown by elemental analyses and infrared spectra. Selective saponification of the ester groups of this compound was achieved with 2 equiv of NaOH as illustrated for its formamido homolog, but conditions could not be found for cleavage of the N-acetyl group of the resulting N-acetyl-3-carboxamido-4-methoxyphenylanine without simultaneous hydrolysis of the aromatic carboxamide groups.

DL-3-(3-Carboxy-4-ethoxyphenyl)alanine Hydrochloride.—Diethyl acetamido(3-carboxy-4-ethoxybenzyl)malonate (4 g, 0.01 mole) was refluxed with 25 ml of 1.2 *N* HCl for 19 hr. The reaction mixture was concentrated *in vacuo* and the crystalline residue was recrystallized from isopropyl alcohol; yield 2.02 g (69.0%).

DL-3-(3-Carboxy-2-methoxyphenyl)alanine Hydrochloride.—Diethyl acetamido(3-carbomethoxy-2-methoxybenzyl)malonate (7 g, 0.0177 mole) was hydrolyzed with 100 ml of 1.2 *N* HCl for 20 hr. Concentration of the reaction mixture *in vacuo* gave a crystalline residue which was recrystallized from a mixture of isopropyl and ethyl alcohol; yield 2.7 g (55%).

DL-3-(3-Carboxy-4-methoxy-*m*-tolyl)alanine Hydrate.—A mixture of 4.5 g (0.0138 mole) of formamido-(3-carboxy-4-methoxy-5-methylbenzyl)malonic acid and 50 ml of 50% ethanol was refluxed for 24 hr. The white crystalline compound which precipitated was filtered off, washed with water, and dissolved in 0.1 *N* $NaHCO_3$ solution. The bicarbonate solution was charcoaled, filtered, and acidified. The precipitate was filtered off, washed with water, and dried; yield 1.8 g (41%).

DL-3-(3-Carboxamido-N-formyl-4-methoxyphenyl)alanine.—Formamido(3-carboxamido-4-methoxybenzyl)malonic acid (6 g, 0.0193 mole) was refluxed for 7 hr with 90 ml of 1:1 ethanol–water. The mixture was concentrated *in vacuo* and gave a syrupy residue which crystallized while standing under ether at ice-bath temperature. It melted at 118–119° after recrystallization from ethanol; yield 4 g (84%).

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.25; N, 10.52. Found: C, 54.43; H, 5.59; N, 9.92.

DL-3-(3-Carboxamido-4-methoxyphenyl)alanine Hydrochloride.—3-(3-Carboxamido-N-formyl-4-methoxyphenyl)alanine (4 g, 0.015 mole) was refluxed for 7 hr with 200 ml of 0.0995 *N* HCl. The reaction mixture was concentrated to dryness *in vacuo*. The oily residue crystallized under a mixture of ether–ethanol and was recrystallized from alcohol; yield 1.5 g (36.5%), mp 243–244°.

DL-3-(3-Carboxamido 4-methoxyphenyl)alanine.—Formamido-(3-carboxamido-4-methoxybenzyl)malonate (7 g, 0.022 mole) was refluxed for 26 hr in a mixture of 300 ml of 1:1 ethanol–water. The solvents were evaporated *in vacuo*, and the oily residue was taken up in the minimum amount of hot ethanol and allowed to crystallize in the refrigerator. The crystalline product was removed by filtration and recrystallized from ethanol; yield 3.5 g (66.6%), mp 269–270°.

DL-4-Carboxy-*m*-tyrosine Hydrate.—DL-3-(Carboxy-3-methoxyphenyl)alanine (3.0 g, 0.0125 mole) was refluxed with 30 ml of 48% HBr for 5 hr and allowed to cool overnight. The crystalline precipitate was filtered off and dissolved in water. The pH of the resulting solution was adjusted to 3.2 with 10% NaOH. The precipitate was filtered off, washed with water, and then dissolved in 0.1 *N* $NaHCO_3$. The bicarbonate solution was clarified (charcoal), acidified to pH 3.2, and filtered. The filter cake was washed well with water and dried; yield 1.55 g (51%).

Synthesis of Potential Antineoplastic Agents. XVII. N,N-Bis(2-fluoroethyl)anilines[1]

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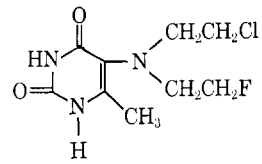
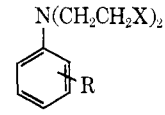
Received November 25, 1966

Prior to the report[2] of the clinical application of the drug ftorpan (I), essentially no work had been reported on the synthesis of 2-fluoroethylamines as potential antineoplastic agents. Since that time, however, a number of reports[3–5] of 2-fluoroethylamines have appeared.[6] In addition to the activity of I additional



I

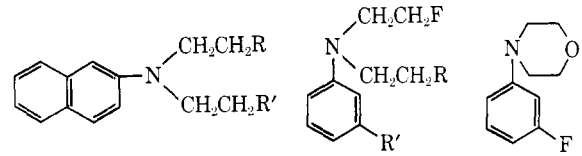


II, X = F
III, X = OH
IV, X = Cl
V, X = OTs

rationale for the synthesis of 2-fluoroethylamines has been presented.[5] We report here the synthesis and some screening results on a number of substituted N,N-bis(2-fluoroethyl)anilines (II).

In an initial approach to the synthesis of II it was found that N,N-bis(2-chloroethyl)aniline (IV, R = H) and N,N-bis(2-chloroethyl)-*m*-toluidine (IV, R = 3-CH_3) could be converted to the corresponding fluoroethylanilines (II) by refluxing with anhydrous potassium fluoride in methanol. However, attempts to extend the generality of this reaction to other chloroethylanilines (IV) failed.

As an alternative approach it was decided to attempt to replace the *p*-tolylsulfonyloxy grouping because of the ease with which they could be prepared and because several of the desired compounds had already been reported.[7] These tosylates (V) were prepared by reaction of III with *p*-toluenesulfonyl chloride in the presence of pyridine; the new compounds so prepared are included in Table I.



VI, R = R′ = OTs
VIII, R = F; R′ = OCH_3
IX, R = F; R′ = OC_2H_5

VII, R = OCH_3
XI, R = OCH_2-$CH_2OCH_2CH_2OH$

X

In initial examples it was found that the tosylate could be readily replaced by fluorine by refluxing V with excess anhydrous KF in methanol. This displacement was accomplished without difficulty to give VI (R = H, R = 3-CH_3, and R = 4-CH_3). These and other N,N-bis(2-fluoroethyl)anilines are included in Table II. However, when applied to V (R = 3-F and R = 3-NO_2) and to VI this method led to the isolation of a N-(2-fluoroethyl)-N-(2-methoxyethyl)aniline (VII and VIII, respectively). These and other related compounds are included in Table III. Use of absolute ethanol in place of methanol with VI led to IX. Several other attempted displacements in methanol gave oils from which pure products could not be separated. Treatment of N,N-bis(2 fluoroethyl)aniline (IX) or compounds of the type VII with refluxing methanol or

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(6) Our work in this area began before these reports[3–5] appeared.

(7) G. M. Timmis, British Patent 662,645 (1951).