dioxane over a period of about 5 min. After being stirred for 15 min in the ice bath and 20 min at ambient temperature, the solution was diluted with 5 ml of petroleum ether. An oil separated which solidified on trituration with fresh petroleum ether. Recrystallization from EtOH–H_2O gave 220 mg (81%) of white crystals, mp 150–152 dec. See Table II for additional data.

2,4-Diamino-5-(3,4-dichlorophenyl)-6-[*p*-(*m*-fluorosulfonylphenylureido)phenoxymethyl]pyrimidine (8) Hemisulfate (Method B).—To a stirred solution of 113 mg (0.3 mmole) of **20b** in 1 ml of DMF cooled in an ice bath was added a solution of 60 mg (0.3 mmole) of *m*-fluorosulfonylphenyl isocyanate in 0.5 ml of DMF. After 15 min at 0° and 15 min at ambient temperature, the solution was treated with 3 ml of 0.5 *N* H_2SO_4. The product was collected on a filter and washed with H_2O. Recrystallization from MeOEtOH–H_2O gave 100 mg (52%) of white powder, mp 217–219° dec. See Table II for additional data.

Method C was the same as method B except that 1.1 mmoles of HOAc was added to the DMF for each millimole of pyrimidine.

Potential Anticancer Agents. IV. Nitrogen Mustards of Methylbenzoic Acids

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The synthesis of the title compounds is described. Physical and biological data are presented. 3-[N,N-Bis(2-chloroethyl)amino]-4-methylbenzoic acid exhibited the highest antitumor activity, together with a low hematopoietic toxicity and was submitted to therapeutic trials. The relationship between the hydrolysis rate of the nitrogen mustards and the basicity of the respective unsubstituted amines was studied and the effects of substituents *ortho* to the nitrogen mustard group are pointed out.

One of the main limiting factors in cancer chemotherapy with alkylating agents is their great hematopoietic toxicity. Our investigations started from the hypothesis[1] that one of the structural features that may contribute to improve the therapeutic index of the aromatic nitrogen mustards, is the presence in the molecule of a "biologically compatible" chemical function, which could exert a strong −M and/or −I effect. Enhancing of the selectivity would then result both from reducing the reactivity of the nitrogen mustard group and from increasing the possibilities of interaction between drug and receptors.

The choice of the carboxyl group as such a function was based on the following pharmacological considerations: (a) the nitrogen mustards of arylcarboxylic acids[2] and aralkylcarboxylic acids[3] (*e.g.*, 4-[*p*-bis(2-chloroethyl)aminophenyl]butyric acid) displayed strong activity against a series of experimental tumors and in therapeutic trials;[4] (b) the carboxyl group confers to 4-[*p*-N,N-bis(2-chloroethyl)aminophenyl]butyric acid an increased selectivity for proteins;[5] (c) diffusion through cellular membranes seems to be promoted by un-ionized carboxyl;[6] benzoic acids (pK_a ranges 5–6) partially fulfill this requirement at physiological pH.

The isomeric nitrogen mustards of benzoic acid,[2] compounds with low chemical reactivity [4% hydrolysis in 0.5 hr in 50% acetone at 66° for the *meta* isomer (ref 6b, p 153)], showed moderate inhibitions against Walker 256 carcinosarcoma (ref 6b, p 123). However, testing against Jensen sarcoma gave inhibitions exceeding 85%,[7] an unusually high activity for the low chemical reactivity of the compounds, which prompted us to ascribe special "carrier" properties to the N-substituted aminobenzoic acids and to continue the investigations in this structural area.

Since carboxyl groups induce too strong a decrease in the chemical reactivity of the nitrogen mustard function (pK_a of aniline, 4.57; pK_a of methyl *o*-, *m*-, and *p*-aminobenzoates, 2.32, 3.57, and 2.49, respectively[8]), we tried to restore it partially by introducing on the benzene nucleus a third, electron-repelling group, which could increase the basicity of the nitrogen atom (pK_a of methyl aminotoluic esters, 2.03–4.06; see Table II). Thus, the ten isomeric nitrogen mustards of methylbenzoic acids were synthesized.

The cancerostatic screening revealed strong antitumor properties for all ten isomers, the best results being obtained with 3-[N,N-bis(2-chloroethyl)amino]-4-methylbenzoic acid (IVj) whose pharmacological behavior was sufficiently promising for clinical trials. The preliminary results are in some respects superior to those of some alkylating drugs in use in cancer chemotherapy (melphalan, thioTEPA), mainly in view of the low leukopenic effect at therapeutic doses.

It is of interest to note, that in IVj, the nitrogen mustard group is *meta* to carboxyl. The advantage of IVj over the other isomers is in accord with some new data on the isomeric nitrogen mustards of benzoic acids,[7,9] the best therapeutic ratio being obtained with the *meta* isomer; a similar observation was made in the case of the *meta* and *para* isomers of melphalan[10a] and of the isomeric nitrogen mustards of β-phenylalanine[10b,c] and of phenylglycine.[10d]

Synthesis.—The general procedure (Scheme I) starts from the aminomethylbenzoic esters (I) which are hydroxyethylated with ethylene oxide in glacial acetic acid and then chlorinated by means of thionyl chloride or phosphorus oxychloride. Acid hydrolysis (concentrated HCl, reflux) of the esters (III) gave the

(1) O. Costăchel, private communication, 1958.

(2) J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 238 (1953).

(3) (a) W. A. Skinner, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 777, 953 (1960); (b) W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *ibid.*, **26**, 1674 (1961).

(4) L. A. Elson, *Ann. N. Y. Acad. Sci.*, **68**, 826 (1958).

(5) J. H. Linford, *Can. J. Biochem. Physiol.*, **40**, 137 (1962).

(6) (a) W. C. J. Ross and G. P. Warwick, *Nature*, **176**, 298 (1955); (b) W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. Ltd., London, 1962, p 124.

(7) V. Dobre, private communication, 1965.

(8) A. Courville, *Compt. Rend.*, **262**, 1169 (1966).

(9) S. C. J. Fu, H. Terzian, and S. Craven, *J. Med. Chem.*, **7**, 759 (1964).

(10) (a) J. M. Luck, *Cancer Res.*, **21**, 262 (1961); (b) W. A. Skinner, V. A. Hyde, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 1756 (1960); (c) J. M. Johnson, *Chem. Ind.* (London), 966 (1960); (d) T. A. Connors, W. C. J. Ross, and J. C. Wilson, *J. Chem. Soc.*, 2994 (1960).

SCHEME I

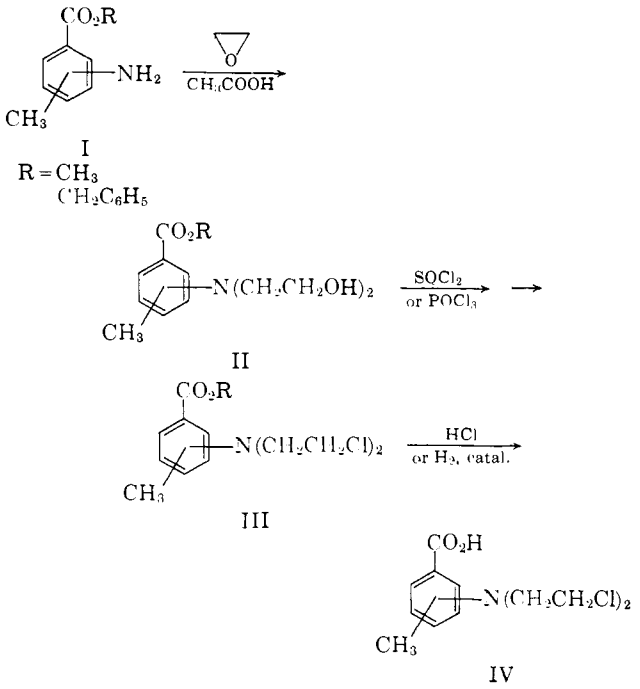
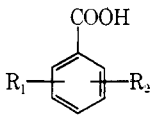


TABLE I
NITROGEN MUSTARDS OF METHYLBENZOIC ACIDS



Compd[a]	R_1	R_2[b]	Yield,[c] %	Mp, °C
IVa	2-CH_3	3-NM	81	89–90
IVb	2-CH_3	4-NM	67	171–173
IVc	2-CH_3	5-NM	62	128
IVe	3-CH_3	2-NM	23	79–80
IVf	3-CH_3	4-NM	31	126–127
IVg	3-CH_3	5-NM	64	179–181
IVh	3-CH_3	6-NM	78	77–78
IVi	4-CH_3	2-NM	48	120–122
IVj	4-CH_3	3-NM	92	118–119

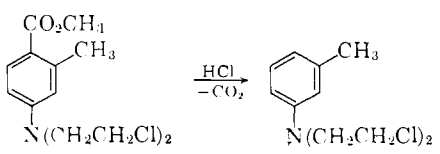
[a] *Anal.* ($C_{12}H_{15}Cl_2NO_2$) C, H, N, Cl. [b] NM = $N(CH_2CH_2Cl)_2$. [c] From dihydroxyethyl derivatives.

desired nitrogen mustards (IV), which are listed in Table I.

Intermediates II and III are, in most cases, obtained as difficultly crystallizable oils. Their purification (by alumina column chromatography, conversion to hydrochlorides, etc.) greatly enhances the yield in the final hydrolysis.

Isomers IVb and IVd could not be obtained by the general procedure. In the case of IVb, the compound underwent decarboxylation during the hydrolysis, yielding the nitrogen mustard of *m*-toluidine (V) (Scheme II), whose structure was proved by comparison

SCHEME II



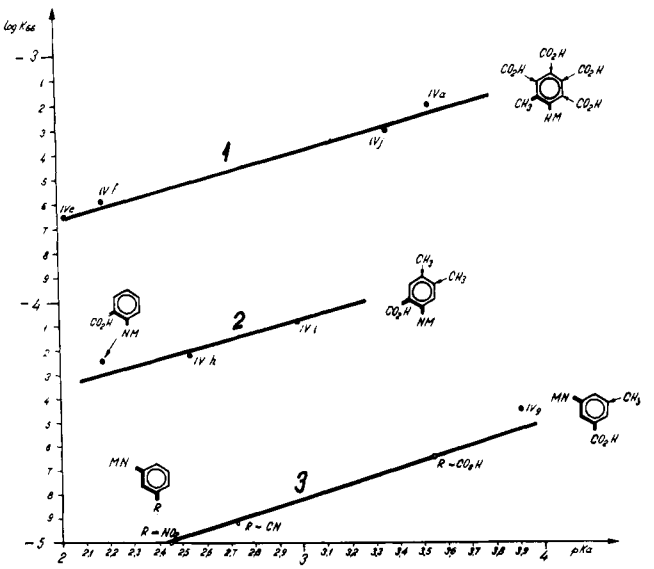


Figure 1.

with an authentic sample of V.[11] A similar decarboxylation reaction was reported in an attempted synthesis of 5-[N,N-bis(2-chloroethyl)amino]indole-3-carboxylic acid.[12]

Physical–Chemical Data.—The per cent hydrolysis of the nitrogen mustards IV, determined by the standard procedure[11] at 37 and 66°, and basicity constants of the amines I, determined spectrophotometrically,[13] are listed in Table II.

TABLE II
PHYSICAL–CHEMICAL AND BIOLOGICAL DATA OF THE NEW NITROGEN MUSTARDS

	% hydrolysis[a]				% inhib[c]	
Compd	37°	66°	pK_a[b] of amines I	LD_{50}, mg/kg in rats	Jensen sarcoma	Walker 256 carcinosarcoma
IVa	8.9	68.7	3.50	15	98	65
IVb	2.3	3.0	2.81	...	...	...
IVc	1.8	12.0	4.06	62	96	75
IVd[d]	...	...	2.90	300	99	54
IVe	6.7	33.0	2.03	20.8	90	50
IVf	4.8	37.3	2.18	16.6	90	70
IVg	2.1	6.4	3.90	51.8	59	40
IVh	2.7	10.2	2.54	25	98	...
IVi	2.6	13.8	2.98	20	100	42
IVj	9.2	58.0	3.34	17.4	100	84

[a] Determined according to Ross:[11] 0.5 hr, H_2O–Me_2CO (1:1), at $\sim 10^{-3}$ *M* by potentiometric titration of free Cl^-. [b] Basicity was determined in alcoholic solution with a CF_4 Optica Milano spectrophotometer; pH measurements made with a Radiometer pH meter. [c] Treatment began 7 days after tumor transplantation. [d] Methyl ester.

In Figure 1, the hydrolysis rate constant k_{66}, calculated according to unimolecular kinetics (hydrolysis under standard conditions at 66° was assumed to proceed through an SN1 mechanism), was plotted against the basicity constants mentioned above. Only a comparison of the basicity of the unsubstituted amines (whose protonation is less sensitive to the steric effect of *ortho* substituents) and the hydrolysis rate of the nitro-

(11) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).
(12) J. deGraw and L. Goodman, *J. Med. Chem.*, **7**, 213 (1964).
(13) I. Niculescu-Duvăz, G. Botez, and A. Serban, private communication.

gen mustards permits a distinction between the mesomeric and/or inductive effects and the steric hindrance. Thus, the shift of plots 1 and 2 as against plot 3 (reflecting only +I and −M effects) may be assigned to the steric effects.

This comparison pointed out a series of interesting *ortho* effects. (a) The first is an abnormal increase of the hydrolysis rate of *o*-methyl-substituted nitrogen mustards. This effect may partly be accounted for by a steric hindrance of mesomerism.[14] This explanation is supported by the fact that N,N-diethyl-*o*-toluidine has an abnormally increased basicity (pK_a = 7.18) as compared with that of the unsubstituted amine (pK_a = 4.39) (in the case of aniline, pK_a increases by diethylation only from 4.57 to 6.56).[11] Nevertheless, a methyl group, owing to its relatively small volume, can generate only a moderate steric repulsion which cannot explain the unusual increase in hydrolysis rate, even if one takes into account the +I effect of the group (see Figure 1, plot 1).

(b) A similar, but weaker, effect is obtained by *o*-carboxyl substitution of the nitrogen mustards. A similar explanation may be advanced, but in this case, enhancing of the basicity of the nitrogen atom by the decrease in the $p-\pi$ conjugation due to the steric repulsion of the two groups is partially counteracted by the strong −M effect of the carboxyl function (see Figure 1, plot 2). This observation is also interesting from a practical point of view, because it shows that attempts to deactivate aromatic nitrogen mustards by introducing bulky, electron-attracting *ortho* substituents may result in an opposite effect, and because it may be exploited in a more accurate control of the rate of hydrolysis of aromatic nitrogen mustards by an appropriate substitution.

Using plots in Figure 1, the rates of hydrolysis of nitrogen mustards may be predicted from amine structure and basicity.

Biological Results.—The ten isomeric nitrogen mustards have been screened against Jensen sarcoma and Walker 256 carcinosarcoma. Treatment in all of the cases began 7 days after tumor transplantation and lasted 14 days. Doses (0.2–0.1 LD_{50}) were administered daily. Tumor growth inhibition was calculated according to the formula $\%I = [(C - T)/C] \times 100$, where C and T are the average weights of tumors in the control group and in treated animals, respectively (see Table II).

Testing was extended for IVj against a broader spectrum of experimental animal tumors (Table III). At therapeutic doses, the leukopenic effect of this derivative is very low.[15] In clinical trials against various forms of neoplastic disease in humans, preliminary data on 65 cases[16] have confirmed the high cytostatic activity and the absence of leucopenic effect at therapeutic doses.

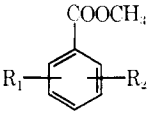
Table III
Antitumor Activity of 3-[N,N-Bis(2-chloroethyl)amino]-4-methylbenzoic Acid (IVj)[a]

Tumor	Dose,[b] mg/kg day	Tumor wt, g T C[c]	Inhib, %	Complete regression[d]
Jensen sarcoma	3.5	0 35.5 ± 3.7	100	10/10
Sarcoma 45	3.5	0 27.4 ± 2.5	100	10/10
Lymphosarcoma	3.5	0.6 ± 0.6 47.0 ± 2.1	98	8/10
Walter 256 carcinosarcoma	3.5	8.6 ± 1.4 52.6 ± 2.4	86	3/10
Guérin T8 carcinoma	3.5	4.1 ± 1.1 29.5 ± 2.9	86	2/10
Sarcoma 180	3.5	1.7 ± 0.6 4.8 ± 0.8	64	0/10
Ehrlich carcinoma	3.5	2.0 ± 0.6 6.2 ± 0.9	67	0/10

[a] Reference 15. [b] LD_{50} = 17.4 mg/kg in rats. [c] T = treated, C = control. [d] After the end of the treatment, leucogram was normal in all cases.

EtOH solution, room temperature, atmospheric pressure) of the corresponding nitro esters, obtained by conventional procedures. The physical constants of the compounds used as starting materials in the hydroxyethylating reaction are shown in Table IV.

Table IV
Amino Esters[a]



Compd[b]	R_1	R_2	Mp, °C	Ir ν_{NH}, cm^{-1}
Ia	2-CH_3	3-NH_2	Oil	1621
Ib	2-CH_3	4-NH_2	68	1631
Ic	2-CH_3	5-NH_2	39–40	1630
Id	2-CH_3	6-NH_2	15–16	1615[c]
Ie	3-CH_3	2-NH_2	Oil	1620
If	3-CH_3	4-NH_2	120–121	1636
Ig	3-CH_3	5-NH_2	67	1630
Ih	3-CH_3	6-NH_2	58	1634
Ii	4-CH_3	2-NH_2	35	1632
Ij	4-CH_3	3-NH_2	116	1632

[a] *Anal.* ($C_9H_{11}NO_2$) N. [b] In the following tables the same letter will designate the same position of the substituents. [c] In CCl_4.

To avoid the drastic conditions of the final acid hydrolysis, benzyl esters of isomers b and d were prepared to be cleaved by final catalytic hydrogenolysis.

Benzyl 6-Nitro-2-methylbenzoate (VId).—6-Nitro-2-methylbenzoic acid (22.2 g, 0.12 mole) (mp 155–156°, lit.[17] mp 155°) was dissolved in 400 ml of dry C_6H_6. After the addition of 26.6 ml (0.13 mole) of $SOCl_2$, the mixture was refluxed for 10 hr. The solvent and the excess of $SOCl_2$ were removed under reduced pressure, then, after addition of 200 ml of benzyl alcohol, the solution was heated for 4 hr at 95–100° under N_2. It was cooled, diluted with H_2O (500 ml), neutralized with Na_2CO_3, and extracted (C_6H_6). After drying the C_6H_6 solution (Na_2SO_4), removal of solvent *in vacuo* gave 18 g (54.2%) of VId, mp 86–87° (from petroleum ether (bp 90–120°)). *Anal.* ($C_{15}H_{13}NO_4$) N.

Benzyl 4-nitro-2-methylbenzoate (VIb) was similarly prepared, but was not isolated, the residue from the benzene solution being reduced as such.

Benzyl 6-Amino-2-methylbenzoate (Id, R = Bz).—To a warm (45°) solution of 1 g (0.0037 mole) of VId in 10 ml of MeOH–AcOH (1:1), a solution of 5 g (0.022 mole) of $SnCl_2 \cdot 2H_2O$ in 5 ml of concentrated HCl was added in small portions with stirring. The temperature rose to 47–48°. The mixture

Experimental Section

Amino Esters.—Methyl esters of aminomethylbenzoic acids (1a–j) were prepared by catalytic hydrogenation (5% Pd-C,

(14) B. M. Wepster, *Rec. Trav. Chim.*, **76**, 357 (1957).

(15) V. Dobre, *Farmacia* (Bucharest), **15**, 103 (1967).

(16) (a) O. Costăchel and I. Mogoş, 5th Scientific Symposium, I.C.C.F. (Chemical-Pharmaceutical Research Institute), Bucharest, 1967; (b) I. Mogoş and O. Costăchel, 5th International Congress of Chemotherapy, Vienna, 1967; (c) O. Costăchel and I. Mogoş, *Chemotherapia*, in press.

(17) D. Peltier, Thèses présentées à la Faculté des Sciences de l'Université de Rennes, 1956, p 22.

was then allowed to cool at room temperature and after 2–3 hr was made strongly alkaline with excess NaOH. The precipitated amine was filtered and converted to 0.8 g (90%) of a hydrochloride, mp 127–129° (from MeOH–H_2O). *Anal.* ($C_{15}H_{15}NO_2 \cdot HCl$) N.

Benzyl 4-amino-2-methylbenzoate (Ib, R = Bz), was similarly prepared, mp 88–90° (from petroleum ether). *Anal.* ($C_{15}H_1NO_2$) N.

Esters of x-[N,N-Bis(2-hydroxyethyl)amino]-y-methylbenzoic Acids (IIa–j).—Ethylene oxide (0.06 mole) was added to a cooled solution of 0.02 mole of I in 50 ml of AcOH. After 24 hr at room temperature, the solution was evaporated under reduced pressure below 70°, and the residue was triturated two to three times with 20 ml of anhydrous toluene and concentrated to dryness *in vacuo*. The resulting oils were purified by the following methods: (A) washing with 10% aqueous Na_2CO_3, triturating with C_6H_6, drying the C_6H_6 solution (Na_2SO_4), treating with active charcoal, and evaporating to dryness under reduced pressure; (B) chromatography on an alumina column in anhydrous C_6H_6; (C) conversion to hydrochlorides (in ethanolic HCl), recrystallization, and recovery of the free base. The hydroxyethyl derivatives are listed in Table V.

TABLE V
HYDROXYETHYL DERIVATIVES[a]

Compd[b]	Mp, °C	Formula[c]	Ir ν_{OH}, cm^{-1}	Purifcn method	Recrystn solvent
IIa	Oil	$C_{13}H_{19}NO_4$	3390	A + B + C	...
IIb	82–83	$C_{13}H_{19}NO_4$	3410, 3450[e]	A	Petr ether[d]
IIb[f]	84–85	$C_{19}H_{33}NO_4$	3336	A + B	Petr ether–C_6H_6
IIc	Oil	$C_{13}H_{19}NO_4$	3350	A + B	...
IId	98–100	$C_{13}H_{19}NO_4$	3460	A	Petr ether
IId[f]	Oil	$C_{19}H_{23}NO_4$	3510	A + B	...
IIe[g]	155	$C_{13}H_{20}ClNO_4$	3290	A + B + C	EtOAc
IIf	71–73	$C_{13}H_{19}NO_4$	3430	A + B	Et_2O
IIg	Oil	$C_{13}H_{19}NO_4$	3412	A + B + C	...
IIh	Oil	$C_{13}H_{19}NO_4$	3470[e]	A + B	...
IIi[g]	157	$C_{13}H_{20}ClNO_4$	3210	A + C	EtOAc
IIj	66–68	$C_{13}H_{19}NO_4$	3420	A + B + C	Petr ether

[a] Methyl esters, except where otherwise noted. [b] See Table IV, footnote *b*. [c] All compounds were analyzed for N. [d] Petroleum ether, bp 90–120°. [e] In CCl_4. [f] Benzyl esters. [g] Hydrochloride.

Esters of x-[N,N-Bis(2-chloroethyl)amino]-y-methylbenzoic Acids (IIIa–j). Method D.—II (0.02 mole) was added under stirring to ~0.4 mole of $POCl_3$, previously cooled at 0°. After the addition, the mixture was heated for 0.5–2 hr on a steam bath (intense evolution of HCl). Excess $POCl_3$ was removed *in vacuo* and traces of $POCl_3$ were decomposed by adding small pieces of ice to the viscous residue. The mixture was extracted (C_6H_6) and the compound was obtained from the benzene solution after drying (Na_2SO_4), chromatography on an alumina column, and concentration under reduced pressure.

Method E.—$SOCl_2$ (0.1–0.15 mole) was added to a solution of 0.02 mole of II in 50 ml of anhydrous C_6H_6 or $CHCl_3$ and the mixture was refluxed for 0.5–1.5 hr. Solvent and excess $SOCl_2$ were removed *in vacuo* with the aid of C_6H_6. The residue was worked up as in method D. Physical constants and analytical data for compounds III are given in Table VI.

TABLE VI
ESTERS OF THE NITROGEN MUSTARDS[a]

Compd[b]	Prepn method	Mp, °C	Formula[c]	Ir $\nu_{C=O}$, cm^{-1}
IIIa	D	Oil	$C_{13}H_{17}Cl_2NO_2$	1721
IIIb	E	85–87	$C_{13}H_{17}Cl_2NO_2$	1709
IIIb[d]	E	61–63	$C_{19}H_{21}Cl_2NO_2$	1716[e]
IIIc	D	Oil	$C_{13}H_{17}Cl_2NO_2$	1722
IIId	D, E	Oil	$C_{13}H_{17}Cl_2NO_2$	1740[e]
IIId[d]	E	Oil	$C_{19}H_{21}Cl_2NO_2$	1732[e]
IIIe	D, E	Oil	$C_{13}H_{17}Cl_2NO_2$	1735
IIIf	D	Oil	$C_{13}H_{17}Cl_2NO_2$	1730[e]
IIIh	D	Oil	$C_{13}H_{17}Cl_2NO_2$	1730
IIIi	D	Oil	$C_{13}H_{17}Cl_2NO_2$	1730
IIIj	D	Oil	$C_{13}H_{17}Cl_2NO_2$	1730[e]

[a] Methyl esters, except where otherwise noted. [b] See Table IV, footnote *b*. [c] All compounds were analyzed for C, H, N, Cl. [d] Benzyl ester. [e] In CCl_4.

x-[N,N-Bis(2-chloroethyl)amino]-y-methylbenzoic Acids (IVa–j). Hydrolysis.—A mixture of 0.01 mole of III and 50 ml of concentrated HCl was refluxed for 0.5–2 hr. The solution was treated with activated charcoal and diluted with H_2O (300 ml) when the nitrogen mustard precipitated. It was filtered and recrystallized from the appropriate solvent.

Hydrogenolysis.—Concentrated HCl (3 ml) and PtO_2 (0.4 g) were added to a solution of 1 g (0.0027 mole) of IIIb (R = Bz) in THF (40 ml). After consumption of the theoretical amount of H_2 (room tempeature, atmospheric pressure), the catalyst was removed by filtration and the solution was evaporated to dryness under reduced pressure. The solid residue was washed (H_2O) and extracted (Et_2O). Evaporation of the dried (Na_2SO_4) ethereal solution gave 0.5 g (67%) of IVb, mp 171–173° (from petroleum ether).

Compound IVd could be obtained neither by acid hydrolysis of the methyl ester (uncrystallizable oils) nor by hydrogenolysis (recovery of the benzyl ester).

Ir Spectra.—The compounds were also characterized by means of their ir spectra, determined on a UR 10 Zeiss Jena spectrophotometer in KBr disks, except where otherwise noted. The carbonyl band (<1700 cm^{-1}) must probably be assigned to the dimeric carboxyl form,[18] except in those isomers in which the nitrogen mustard group is *ortho* to the carboxyl group (IIId, 1740; IVe, 1715; IVh, 1710; IVi, 1715 cm^{-1}). In these cases the acid could exist as a monomer, because of the steric interactions.

Acknowledgments.—Grateful acknowledgment is made to Professor O. Costăchel, whose ideas were the starting point of this work, for his continued interest and assistance. Our thanks are due to Mrs. G. Botez and A. Serban for carrying out the basicity and hydrolysis measurements, to Mr. R. Homescu for the determination of infrared spectra, to Mrs. E. Tărnăuceanu and C. Bogutchi for performing elemental analyses, to Mr. V. Dobre for kindly making the screening data available to us, and to Mrs. M. Isvoranu for technical assistance.

(18) D. Peltier and A. Pichevin, *Bull. Soc. Chim. France*, 1141 (1960).