Anal. Calcd. for $C_{15}H_{21}Cl_2NO_2$.HCl: C, 50.7; H, 6.20; Cl, 30.2; N, 3.95. Found: C, 50.7; H, 6.12; Cl, 30.7; N, 4.02.

p-[Bis(2-chloroethyl)aminomethyl]hydrocinnamic acid hydrochloride (XII). A solution of 0.90 g. (2.5 mmoles) of methyl *p*-[bis(2-chloroethyl)aminomethyl]cinnamate hydrochloride (XII) in 10 ml. of 12*N* hydrochloric acid was refluxed for 30 min., then concentrated to about one-half volume *in vacuo* and cooled in an ice bath. The product was collected on a glass filter; yield, 0.70 g. (81%), m.p. 171–175°. A sample was recrystallized by solution in hot water, then addition of five volumes of 12*N* hydrochloric acid to give white crystals, m.p. 176–177°; $\lambda_{max\ \mu}^{Nujol}$ 3.75, 3.87 (NH^+ and acidic OH); 5.80 (carboxyl C=O); 12.0 (*p*-disubstituted benzene); 13.4 (C—Cl).

Anal. Calcd. for $C_{14}H_{19}Cl_2N_2O_2$.HCl: C, 49.3; H, 5.87; Cl, 31.3; N, 4.12. Found: C, 49.2; H, 5.95; Cl, 31.1; N, 4.15.

Methyl p-(aminomethyl)hydrocinnamate hydrochloride (X). To a stirred solution of 7.0 g. (0.050 mole) of hexamethylenetetramine[14] in 100 ml. of 95% methanol was added 8.5 g. (0.050 mole) of potassium iodide followed by 10.6 g. (0.050 mole) of methyl *p*-(chloromethyl)hydrocinnamate (VII). The reaction mixture was refluxed with stirring for 40 min., then filtered hot to remove potassium chloride. The filtrate was cooled to 0° and deposited 20.0 g. (115%) of the hexamine complex that was contaminated with some salts.

A suspension of 20 g. of the hexamine complex in 150 ml. of methanol was saturated with hydrogen chloride,[14] refluxed for 30 min., then evaporated to dryness *in vacuo*. The residue was dissolved in hot dichloromethane and filtered from some inorganic material. Evaporation of the combined filtrate and washings to dryness *in vacuo* afforded 8.8 g. (77%) of an amorphous solid, m.p. 150–155°, that gave a paper chromatogram and infrared absorption spectrum identical with the analytical sample. Crystallization of a sample from methanol ether afforded white crystals, m.p. 208–217°; $\lambda_{max\ \mu}^{Nujol}$ 3.50, 4.20, 4.85 (NH^+); 5.72 (ester C=O); 8.50 (ester C—O—C); 12.1 (*p*-disubstituted benzene). The compound traveled as a single spot (R_f 0.76) in solvent B[11] when detected by iodoplatinate spray (gray color).

This compound (X), when allowed to react in the usual manner[8] with ethylene oxide in dilute acetic acid containing an equivalent of sodium acetate, was not converted to IX as expected, but was recovered unchanged. It appears that hydroxyethylation in dilute acetic acid fails to take place because of the stronger protonation of aliphatic amines, such as X, compared to the arylamines usually employed under these conditions.[8]

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MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XLVI. Analogs of Chlorambucil. V.[2] Alkylating Agents Derived from ω-Phenoxyalkanoic Acids

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Several analogs of the chlorambucil isostere 3-*p*-{[bis(2-chloroethyl)amino]phenoxy}propionic acid (I, $n = 2$) have been synthesized for evaluation as potential anticancer agents and as potential irreversible inhibitors of lactic dehydrogenase.

A series of ω-{*p*-[bis(2-chloroethyl)amino]phenoxy}alkanoic acids (I) have been synthesized[3] and evaluated as anticancer agents against Walker rat Sarcoma 256. All four of these acids showed inhibitory action. The maximum effect was shown by the propionic acid derivative (I, $n = 2$), which was considered[3] to be an isostere of chlorambucil, 4-{*p*-[bis(2-chloroethyl)amino]phenyl}butyric acid.[4] As *m*-phenylalanine mustard[5] appears to be more effective against some tumors[6] than *p*-phenylalanine mustard,[7,8] the synthesis of the *o*- and *m*-isomers of I ($n = 1,2$) was deemed advisable in order to determine whether or not these changes would cause a change in tumor spectrum.[9,10] These

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(2) For paper IV on chlorambucil analogs, see W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, *J. Org. Chem.*, 25, 148 (1960), Paper XLIII of this series.

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(4) J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 2386 (1953).

(5) H. F. Gram, C. W. Mosher, and B. R. Baker, Paper XVII of this Series, *J. Am. Chem. Soc.*, 81, 3103 (1959).

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(7) F. Bergel, V. C. E. Burnop, and J. A. Stock, *J. Chem. Soc.*, 1223 (1955); F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954). These authors use the synonym of Merphalan for the racemate of *p*-phenylalanine mustard and Melphalan for the L-isomer.

(8) L. F. Larionov, A. S. Khokhlov, E. N. Shkodinskaia, O. S. Vasina, V. I. Trusheikina, and A. M. Novikova, *Lancet*, 269, 169 (1955). These authors use the synonym of sarcolysin for the racemate of *p*-phenylalanine mustard.

compounds are also of interest as potential irreversible inhibitors of lactic dehydrogenase.[11]

The synthesis of [*m*-[bis(2-chloroethyl)amino]-phenoxy]acetic acid (VI) and 3-{*m*-[bis(2-chloroethyl)amino]phenoxy}propionic acid (VII) was similar to the route used earlier for the synthesis of the *para* series (I).[3]

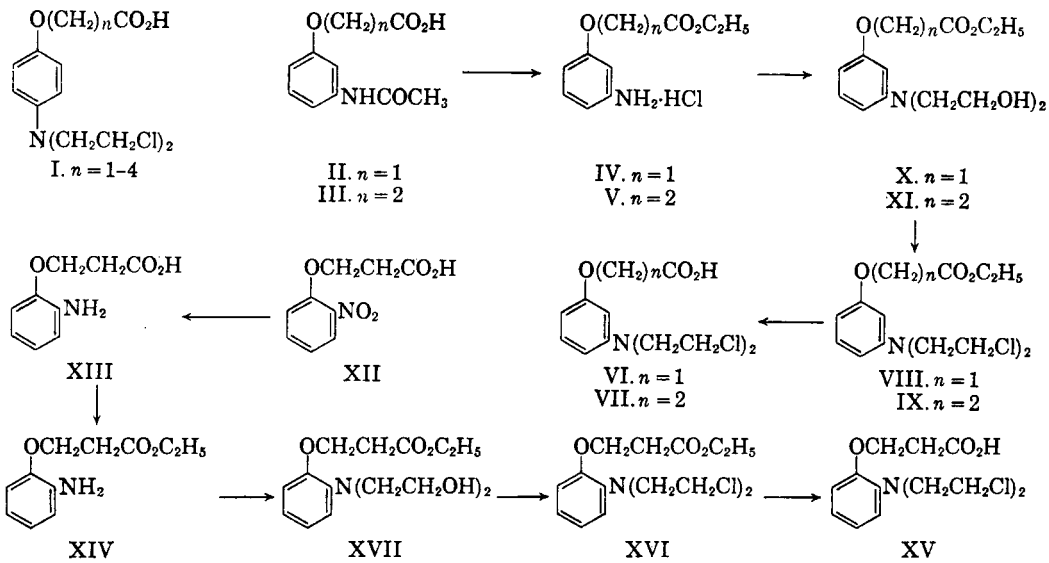
(*m*-Acetamidophenoxy)acetic acid (II) was prepared from *m*-hydroxyacetanilide in 72% yield by the method of Howard.[12] Simultaneous alcoholysis of the acetamido group and esterification with ethanolic hydrogen chloride gave crystalline ethyl (*m*-aminophenoxy)acetate hydrochloride (IV) in 62% yield. Hydroxyethylation using ethylene oxide in aqueous acetic acid afforded ethyl {*m*-[bis(2-hydroxyethyl)amino]phenoxy}acetate (X) as a nearly analytically pure oil in 92% yield that was uniform when chromatographed on paper in System A,[13] showing a single spot (R_f 0.61).

Chlorination of X by refluxing in phosphorus oxychloride for fifteen minutes gave ethyl {*m*-[bis(2-chloroethyl)amino]phenoxy}acetate (VIII) in 88% yield as a low-melting solid, m.p. 38–39°, R_f 0.52 in System A.[13] Hydrolysis of VIII with hot concentrated hydrochloric acid gave the desired *m*-phenoxyacetic acid mustard (VI) in 87% yield as an analytically pure solid.

Ethyl 3-(*m*-aminophenoxy)propionate hydrochloride (V) was prepared in 82% yield by simultaneous alcoholysis and esterification of 3-(*m*-acetamidophenoxy)propionic acid (III) with alcoholic hydrogen chloride. Hydroxyethylation of V with ethylene oxide in aqueous acetic acid proceeded smoothly to give a quantitative yield of ethyl 3-{*m*-[bis(2-hydroxyethyl)amino]phenoxy}propionate (XI) obtained as an analytically pure solid, m.p. 53–54°, R_f 0.61 (System A[13]). Treatment of XI for thirty minutes in hot phosphorus oxychloride gave a 96% yield of ethyl 3-{*m*-[bis(2-chloroethyl)amino]phenoxy}propionate (IX), m.p. 31–32°, R_f 0.61 (System A[13]).

Hydrolysis of IX with hot concentrated hydrochloric acid yielded the desired *m*-phenoxypropionic acid mustard (VII) in 88% yield, m.p. 138–139°. The analytical sample traveled as a single spot (R_f 0.70) on paper in System A.[13]

Attempts to react *o*-hydroxyacetanilide with 3-bromopropionic acid in aqueous sodium hydroxide resulted in low yields (8%) of 3-(*o*-acetamidophenoxy)propionic acid. By the method of Chakravarti and Dutta,[14] *o*-nitrophenol and 3-bromopropionic acid were allowed to react in aqueous sodium hydroxide to give a 30% yield of 3-(*o*-nitrophenoxy)propionic acid (XII). Hydrogenation of XII with palladium-on-charcoal at room temperature and atmospheric pressure afforded crystalline 3-(*o*-aminophenoxy)propionic acid (XIII) in 82% yield, readily esterified to XIV with ethanolic hydrogen



The reaction of *m*-hydroxyacetanilide with 3-bromopropionic acid in alkaline solution gave 3-(*m*-acetamidophenoxy)propionic acid (III) as an analytically pure hydrated solid in 17% yield. Substitution of lithium hydroxide for sodium hydroxide or ethyl 3-bromopropionate for 3-bromopropionic acid resulted in none of the desired product (III). A 6% yield of III was obtained when the reaction was carried out in absolute ethanol using sodium ethoxide in place of sodium hydroxide.

(9) J. Scholler, E. Tholen, and L. H. Schmidt, *Proc. Am. Assoc. Cancer Research*, 3, 60 (1959).

(10) L. F. Larionov, *Akad. Med. Nauk. Vestnik*, 14, No. 6, 25 (1959).

(11) B. R. Baker, *Cancer Chemotherapy Reports*, 4, 1 (1959), published by the National Cancer Institute.

(12) C. C. Howard, *Ber.*, 30, 546 (1897).

(13) Paper chromatograms were run by the descending technique with benzene–methanol–water (2/6/1) on Schleicher and Schuell No. 2495 acetylated paper (System A) or on Whatman No. 1 paper (System B). Spots were detected by visual examination under ultraviolet light.

(14) D. Chakravarti, and J. Dutta, *J. Indian Chem. Soc.*, 16, 639 (1939).

chloride in 88% yield. Hydroxyethylation of the free base of XIV with ethylene oxide in aqueous acetic acid gave ethyl 3-{*o*-[bis(2-hydroxyethyl)-amino]phenoxy}propionate (XVII) as a nearly analytically pure viscous oil in 81% yield, which was homogeneous on paper in System A[13] (R_f 0.74). As in all of the hydroxyethylation reactions, thorough washing of a dichloromethane solution of the bishydroxyethyl compound (XVII) with water was necessary to remove polymeric glycol by-products. Chlorination of XVII in the usual manner with phosphorus oxychloride resulted in 82% yield of XVI as an amber oil, which melted below 20° and had R_l 0.71 in System A.[13]

Hydrolysis of XVI with concentrated hydrochloric acid gave 3-{*o*-[bis(2-chloroethyl)amino]-phenoxy}propionic acid (XV) as a pure solid, m.p. 71.5–73°, in 87% yield.[15] In common with the other phenoxyalkanoic acid mustards, this compound (XV) is light-sensitive, giving a green coloration upon exposure.

Attempts to chlorinate the various bis(hydroxyethyl)amines with thionyl chloride in methylene chloride or chloroform resulted in low yields of the mustards and led to difficulties in purification of the final compounds. Phosphorus oxychloride was found to give a much cleaner chlorination in this series.

EXPERIMENTAL[16]

3-(m-Acetamidophenoxy)propionic acid (III). To a hot solution of 1.51 g. (10 mmoles) of *m*-hydroxyacetanilide in 10 ml. of 4% aqueous sodium hydroxide was added a solution of 1.53 g. (10 mmoles) of 3-bromopropionic acid in 20 ml. of water containing 0.40 g. of sodium hydroxide. The solution was placed on a steam-bath and allowed to evaporate overnight. The residue was dissolved in 10 ml. of water, acidified to *p*H 5 and cooled in an ice bath. The unchanged phenol was removed by filtration, then the combined filtrate and washings were acidified to *p*H 1; yield, 0.41 g. (17%) of product m.p. 70–100°, resolidifies and remelts at 130–131°; $\lambda_{max(\mu)}^{Nujol}$ 2.97 (NH and H_2O); 325–4.00 (acidic OH); 5.83 (carboxyl C=O); 6.05, 6.35 (amide); 13.00 (*m*-disubstituted benzene).

Anal. Calcd. for $C_{11}H_{13}NO_4.H_2O$: C, 54.8; H, 6.27. Found: C, 54.4; H, 6.48.

Ethyl 3-(m-aminophenoxy)propionate hydrochloride (V). A solution of 18.6 g. (0.084 mole) of 3-(*m*-acetamidophenoxy)-propionic acid (III) in 240 ml. of absolute ethanol saturated with hydrogen chloride was refluxed for 1 hr., cooled, and concentrated to dryness *in vacuo* leaving 21.6 g. (105%) of solid, m.p. 95–99°. Recrystallization from ethyl acetate gave 16.8 g. (82%) of crystals, m.p. 112–113°; $\lambda_{max(\mu)}^{Nujol}$ 3.85, 4.85 (NH_3^+); 5.75 (ester C=O); 8.40, 8.52 (ester C—O—C); 12.90 (*m*-disubstituted benzene); no amide band near 6.0. The compound traveled as a single spot (R_f 0.57) in System A[13] on paper.

Anal. Calcd. for $C_{11}H_{15}NO_3.HCl$: C, 53.8; H, 6.52; Cl, 14.1. Found: C, 53.7; H, 6.62; Cl, 14.1.

Similarly, 15.0 g. of (*m*-acetamidophenoxy)acetic acid (II)[12] gave, after recrystallization from ethyl acetate, 10.3 g. (62%) of *ethyl (m-aminophenoxy)acetate hydrochloride* (IV), m.p. 129–130°; $\lambda_{max(\mu)}^{Nujol}$ 3.85, 4.97 (NH_3^+); 5.72 (ester C=O); 8.45, 8.65 (ester C—O—C); 12.95 (*m*-disubstituted benzene). The compound traveled as a single spot (R_f 0.45) in System A.[13]

Anal. Calcd. for $C_{10}H_{13}NO_3.HCl$: C, 51.9; H, 6.05. Found: C, 52.3; H, 6.22.

3-(o-Aminophenoxy)propionic acid (XIII). A mixture of 1.00 g. (4.7 mmoles) of 3-(*o*-nitrophenoxy)propionic acid (XII),[14] 75 mg. of 5% palladium-on-charcoal moistened with 2-methoxyethanol and 50 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure for 15 min. when reduction was complete. The catalyst was removed by filtration and the combined filtrate and washings were evaporated to dryness *in vacuo* leaving 0.70 g. (82%) of tan needles, m.p. 105–106°; $\lambda_{max(\mu)}^{Nujol}$ 3.60–4.00 (acidic OH); 5.95 (acid C=O); 13.17 (*o*-disubstituted benzene).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.7; H, 6.12. Found: C, 59.3; H, 5.97.

Ethyl 3-(o-aminophenoxy)propionate hydrochloride (XIV). A solution of 2.68 g. (0.015 mole) of 3-(*o*-aminophenoxy)-propionic acid (XII) in 30 ml. of absolute ethanol saturated with hydrogen chloride was refluxed for 1 hr. The solution was evaporated to dryness *in vacuo* and the residue triturated with ether; yield 3.20 g. (88%), m.p. 172–173°; $\lambda_{max(\mu)}^{Nujol}$ 3.50–4.50 (NH^+); 5.79 (ester C=O); 8.25, 8.41, 8.54 (ester C—O—C); 13.20 (*o*-disubstituted benzene). The compound traveled as a single spot (R_f 0.46) in System A.[13]

Anal. Calcd. for $C_{11}H_{15}NO_3.HCl$: C, 53.9; H, 6.53. Found: C, 53.8; H, 6.71.

Ethyl m-[bis(2-hydroxyethyl)amino]phenoxyacetate (X). To a solution of 12.1 g. (0.052 mole) of ethyl (*m*-aminophenoxy)acetate hydrochloride (IV) in 150 ml. of water was added 5.0 g. of sodium bicarbonate, 82 ml. of glacial acetic acid, and 10 ml. of ethanol. The stirred solution was cooled to −5° in an ice bath and 30 ml. of ethylene oxide was added slowly. The reaction flask was stoppered and the mixture stirred for 24 hr. at room temperature. The solution was neutralized with solid sodium bicarbonate and extracted with dichloromethane (3 × 125 ml.). The combined extracts were washed with water (4 × 125 ml.) to remove glycol polymers and then dried over anhydrous magnesium sulfate. The solution was evaporated *in vacuo* to yield 15.0 g. (100%) of a light reddish oil. The oil was dissolved in hot ether, the ether solution was filtered, the concentrated *in vacuo* to yield 14.0 g. (92%) of a light red oil; $\lambda_{max(\mu)}^{film}$ 3.00 (OH); 5.78 (ester); 8.50 (ester C—O—C); 9.0 10.0 (C—OH); 13.3 (*m*-disubstituted benzene). The compound traveled as a single spot (R_f 0.61) in System A[13] and was essentially pure.

Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.4; H, 7.47. Found: C, 58.9; H, 7.57.

Ethyl 3-{m-[bis(2-hydroxyethyl)amino]phenoxy}propionate (XI). Hydroxyethylation of ethyl 3-(*m*-aminophenoxy)-propionate hydrochloride (V), as described for the preparation of X, gave a quantitative yield of product that crystallized on standing and was suitable for the next step. Recrystallization of a sample from ether gave crystals with m.p. 53–54° and $\lambda_{max(\mu)}^{Nujol}$ 2.95, 9.49, 9.68 (C—OH); 5.82, 8.30, 8.36, 8.50 (ester); 13.50 (*m*-disubstituted benzene). The compound traveled in System A[13] as a single spot with R_f 0.65.

Anal. Calcd. for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.80. Found: C, 60.9; N, 7.96.

Similarly, ethyl *3-{o-[bis(2-hydroxyethyl)amino]phenoxy}-propionate* (XVII) was obtained in 81% yield as an essentially pure oil with R_f 0.74 in System A[13] and $\lambda_{max(\mu)}^{film}$ 2.95, 9.30–9.80 (C—OH); 5.75, 8.40 (ester); 13.30 (*o*-disubstituted benzene).

Anal. Calcd. for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.80; N, 4.71. Found: C, 60.0; H, 8.17; N, 4.33.

(15) This route was not considered feasible for synthesis of *o*-phenoxyacetic acid mustard, because of the ease of lactam formation of (*o*-aminophenoxy)acetic acid and its derivatives.

(16) Melting points were taken on a Fisher-Johns block and are uncorrected.

Ethyl m-[bis(2-chloroethyl)amino]phenoxy acetate (VIII). A mixture of 1.0 g. (3.5 mmoles) of ethyl *m*-[bis(2-hydroxyethyl)amino]phenoxy acetate (X) and 7.5 ml. of freshly distilled phosphorus oxychloride was refluxed for 15 min. The green-colored solution was poured into 100 ml. of ice and stirred well for 10 min. The mixture was neutralized with sodium acetate to *p*H 5 and extracted with 100 ml. of dichloromethane. The extract was washed with 50 ml. of water, dried over anhydrous magnesium sulfate, then concentrated *in vacuo* to yield a yellow-green oil. This oil was dissolved in 10 ml. of dichloromethane and 50 ml. of toluene and evaporated to dryness (bath 50°) *in vacuo* to remove acetic acid. The residue oil crystallized upon standing; yield, 1.0 g. (88%), m.p. 38–39°; $\lambda_{max(\mu)}^{film}$ 5.63 (ester C=O); 8.30, 8.56 (ester C—O—C); 13.30 (*m*-disubstituted benzene); free of COH near 3.0 and 9.5. The compound traveled as a single spot (R_f 0.52) in System A.[13]

Anal. Calcd. for $C_{14}H_{19}Cl_2NO_3$: C, 52.5; H, 5.95; Cl, 22.2. Found: C, 52.3; H, 6.29; Cl, 22.1.

Ethyl 3-{m-[bis(2-chloroethyl)amino]phenoxy}propionate (IX). The chlorination of 1.0 g. (3.0 mmoles) of ethyl 3-{*m*-[bis(2-hydroxyethyl)amino]phenoxy}propionate (XI) was performed in essentially the same manner as described for X except that XI was heated for 30 min. with phosphorus oxychloride on a steam bath, rather than refluxed for 15 min. The product (IX), after crystallization from ether-petroleum ether (b.p. 30–60°), was obtained in 96% yield, m.p. 31–32°; $\lambda_{max(\mu)}^{Nujol}$ 5.78 (ester C=O); 8.40, 8.60 (ester C—O—C); 13.32 (*m*-disubstituted benzene); 13.90 (C—Cl); absence of OH near 3.0 and 9.5. The compound traveled as a single spot (R_f 0.61) in System A.[13]

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_3$: C, 53.9; H, 6.29; Cl, 21.3. Found: C, 54.1; H, 6.49; Cl, 21.5.

Ethyl 3-{o-[bis(2-chloroethyl)amino]phenoxy}propionate (XVI). Treatment of 1.0 g. (3.0 mmoles) of ethyl 3-{*o*-[bis-(2-chloroethyl)amino]phenoxy}propionate (XVIII) with phosphorus oxychloride in the same manner as for X yielded 0.95 g. (82%) of a light amber oil which crystallized to fine needles melting below 20°; $\lambda_{max(\mu)}^{film}$ 5.72 (ester C=O); 8.42 (ester C—O—C); 13.30 (*o*-disubstituted benzene); 13.90 (C—Cl); absence of OH near 3.0 and 9.5. The compound traveled as a single spot (R_f 0.71) in System A,[13] and analysis showed it was nearly pure.

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_3$: C, 53.9; H, 6.29; Cl, 21.3; N, 4.19. Found: C, 54.7; H, 6.53; Cl, 20.7; N, 4.34.

{m-[Bis(2-chloroethyl)amino]phenoxy}acetic acid (VI). A solution of 0.10 g. (0.30 mmole) of ethyl {*m*-[bis(2-chloroethyl)amino]phenoxy}acetate (VIII) in 2 ml. of concd. hydrochloric acid was refluxed for 10 min., cooled, and neutralized with sodium acetate to *p*H 5. The product was extracted with 25 ml. of dichloromethane; the extract was washed with 10 ml. of water, dried over anhydrous magnesium sulfate, then concentrated to dryness *in vacuo*. The white solid was dissolved in toluene and again concentrated *in vacuo* to yield 0.080 g. (87%) of white crystals m.p. 127–128°; $\lambda_{max(\mu)}^{Nujol}$ 3.50–4.00 (acidic OH); 5.72 (carboxyl C=O); 13.28 (*m*-disubstituted benzene); 13.45 (C—Cl). The compound traveled as a single spot (R_f 0.87) in System B.[13]

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_3$: C, 49.3; H, 5.14; Cl, 24.3. Found: C, 49.6; H, 5.43; Cl, 24.4.

3-{m-[Bis(2-chloroethyl)amino]phenoxy}propionic acid (VII). The hydrolysis of 0.90 g. (3.0 mmoles) of ethyl 3-{*m*-[bis(2-chloroethyl)amino]phenoxy}propionate (IX) was carried out in the same manner as was that of VIII except that the time of reflux was lengthened to 30 min. An 88% yield of product, m.p. 134–136°, was obtained. Recrystallization from petroleum ether (b.p. 30–60°) gave an analytical sample, m.p. 138–139°; $\lambda_{max(\mu)}^{Nujol}$ 3.50–4.00 (acidic OH); 5.83 (carboxy C=O); 13.30 (*m*-disubstituted benzene); 13.90 (C—Cl); absence of OH near 3.0. The compound traveled as a single spot (R_f 0.70) on paper in System A.[13]

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3$: C, 51.0; H, 5.55; Cl, 23.2; N, 4.57. Found: C, 51.1; H, 5.62; Cl, 23.1; N, 4.75.

3-{o-[Bis(2-chloroethyl)amino]phenoxy}propionic acid (XV). Hydrolysis of 0.50 g. (1.5 mmoles) of ethyl 3-{*o*-[bis-(2-chloroethyl)amino]phenoxy}propionate (XVI) with concd. hydrochloric acid in the same manner as described for VIII yielded 0.40 g. (87%) of crystalline product, m.p. 65–67°. Recrystallization from petroleum ether (b.p. 30–60°) yielded an analytical sample, m.p. 71.5–73°; $\lambda_{max(\mu)}^{Nujol}$ 3.80–4.20 (acidic OH); 5.80 (carboxyl C=O); 13.00 (*o*-disubstituted benzene); 13.89 (C—Cl). The compound traveled as a single spot (R_f 0.77) in System A.[13]

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3$: C, 51.0; H, 5.56; Cl, 23.2; N, 4.57. Found: C, 50.9; H, 5.60; Cl, 22.9; N, 4.61.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Chiapagenin and Isochiapagenin. Two New Steroidal Sapogenins from *Dioscorea chiapasensis*[1]

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Dioscorea chiapasensis Matuda was found to contain diosgenin, yamogenin, correlogenin (neobotogenin), and two new dihydroxy sapogenins, now named chiapagenin and isochiapagenin. Chiapagenin was shown to be 12β-hydroxyyamogenin by appropriate interconversions with correlogenin and with sisalagenin. Isochiapagerin has been identified as 12β-hydroxydiosgenin.

During the past few years relatively few new steroidal sapogenins have been isolated, most of them being C-1 hydroxylated steroids (*e.g.*, ruscogenin, rhodeasapogenin, tokorogenin, kogagenin).[3] Of particular interest is the recent report by

(1) Supported by a research grant from The Rockefeller Foundation.

(2) Research Laboratories, Syntex, S.A., Mexico, D. F.

(3) For detailed review and references on these and other steroidal sapogenins see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, chap. 21.