free of starting material according to paper chromatography and infrared spectroscopy. Deacetylation of 150 mg. of the triacetate (XX) with methanolic sodium methoxide in the usual fashion gave 75 mg. (71%) of the desired product (XXI), m.p. 211.0–212.5° dec. Recrystallization from water gave the analytical sample, m.p. 227–228° dec.; $[\alpha]^{33}D$ −80° (1% in 0.1 *N* sodium hydroxide); $\lambda_{max}^{pH\ 1}$ 322.5 mμ (ε 23,000), $\lambda_{max}^{pH\ 7}$ 318 mμ (ε 18,500), $\lambda_{max}^{pH\ 13}$ 311.5 mμ (ε 23,000). The product was homogeneous on paper chromatography with R_{Ad} 1.74 (solvent B).

Anal. Calcd. for $C_{11}H_{14}N_4O_4S$: C, 44.3; H, 4.73; N, 18.8; S, 10.7. Found: C, 44.1; H, 4.64; N, 18.9; S, 10.9.

Acknowledgment.—The authors are indebted to Dr. Peter Lim and staff for the paper chromatograms, optical rotations, ultraviolet spectra, and interpretation of the infrared spectra, and to Mr. O. P. Crews and his staff for the large-scale preparations of intermediates.

Potential Anticancer Agents. LXXVIII.[1] Nonclassical Antimetabolites. IV.[2] Synthesis of Compounds Related to 4-(Iodoacetamido)salicylic Acid, an Exo-Alkylating Irreversible Inhibitor

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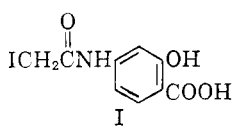
A number of compounds that are related to 4-(iodoacetamido)salicylic acid, an exo-alkylating irreversible enzyme inhibitor, have been synthesized in order to make them available for enzyme studies. These compounds are derivatives of oxanilic and salicylic acids that contain alkylating groups such as haloacyl, haloacetamido, and nitrogen mustard functions.

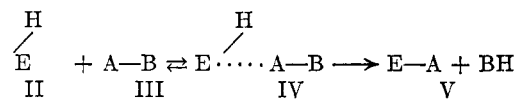
Nonclassical antimetabolites—relatively large molecules compared to the substrate—capable of inhibiting the lactic acid dehydrogenase (LDH) catalyzed reduction of pyruvate by reduced diphosphopyridine nucleotide (DPNH) have been found.[5] Examples are such compounds as salicylate, oxanilate, and phenylpyruvate, with I_{50} values[6] of 19, 14, and 21, respectively.

These compounds also inhibited the glutamic acid dehydrogenase (GDH) catalyzed conversion of L-glutamate to α-oxoglutarate with I_{50} values of 20, 19, and 36, respectively. Therefore, 4-(iodoacetamido)salicylic acid (I) was investigated as a possible irreversible inhibitor of these two enzymes.



I

In a previous paper,[2] it was shown that I was an irreversible inhibitor of both LDH and GDH. Strong evidence was presented[2] that this inhibitor complexed reversibly with the active site of these enzymes, then became irreversibly bound by alkylation of the enzyme adjacent to the active site; this phenomenon was predicted earlier[7] and was termed "exo-alkylation." The phenomenon of exo-alkylation is shown diagramatically by the sequence II–V. An important facet of this problem



was to eliminate the possibility that II and III reacted bimolecularly with direct formation of V without intervention of the reversible complex, IV; this type of irreversible inhibition was termed "tail-alkylation."[2] In the case of I and GDH, only exo-alkylation took place and there was no measurable amount of tail-alkylation.[2] Similarly, I and LDH interacted by the exo-alkylation route, but the possibility of a small amount of tail-alkylation could not be eliminated.[8]

A series of compounds related to I that might be more selective for one enzyme over the other were needed. These compounds can be grouped as follows: (1) variation of the bridge length in the reversible complex (IV) between the halogen and

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute National Institute of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series see E. J. Reist, A. Benitez, W. W. Lee, B. R. Baker, and L. Goodman *J. Org. Chem.*, **27**, 3279 (1962).

(2) For paper III see B. R. Baker, W. W. Lee, E. Tong, and L. O. Ross, *J. Am. Chem. Soc.*, **83**, 3713 (1961).

(3) School of Pharmacy, University of Buffalo, Buffalo 14, New York.

(4) To whom inquiries should be sent.

(5) B. R. Baker, W. W. Lee, W. A. Skinner, A. P. Martinez, and E. Tong, *J. Med. Pharm. Chem.*, **2**, 633 (1960), paper II on nonclassical antimetabolites.

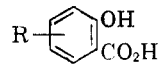
(6) An I_{50} value is defined[5] as the millimolar concentration of inhibitor necessary to give 50% reversible inhibition of an enzyme in the presence of 1 millimolar concentration of substrate.

(7) B. R. Baker, *Cancer Chemotherapy Reports*, No. **4**, 1 (1959), National Cancer Institute, paper I on nonclassical antimetabolites.

(8) B. R. Baker, W. W. Lee, and E. Tong, *J. Theoretical Biology*, in press.

TABLE I

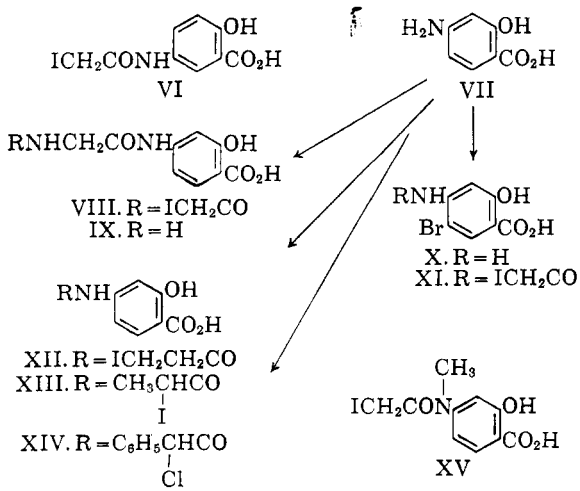
4- or 5-(α-HALOACYLAMIDO)SALICYLIC ACIDS



Compound	Substituents	M.p., °C.[a]	Yield, %[a]	R_f[b]	Formula		C	H	X[c]	N
VI	5-(ICH_2CONH)	244–246[d] (237–239)	20 (34)	0.95 (D)	$C_9H_8INO_4$	Calcd.			39.6	
						Found			39.2, 39.5	
VIII	4-($ICH_2CONHCH_2CONH$)	235–237[d] (220–225)	44 (84)	0.75 (E)	$C_{11}H_{11}IN_2O_5$	Calcd.	34.9	2.91	33.5	7.47
						Found	34.7	2.89	33.5	7.39
XI	5-Br-4-(ICH_2CONH)	230–232[d] (233–235)	36 (63)	[e]	$C_9H_7BrINO_4$	Calcd.	26.5	1.76	19.9[f], 31.7	3.52
						Found	26.9	1.81	19.8[f], 31.6	3.52
XII	4-(ICH_2CH_2CONH)	228–230[g] (220–228)	35 (75)	0.83 (A)	$C_{10}H_{10}INO_4$	Calcd.	35.8	3.00	37.5	4.17
						Found	36.0	3.15	37.6	4.25
XIII	4-($CH_3CHICONH$)	233–235[h] (187–190)	60 (72)	0.22 (B)	$C_{10}H_{10}INO_4$	Calcd.	35.8	3.00	37.5	4.17
						Found	35.5	2.69	37.7	4.15
XIV	4-($C_6H_5CHClCONH$)[i]	208–210[j] (198–200)	50 (63)	0.84 (A)	$C_{15}H_{12}ClNO_4$	Calcd.	59.1	3.96	11.6	4.59
						Found	59.1	3.61	11.7	4.67
XV	4-($ICH_2CON(CH_3)$)	159–160[k] (157–160)	63 (74)	0.22 (B), 0.85 (F)	$C_{10}H_{10}INO_4$	Calcd.	35.8	3.00	37.5	4.17
						Found	35.5	3.08	37.7	4.18

[a] Melting points and yields are for analytical samples. Corresponding values in parentheses are for crude product. [b] See ref. 33 for solvent system code. [c] X is appropriate halogen. [d] Recrystallized from ethanol. [e] Not separable from starting material in solvent systems tried. [f] First value is for Br; second, for I. [g] Recrystallized from 1,2-dimethoxyethane–Skellysolve B (1:1). [h] Recrystallized from acetone–water. [i] See ref. 39 for synthesis of α-chlorophenylacetyl chloride. [j] Recrystallized from 40% ethanol. Reported m.p. 200–202° in ref. 9. [k] Triturated with hot benzene.

the nucleophilic group on the enzyme (compounds VI, VIII, XII); (2) bulk tolerance of the enzyme (II) near this nucleophilic group on the enzyme that could be used to differentiate the enzymes or to decrease the extent of tail-alkylation (compounds XI, XIII, XIV, XV); (3) other alkylating groups attached to salicyclic acid that may differentiate the enzymes by the fact that the nucleophilic group involved on LDH and GDH may not be the same (compounds XXXIA, XLIVA, and XLVI); (4) the effect of oxanilic acid[5] as a carrier of an alkylating function (compounds LIII, LVII, and LX). This paper describes the synthesis of these compounds; the biological results will be reported in a subsequent paper.



The various N-acylaminosalicylic acids that form groups 1 and 2 were prepared by the general method of condensing the appropriate acyl chloride with the appropriate aminosalicylic acid in aqueous solution containing excess sodium bicarbonate. Thus, 4-(β-iodopropionamido)salicylic acid (XII), 4-(α-iodopropionamido)salicylic acid (XIII), and 4-(α-chloro-α-phenylacetamido)salicylic acid (XIV)[9] were readily obtained from 4-aminosalicylic acid (VII). In a similar way, 5-(iodoacetamido)salicylic acid (VI) was obtained from 5-aminosalicylic acid and iodoacetyl chloride. The general procedure is illustrated in the Experimental by the preparation of VI. The results for the others are summarized in Table I.

Two methods were investigated for the preparation of 4-(iodoacetyl-glycylamino)salicylic acid (VIII). Condensation of 4-aminosalicyclic acid and iodoacetylglycine by the mixed anhydride method gave unattractive oils. The reaction of 4-(glycylamino)salicylic acid (IX)[10] with iodoacetyl chloride in cold aqueous sodium hydroxide, however, gave an 84% yield of VIII. The glycylamino acid (IX) was prepared in excellent yield by reaction of 4-(chloroacetamido)salicylic acid[9] with concentrated aqueous ammonia.

5-Bromo-4-(iodoacetamido)salicyclic acid (XI) was obtained by the same general method of condensing iodoacetyl chloride with 4-amino-5-bromosalicylic acid (X).[11]

(9) C. van der Stelt, A. J. Z. Vourspuij, and W. Th. Nauta, *Arzneimittel-Forsch.*, **4**, 544 (1954).

(10) A. A. Goldburg and N. L. Thomas, British Patent 665,675, January 30, 1952, reported m.p. 218–222° for IX. Our product appeared to exist as an internal salt that did not melt below 300° and was chromatographically homogeneous.

4-[(N-Methyl)iodoacetamido]salicylic acid (XV) was also readily obtained by the reaction of iodoacetyl chloride with 4-(methylamino)salicylic acid (XXV), whose preparation will be described later.

In synthesizing the three salicylic acid mustards (XXXIA, XLIVA, and XLVI) and 4-[(N-methyl)-iodoacetamido]salicylic acid (XV), the main problem was suitably to block and deblock the three functional groups of 4-aminosalicylic acid so that the appropriate groups could be attached to the group. Unsuccessful attempts directly to hydroxyethylate 4-aminosalicylic acid made it clear that a blocked derivative of that acid would be required. One additional concern was the extreme ease of acid decarboxylation of salicylic acid derivatives that have electron-donating substituents.[12]

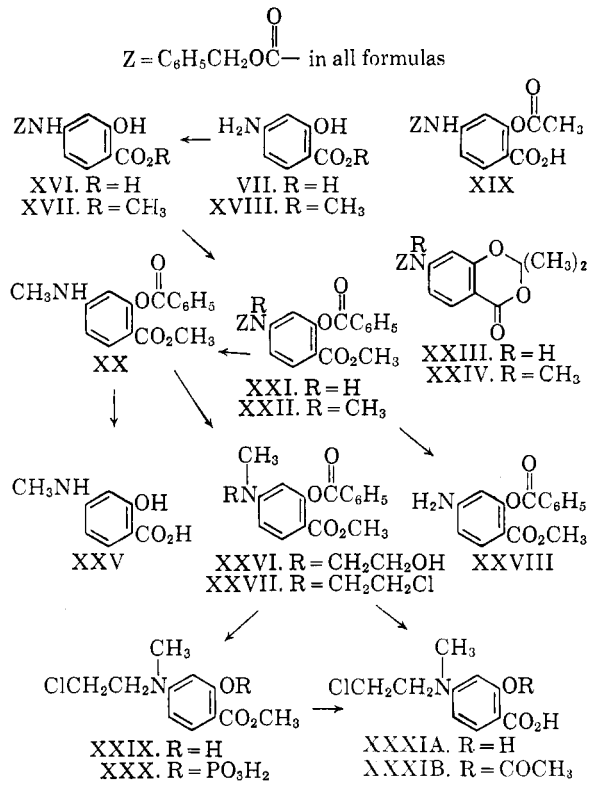
An attempt simultaneously to block the phenolic and carboxyl groups of 4-aminosalicylic acid did not lead to a useful intermediate. Mowry and colleagues[13] have converted salicylic acid to various benzo-1,3-dioxan-4-ones by reaction with enol acetates or aldehyde diacetates in the presence of sulfuric acid and mercuric salts. In the present work, 4-(benzyloxycarbonylamino)salicylic acid (XVI), prepared from 4-aminosalicylic acid and carbobenzoxy chloride in cold aqueous sodium bicarbonate, was converted in fair yield to 7-(benzyloxycarbonylamino)-2,2-dimethyl-1,3-benzodioxan-4-one (XXIII) by treatment with isopropenyl acetate in the presence of sulfuric acid and mercuric acetate under long reflux. Under less drastic conditions, the product was O-acetyl-4-(benzyloxycarbonylamino)salicylic acid (XIX).

Attempts to N-alkylate XXIII with methyl iodide using sodium hydride in N,N-dimethylformamide did not lead to the N-methyl derivative (XXIV). The products were not identified but the infrared spectrum showed that N-methylation had not occurred and that deep-seated changes had taken place in the molecule.

Attention was now directed toward conventional stepwise blocking of VII. It was converted to methyl 4-(benzyloxycarbonylamino)salicylate (XVII), either *via* the N-acyl acid (XVI) or *via* the ester (XVIII)[14]; the latter route was preferred. Reaction of XVII with benzoyl chloride in pyridine gave methyl 4-(benzyloxycarbonylamino)-o-benzoylsalicylate (XXI).

From XXI, the two N-methyl compounds (XV and XXXIA) were synthesized first; the experience gained with these two compounds guided our synthesis of the last two mustards, XLIVA and XLVI.

N-Methylation of XXI by the use of sodium hydride and methyl iodide in N,N-dimethylformamide proceeded very smoothly, in contrast to our experience with the benzodioxanone (XXIII). The benzyloxycarbonyl group was readily removed, either by hydrogenolysis[15] or with hydrogen bromide in acetic acid,[16] to give XX. Some attempts were made to convert XXII directly to XXV without isolation of XX; however, these were not successful.



At this point, the hydrolysis of XX to 4-(methylamino)salicylic acid (XXV) had high priority. This experiment would indicate whether decarboxylation would be a serious side reaction in the final step of the projected sequence in which acid hydrolysis of the mustard esters would give the mustard acids (XXXIA, XLIVA, and XLVI). It was found that XX was convertible by either acid or base hydrolysis to XXV in reasonable yields. Acid hydrolysis gave a slightly cruder product, suggesting that a minor side reaction was occurring in acid. The successful acid hydrolysis of XX suggested that for these salicylic acid derivatives, decarboxylation in the presence of acid might not be too serious.

The preparation of the N-methyl mustard (XXXIA) from XX proceeded smoothly through the hydroxyethylation step to XXVI and through the chlorination step with thionyl chloride to give XXVII; both XXVI and XXVII were oils that could be used in subsequent experiments without any purification. Compound XXVI was obtained in analytical purity by column chromatography.

(11) W. Berends, J. M. Waisvisz, and A. K. J. Mulder, *Rec. trav. chim.*, **74**, 1323 (1955).

(12) A. V. Willi, *Trans. Faraday Soc.*, **55**, 433 (1959).

(13) D. T. Mowry, W. H. Yanko, and E. L. Ringwald, *J. Am. Chem. Soc.*, **69**, 2358 (1947); D. T. Mowry, *ibid.*, **69**, 2362 (1947).

(14) D. J. Drain, D. D. Martin, W. Mitchell, D. E. Seymour, and F. S. Spring, *J. Chem. Soc.*, 1498 (1949).

(15) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(16) D. Ben-Ishai, *J. Org. Chem.*, **19**, 62 (1954).

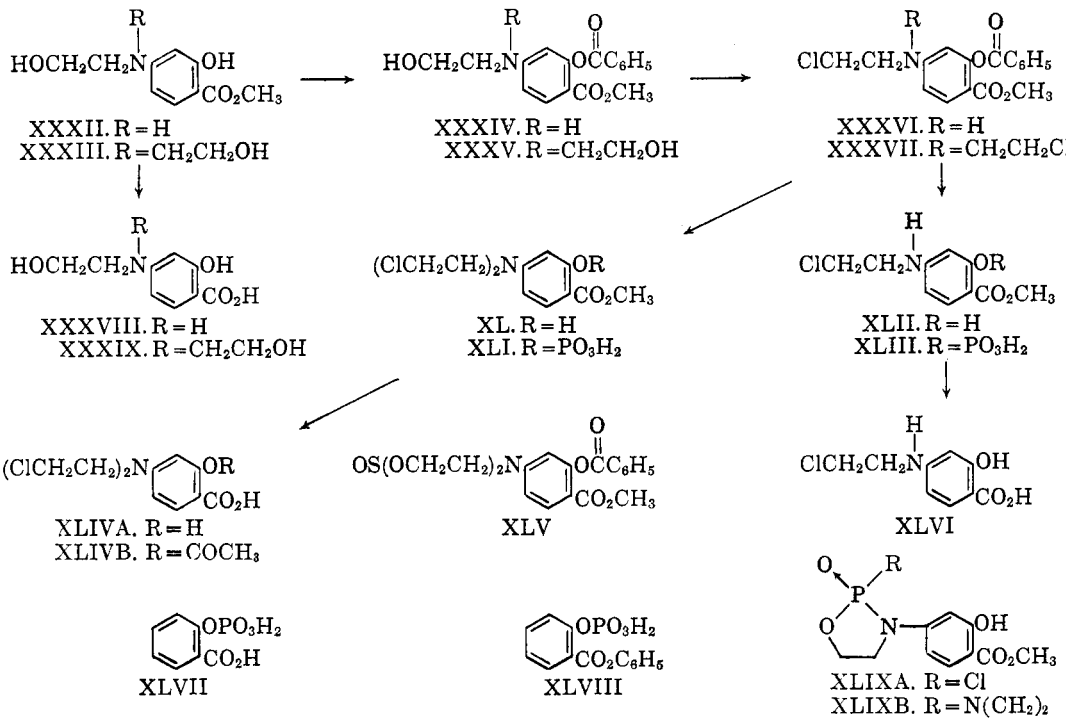
Hydrolysis of XXVII by heating for 45 minutes with concentrated hydrochloric acid gave the desired 4-[(2-chloroethyl)methylamino]salicylic acid (XXXIA) in only 12% yield (from XXVI). This yield could not be increased, suggesting that side reactions, presumably including decarboxylation, were more serious than anticipated on the basis of the successful acid hydrolysis of XX to XXV.

From our experience with XXIA, the synthesis of the bismustard XLIVA appeared to be feasible if decarboxylation did not become more serious than with XXXIA.

Initial attempts to prepare XLIVA proceeded *via* hydroxyethylation of XVIII in glacial acetic acid[17] to give XXXIII. All attempts to chlorinate XXXIII with phosphorus oxychloride or thionyl chloride gave dark, unattractive oils; this suggested that blocking the phenolic hydroxyl was necessary before chlorination. However, as will be mentioned later, it was possible to proceed from XXXIII to the bismustard XLIVA in low yield without using the O-benzoyl blocking group.

nature of the amine group of XXVIII.[19] However, when glacial acetic acid[17] was used as the solvent, the bishydroxyethyl compound (XXXV) was obtained in good yield. Compound XXXV was also obtained by reaction of XXXII with benzoyl chloride in the presence of base, all reactants being in equimolar quantities. The over-all yields by either the shorter route (*via* XXXII) or the longer route (*via* XXVIII) were comparable.

The chlorination of methyl O-benzoyl-4-[bis(2-hydroxyethyl)amino]- salicylate (XXXV) proceeded readily when heated in refluxing phosphorus oxychloride for 30 minutes to give the crystalline blocked bismustard XXXVII in 74% yield. When XXXV was treated with thionyl chloride in refluxing methylene chloride, a solid of much higher melting point was obtained. The infrared spectrum and elemental analysis fitted those of a cyclic sulfite such as XLV. A similar cyclic sulfite has been described.[20] The chlorination of XXXV with thionyl chloride in refluxing chloroform gave, after 20 hours' reaction time, some of the desired



Further attempts to prepare the bismustard XLIVA utilized the completely blocked derivative (XXVIII), which was prepared in excellent yield from XXI either by hydrogenolysis or with hydrogen bromide. Reaction of XXVIII with excess ethylene oxide in aqueous acetic acid gave a mixture of products and starting material from which a 40% yield of the monohydroxyethyl derivative (XXXIV) was obtained. Evidently bishydroxyethylation[18] is precluded by the very weakly basic

mustard (XXXVII), though not in as high yield as with refluxing phosphorus oxychloride. All attempts to hydrolyze the blocked mustard (XXXVII) in hydrochloric acid, either alone or with diluents, were unsuccessful. Compound XXXVII was either extremely insoluble or extremely unreactive when soluble.

Debenzoylation of XXXVII in hot methanolic hydrogen chloride gave XL. This compound, although readily soluble in hot hydrochloric acid, was

(17) A. H. Soloway and E. Nyilas, *J. Org. Chem.*, **26**, 1091 (1961).
(18) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).
(19) A. V. Willi and W. Meier, *Helv. Chim. Acta*, **39**, 318 (1956).
(20) W. C. J. Ross and G. P. Warwick, *J. Chem. Soc.*, 1364 (1956).

hydrolyzed to XLIVA in only 4% yield. This was much poorer than the yields obtained in the similar hydrolysis of either the corresponding bishydroxyethyl ester (XXXIII) (54% yield) or the N-methyl mustard ester (XXVII) (12% yield). The acid hydrolysis of XL gave, as a major product, a highly colored material that appeared to result from decarboxylation. This material was insoluble in aqueous bicarbonate solution and lacked carbonyl absorption in its infrared spectrum. Rate comparisons by means of paper chromatography confirmed the fact that this chromatographically homogeneous by-product formed so rapidly in the hydrolysis of XL that the desired XLIVA was never present in large quantity.

A minute amount of the bismustard XLIVA was obtained from the treatment of the bis(2-hydroxyethyl)amine (XXXV) with phosphoryl chloride. The reaction mixture was decomposed with ice and water and, on long standing, a small amount of the crystalline mustard XLIVA precipitated from the aqueous solution. It seemed possible that XLIVA resulted from loss of the O-benzoyl group[21] during chlorination to give, first, XL and then the dichlorophosphate of XL by further reaction with phosphoryl chloride. During the hydrolysis, the dichlorophosphate was converted to the phosphate (XLI), which gradually hydrolyzed to XLIVA.

The above speculations and the behavior of salicyl phosphate (XLVII)[22] and salol phosphate (XLVIII),[23] which are much more readily hydrolyzed than the corresponding *meta* and *para* isomers in the pH 3–7 region, suggested that the O-phosphate derivative (XLI) should be deliberately prepared and hydrolyzed at near neutral pH to obtain XLIVA. This pH would minimize acid-catalyzed decarboxylation[12] while at the same time the hydrolysis would be facilitated by participation of the O-substituent.

Treatment of XL with phosphorus pentachloride by the procedure of Chanley, Gindler, and Sobotka[22] gave the presumed O-phosphate (XLI) as an oil. This was immediately heated for ten minutes at about 80° in aqueous disodium hydrogen phosphate, adjusted to pH 5–7, to give XLIVA in 48% yield (from XL). The over-all yield from XVIII to XLIVA is 13%.

The O-phosphate (XLI) can conceivably be prepared from XXXIII directly by reaction with phosphorus pentachloride, either alone or with phosphorus oxychloride. Two experiments indicated that the mustard XLIVA was obtainable in 7–10% yield directly from XXXIII. No further effort was made to establish optimum conditions. The over-all yield from XVIII to XXXIII to XLIVA was 5–6%.

The O-phosphate approach also proved to be the method of choice for preparing XXXIA.

The corresponding O-benzoyl blocked mustard (XXVII) was debenzoylated to the crystalline XXIX by methanolic hydrogen chloride in 70% yield. This was similarly O-phosphorylated and then hydrolyzed to the final mustard acid (XXXIA) in 43% yield (from XXIX).

Acetylation should convert the two mustards, XXXIA and XLIVA, to the corresponding "aspirin" mustards, XXXIB and XLIVB, respectively. It is of interest to compare the last two with the first two as potential anticancer agents, since the acetylated mustards, like acetylsalicylic acid (aspirin), may possibly show transport properties in biological systems different from those of the corresponding unacetylated molecules. Accordingly, XXXIB and XLIVB have been synthesized.

The fact that the reaction of XXVIII with excess ethylene oxide in aqueous acetic acid afforded the monohydroxyethyl derivative (XXXIV) in low but usable yields encouraged us to prepare the one-armed mustard (XLVI).

Some attempts were made to improve the yields of XXXIV. When XXVIII was treated with one mole of ethylene oxide in glacial acetic acid, XXXIV could not be isolated. The reaction mixture appeared to consist mainly of unreacted XXVIII and the bishydroxyethyl product, XXXV. However, when methyl 4-aminosalicylate was treated with one mole of ethylene oxide in glacial acetic acid, the monohydroxyethyl derivative, XXXII, could be isolated in good yield. This was not entirely free of bishydroxyethyl contaminant, but the crude product was suitable for further reactions. Benzoylation of XXXII in aqueous base gave XXXIV in 52% yield. For the monohydroxyethyl series, this shorter route appeared to be preferable.

Chlorination of XXXIV with phosphorus oxychloride at reflux temperature gave the noncrystalline XXXVI, which was not characterized. The crude XXXVI was debenzoylated by the usual method to the crystalline XLII in 61% yield (from XXXIV). Hydrolysis in concentrated hydrochloric acid at 75° for 55 minutes afforded the desired mustard (XLVI) in 24% yield. One attempt to utilize the O-phosphate derivative (XLIII) in preparing XLVI was unsuccessful, perhaps because of side reactions involving the secondary amino group in XLII. This was not unexpected, since treatment of XXXII at 85–88° with phosphorus oxychloride, either alone or with benzene, gave a crystalline compound that was assigned the structure of XLIXA on the basis of its elemental analysis, very strong ferric chloride test, and infrared spectrum that had strong absorption at 7.75–7.85 μ (P=O)[24] and no absorption at 3.0 μ (N—H).

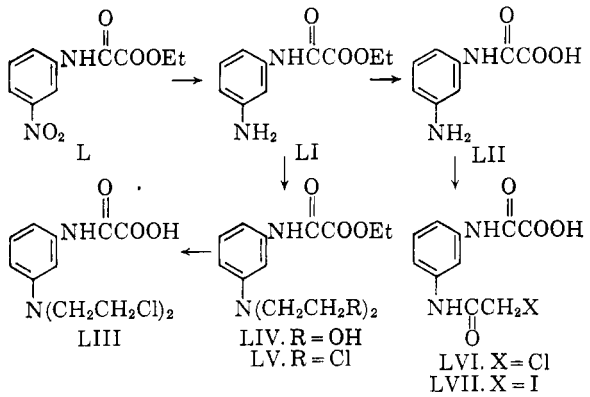
(21) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 3401 (1957), and references given in E. R. Garrett, *ibid.*, **82**, 711 (1960).

(22) J. D. Chanley, E. M. Gindler, and H. Sobotka, *ibid.*, **74**, 4347 (1952).

(23) J. Arai, *J. Biochem.*, **20**, 465 (1934); A. Michaelis and W. Kerkhof, *Ber.*, **31**, 2172 (1898).

Reaction of XLIXA with ethylenimine gave the corresponding derivative (XLIXB). This was synthesized for anticancer screening since it, like some known agents with antitumor activity, contains an alkylating group attached to the phosphorus.[25]

m-[Bis(2-chloroethyl)amino]oxanilic acid (LIII)[26] is of interest not only as a potential irreversible inhibitor of LDH, but also as an example of a modified chlorambucil side chain.[27] The sequence for the preparation of LIII proceeded from ethyl *m*-nitrooxanilate (L) through LI, LIV, and LV. This sequence follows the usual aryl mustard synthesis except that acid hydrolysis of the final ester (LV) has to be carefully controlled to avoid concomitant hydrolysis of the oxamide linkage.

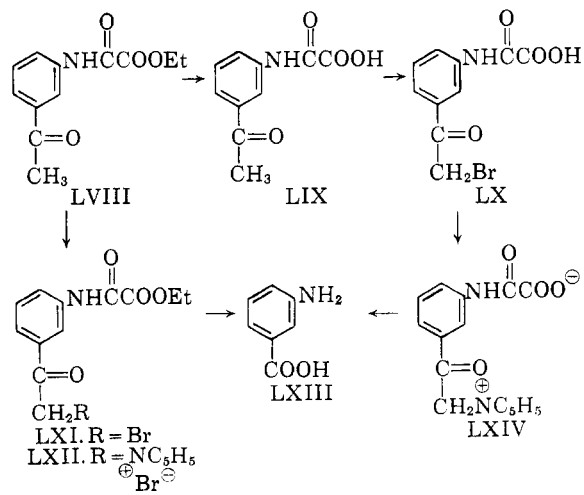


Ethyl *m*-nitroöxanilate (L) was obtained in excellent yield by the addition of one mole of ethyl oxalyl chloride to two moles of *m*-nitroaniline in refluxing methylene chloride. The *m*-nitroaniline hydrochloride, which precipitated, was readily separated from the solution of the product ester. Hydrogenation at room temperature with palladium catalyst reduced L to LI. This in turn gave the crystalline bis(hydroxyethyl)amino compound (LIV) in over 82% yield when treated with ethylene oxide in aqueous acetic acid. Heating LIV in phosphorus oxychloride at reflux for ten minutes gave the crystalline ester (LV) in 65% yield. Too long a reaction time (over 30 minutes) gave an impure, red oil containing decomposition products. The infrared spectrum suggested that reaction with the oxamide linkage had occurred. The optimum conditions were established by experiments in which the rates of product and by-product formation were followed by paper chromatography. The final mustard (LIII) was obtained in 55% yield by hydrolysis for three hours at 25° with concentrated (12 *N*) hydrochloric acid.

The amino ester (LI) was readily hydrolyzed to the known *m*-aminoöxanilic acid (LII)[28] in excellent yields by heating for 15 minutes in 12 *N* hydrochloric acid. The product precipitated from solution as rapidly as it was formed, consequently there was little or no amide hydrolysis as a side reaction. While the infrared spectrum suggested that LII initially precipitated as the hydrochloride salt, it was converted to an internal salt or zwitterion upon recrystallization from N,N-dimethylformamide and water. Elemental analyses of the recrystallized product agreed with the free base or zwitterion form; no chlorine was present.

The amine (LII) was also prepared by reversing the sequence of the reduction and hydrolysis steps. The nitro ester could be hydrolyzed to *m*-nitrooxanilic acid[29] in 76% yield with hot 0.2 *N* sodium hydroxide solution. *m*-Nitroöxanilic acid was readily reduced to LII by hydrogen with palladium (5% on charcoal) in 2-methoxyethanol. Reaction of LII with the appropriate acyl chloride by the standard procedure readily afforded *m*-(chloroacetamido)oxanilic acid (LVI) and *m*-(iodoacetamido)oxanilic acid (LVII).

In the preparation of *m*-(bromoacetyl)oxanilic acid (LX), the bromination of both *m*-acetyloxanilic acid (LIX) and its ethyl ester (LVIII) was examined. The use of the ester might offer some advantages, since it was considerably more soluble than the acid in most solvents. Furthermore, ethyl *o*-acetyloxanilate was known[30] to give the α-bromo derivative when brominated in chloroform. If the bromo ester (LXI) could be prepared, then it could conceivably be hydrolyzed to the acid LX.



The bromination of LVIII and LIX was attempted in a number of solvents and under a variety of conditions. In all cases, the products had broad

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 312.

(25) For tri(1-aziridinyl)phosphine oxide, see M. V. Nadkarni, E. G. Trams, and P. K. Smith, *Cancer Res.*, **19**, 713 (1959); for alkyl *N*-[bis(ethylenimido)phosphoro]carbamates, see T. J. Bardos, Z. B. Papanastassiou, A. Segaloff, and J. L. Ambrus, *Nature*, **183**, 399 (1959).

(26) Synthesis of the *para* isomer was reported recently after this work on the *meta* mustard was completed; see M. H. Benn, A. M. Creighton, L. N. Owen, and G. R. White, *J. Chem. Soc.*, 2365 (1961).

(27) For paper IX on chlorambucil, see A. P. Martinez, W. W. Lee, and B. R. Baker, *J. Org. Chem.*, **26**, 4501 (1961).

(28) A. Albert, *J. Chem. Soc.*, 121 (1941).

(29) Anselmino, *Chem. Zentr.*, **I**, 753 (1906).

(30) H. de Diesbach, A. Schürch, and G. Cavin, *Helv. Chim. Acta*, **31**, 716 (1948).

melting point ranges and were mixtures of mono and dibromo derivatives. These could be separated by fractional crystallization in fair yields. However, it was found that a single monobromo product could be obtained in 80–90% yields when either LVIII or LIX was treated with one mole of bromine in refluxing ether with light to catalyze the reaction. The acid was only partially soluble in ether; however, as the bromination proceeded, it gradually dissolved and LX gradually precipitated. The structures of the monobromo products from LVIII and LIX were shown to be those of the α-bromo derivatives, LXI and LX, respectively, by Kröhnke's method.[31] Reaction with pyridine gave high yields (97% and 80%, respectively) of the α-pyridinum salts. The acid (LX) gave an internal salt (LXIV); the ester (LXI) gave the normal bromide salt (LXII). These pyridinum salts were degraded in hot sodium hydroxide solution to *m*-aminobenzoic acid (over 50% yield in both cases), which was indistinguishable from an authentic sample by mixed melting points and infrared spectra.

α,α,α-Tribromoacetophenone, a selective reagent known to give sidechain rather than ring bromination,[32] was not satisfactory for the monobromination of LVIII and LIX. One mole of either LVIII or LIX with one mole of α,α,α-tribromoacetophenone under the prescribed conditions[32] did not afford a homogeneous melt and gave a mixture of products. A homogeneous melt was obtained by the use of two moles of α,α,α-tribromoacetophenone to one of LVIII, but the product was an analytically pure dibromo derivative of LVIII, obtained in 67% yield. Presumably this was the α,α-dibromoacetyl derivative, although it was not identified.

Experimental[33]

5-(Iodoacetamido)salicylic Acid (VI).—To an ice-cooled, stirred solution of 10.0 g. (0.065 mole) of 5-aminosalicylic acid in 300 ml. of water containing 34 g. (0.40 mole) of sodium bicarbonate was added dropwise over 15 min. the iodoacetyl chloride prepared from 14.9 g. (0.080 mole) of iodoacetic acid. After stirring at 0–5° for 1 hr., the solution was made strongly acidic with cold 50% nitric acid (6 *N* hydrochloric acid was used in some cases). The precipitate was collected and dried to afford 20.0 g. (96%) of crude product, m.p. 215–220° dec. Recrystallization from aqueous acetone afforded 7.0 g. (34%) of chromatographically homogeneous product, m.p. 237–239° dec. This still contained some solvent. Another recrystallization (from ethanol), followed by drying at 100°/0.5 mm. for 16 hr., gave 4.1 g. (20%) of VI, m.p. 244–246°; $\lambda_{max(\mu)}^{Nujol}$ 3.10 (OH, NH), 5.90, 6.00 (C=O), 6.41 (amide II). Analytical data are given in Table I.

4-(Benzyloxycarbonylamino)salicylic Acid (XVI).—By the above procedure used for VI, 1.53 g. (10 mmoles) of 4-aminosalicyclic acid (VII) and 1.85 g. (11 mmoles) of carbobenzoxy chloride gave 2.42 g. (85%) of product, m.p. 189–190°, which was homogeneous according to paper chromatography and was suitable for use in subsequent reactions.

Recrystallization from ethanol–Skellylsolve B[38] gave the analytical sample of XVI, m.p. 192.0–192.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.02 (NH), 3.6–4.2 (acidic H), 6.05 (COOH, C=O), 5.78 (C=O of urethane), 6.47 (amide II). It had R_f values of 0.22, 0.44, and 0.90 in solvents F, B, and D, respectively. It gave a deep purple color with ferric chloride solution.

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.8; H, 4.57; N, 4.88. Found: C, 62.7; H, 4.75; N, 4.94.

The reaction is not complete with shorter reaction times than 2 hr.

O-Acetyl-4-(benzyloxycarbonylamino)salicylic Acid (XIX).—A solution of 2.9 g. (10 mmoles) of XVI in 30 ml. of acetic anhydride was heated at 85° for 3 hr., the excess acetic anhydride was removed *in vacuo*, and the residue was dissolved in 25 ml. of toluene. The precipitate that gradually appeared was collected and dried to afford 2.0 g. (55%) of product, m.p. 162–167°. Recrystallization from aqueous ethanol gave the analytical sample, m.p. 180–181°; $\lambda_{max(\mu)}^{Nujol}$ 3.08 (NH), 5.75 (C=O of urethane), 5.88 (C=O of acid and ester), 6.50 (amide II); $\lambda_{max(m\mu)}^{EtOH}$ 265 (ϵ 22,500). It moved in solvents F and B with R_f values of 0.46 and 0.50, respectively. It gave a negative test with ferric chloride solution.

Anal. Calcd. for $C_{17}H_{15}NO_6$: C, 62.0; H, 4.60; N, 4.26. Found: C, 61.7; H, 4.70; N, 4.30.

7-(Benzyloxycarbonylamino)-2,2-dimethyl-1,3-benzodioxan-4-one (XXIII).—A stirred mixture of 5.69 g. (19.8 mmoles) of XVI, 45 ml. (*ca.* 0.35 mole) of isopropenylacetate, 0.12 g. of mercuric acetate, a trace of hydroquinone, and 0.1 g. of concentrated sulfuric acid was heated at reflux for 22 hr., then evaporated *in vacuo* at 60°/1 mm. The residue was partitioned between 50 ml. of methylene chloride and 50 ml. of water. The organic layer was separated, washed with 50 ml. of sodium bicarbonate solution and 50 ml. of water, dried, and evaporated *in vacuo* (60°/15 mm.) to afford 6.0 g. of viscous gum. This was crystallized from chloroform–Skellysolve B[38] (5:1) to afford 3.2 g. (49%) of a white solid, m.p. 97–100°. Two recrystallizations from absolute ethanol gave 2.7 g. (42%) of the analytically pure product, m.p. 108.0–108.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.05 (NH), 5.52 (ester C=O), 5.72, 5.75 (C=O of urethane), 6.50 (amide II), 9.42, 9.62 (C—O—C); $\lambda_{max(m\mu)}^{EtOH}$ 282.5 (ϵ 22,450). It gave a negative ferric chloride test and was not separable from starting material by paper chromatography.

Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.1; H, 5.24; N, 4.29. Found: C, 66.3; H, 5.35; N, 4.32.

After storage at room temperature for 6 months, XXIII had decomposed extensively as shown by its new melting

(31) F. Kröhnke, *Chem. Ber.*, **66**, 604 (1933); P. Da Re and L. Cimatoribus, *J. Org. Chem.*, **26**, 3650 (1961).

(32) F. Kröhnke and K. Ellegast, *Chem. Ber.*, **86**, 1556 (1953).

(33) Melting points were obtained with the Fisher-Johns apparatus and are uncorrected. Anhydrous magnesium sulfate was the drying agent used in all experiments. The petroleum ether fraction used had b.p. 30–60°, unless otherwise indicated. Paper chromatograms were run by the descending technique on Whatman No. 1 paper and the spots were detected by visual examination under ultraviolet light except where otherwise indicated. When an R_f value is given, the material is homogeneous and separable from starting material unless otherwise indicated. The solvent systems used were: A, 1-butanol–pyridine–water (35:35:30); B,[34] water-saturated 1-butanol; C,[35] 2-propanol–2 *N* hydrochloric acid (65:35); D,[36] 1-butanol–acetic acid–water (5:3:2); E, 2-methoxyethanol–water (9:1); F,[37] benzene–water–methanol (2:1:6), Schleicher and Schuell No. 2496 acetylated paper or Ederol acetylated paper; G, 1-butanol–methyl ethyl ketone–water–formic acid (4:3:1.5:1.5); H, 5% disodium hydrogen phosphate (no organic phase); I, 1-butanol–benzene–water (1:2:satd.); J, 1-butanol–methyl ethyl ketone–water (5:3:2).

(34) J. G. Buchanan, C. E. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(35) G. R. Wyatt, *Biochem. J.*, **48**, 584 (1951).

(36) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(37) T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

(38) A hydrocarbon fraction, mainly *n*-hexane, b.p. 62–70°.

point of 156–162° and the shift of carbonyl bands to 5.73 and 5.88 μ in its infrared spectrum.

Attempts to prepare XXIII with smaller molar ratios of isopropenyl acetate (5:1 instead of 18:1) and shorter reaction time (4.5 hr.) gave up to 65% of the O-acetylated salicylic acid (XIX), m.p. 177–178°, identical to authentic material as shown by infrared spectrum, mixed melting point, and paper chromatography.

Methyl 4-(Benzyloxycarbonylamino)salicylate (XVII).—A stirred solution of 1.67 g. (10 mmoles) of methyl 4-aminosalicylate (XVIII)[14] in 5 ml. of pyridine and 50 ml. of anhydrous ether was treated with a solution of 2.0 g. (12 mmoles) of carbobenzoxy chloride in 10 ml. of ether. The solution was stirred for 30 min. more and transferred to a separatory funnel. The solution was diluted with 100 ml. of ether, then washed with 50-ml. portions of water, 10% hydrochloric acid solution, saturated sodium bicarbonate solution, and water. The organic layer was dried, concentrated to about 25 ml., and cooled in ice. The white crystals that precipitated were collected, washed with Skellysolve B,[38] and dried to afford 2.18 g. (73%) of product, m.p. 139.0–140.5°, which was homogeneous as shown by paper chromatography and suitable for the next reaction.

Recrystallization from absolute ethanol gave the analytical sample of XVII, m.p. 142.0–142.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.01 (NH), 5.72, 6.02 (C=O), 6.50 (amide II); $\lambda_{max(m\mu)}^{EtOH}$ 272 (ϵ 22,000), 305 (ϵ 10,800). It had R_f values of 0.15 and 0.82 in solvents F and B, respectively, and gave a weak ferric chloride test.

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.8; H, 5.02; N, 4.67. Found: C, 63.8; H, 5.30; N, 4.76.

Methyl O-Benzoyl-4-(benzyloxycarbonylamino)salicylate (XXI).—A solution of 1.2 g. (3.95 mmoles) of the methyl salicylate (XVII), 6 ml. of pyridine, and 0.60 g. (4.27 mmoles) of benzoyl chloride was heated at steam bath temperature for 3 hr. The reaction mixture was poured into 50 ml. of water and extracted with ether. The ether extract was washed successively with 100 ml. of 10% hydrochloric acid solution, 75 ml. of water, and 75 ml. of saturated sodium bicarbonate solution. The ether extract was dried and evaporated *in vacuo* to *ca.* 20 ml., diluted with an equal volume of Skellysolve B,[38] and chilled. The granular white crystals were collected and dried to afford a first crop, 1.25 g. (78%) of XXI, m.p. 128–129°.

Recrystallization from ether–Skellylsolve B gave the analytical sample of XXI, m.p. 128–129°; $\lambda_{max(\mu)}^{Nujol}$ 3.04 (NH), 5.74, 5.82 (C=O), 6.50 (amide II); $\lambda_{max(m\mu)}^{EtOH}$ 232 (ϵ 23,900) and 269 (ϵ 24,500). It moved in solvent B with R_f 0.88, and gave a negative ferric chloride test.

Anal. Calcd. for $C_{23}H_{19}NO_6$: C, 68.1; H, 4.72; N, 3.46. Found: C, 68.3; H, 4.87; N, 3.38.

Methyl O-Benzoyl-4-[N-(benzyloxycarbonyl)-N-methylamino]salicylate (XXII).—A stirred solution of 0.42 g. (1.05 mmoles) of XXI in 3 ml. of N,N-dimethylformamide was treated with 48 mg. (1.08 mmoles) of 54% sodium hydride in oil (washed with ether to remove oil immediately before use). After 15 min. of stirring, a solution of 0.50 g. (3.55 mmoles) of methyl iodide in 2 ml. of N,N-dimethylformamide was added, the reaction mixture was heated on the steam bath for 10 min., then evaporated to dryness *in vacuo* at 40°/0.5 mm. The residue was dissolved in 25 ml. of methylene chloride, washed with 25 ml. of water, dried, and evaporated to dryness to afford 0.32 g. of crude product. Crystallization from ether-petroleum ether gave 0.25 g. (58%) of analytically pure XXII, m.p. 84–85°; $\lambda_{max(\mu)}^{Nujol}$ 5.76, 5.82 (C=O); no absorption at 3 μ (NH). It was not separable from starting material by paper chromatography.

Anal. Calcd. for $C_{24}H_{21}NO_6$: C, 68.8; H, 5.05; N, 3.34. Found: C, 68.7; H, 5.12; N, 3.18.

In larger scale runs, product of m.p. 80–82°, suitable for subsequent experiments, was obtained in 83% yield.

Methyl O-Benzoyl-4-(methylamino)salicylate (XX).—A well stirred mixture of 138 g. (0.329 mole) of XXII in 650 ml. of glacial acetic acid saturated with hydrogen bromide was heated at 40° for 30 min. (complete solution was attained in 20 min.) then concentrated *in vacuo* at 50°. The residue was treated with toluene in 100-ml. portions and evaporated *in vacuo* three times. The sirupy residue was partitioned between 1.5 l. of methylene chloride and 1.5 l. of a saturated solution of aqueous sodium bicarbonate. The organic layer was water-washed, dried, diluted with 0.7 l. of petroleum ether (b.p. 60–110°), and slowly evaporated until crystallization began, then was chilled to afford 85.6 g. (91%) of faintly yellow crystals of XX, m.p. 155–156°, homogeneous by paper chromatography and suitable for subsequent reactions.

Recrystallization from absolute ethanol gave the analytical sample of XX, m.p. 163.0–163.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (NH), 5.83, 5.90 (C=O of esters). It moved as a single spot in solvent systems F, B, and G with R_f values of 0.24, 0.84, and 0.94, respectively.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.31; N, 4.92. Found: C, 67.2; H, 5.29; N, 4.75.

4-(Methylamino)salicylic Acid (XXV). A. Basic Hydrolysis.—A mixture of 0.50 g. (1.75 mmoles) of XX suspended in 25 ml. of 1 *N* sodium hydroxide and 25 ml. of 1,2-dimethoxyethane was heated at a rate such that the 1,2-dimethoxyethane gradually distilled off in 2 hr. The resultant solution was cooled (ice bath) and acidified with concentrated hydrochloric acid to pH 2, at which point precipitation began. The mixture was extracted with ether (3 × 50 ml.) and the combined ether solutions were evaporated *in vacuo*. The residue was triturated with 25 ml. of warm, concentrated hydrochloric acid and washed with ether (3 × 50 ml.) to remove benzoic acid. The aqueous acid phase was evaporated to dryness and the residue was triturated with warm water, then collected on a filter to afford, after drying, 0.25 g. (86%) of XXV, m.p. 134.5–135.0°. Recrystallization of the product from a charcoal-treated aqueous ethanol solution gave 0.26 g. (68%) of the analytically pure XXV, m.p. 136.0–136.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.95 (NH), 3.6–4.2 (acidic OH), 6.12 (C=O of COOH). It moved with R_f 0.44 in solvent G.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.4; H, 5.42; N, 8.38. Found: C, 57.5; H, 5.38; N, 8.26.

B. Acid Hydrolysis.—A mixture of 0.10 g. (0.35 mmole) of XX, 5 ml. of concentrated hydrochloric acid, and 1 ml. of 1,2-dimethoxyethane was heated on a steam bath for 2 hr., during which time the 1,2-dimethoxyethane was allowed to distill. The reaction mixture was cooled, extracted with three 15-ml. portions of ether (to remove benzoic acid), and then evaporated to dryness to afford a light tan residue. This was triturated with water, collected on a filter, and dried to give 0.05 g. (85%) of XXV, m.p. 128.0–129.5°, identical to XXV above by comparison of infrared spectra and paper chromatography.

Methyl O-Benzoyl-4-[N-(2-hydroxyethyl)-N-methylamino]salicylate (XXVI).—To a cooled mixture of 84.0 g. (0.295 mole) of the methylamine (XX) and 300 ml. of glacial acetic acid was added 58 ml. of cooled ethylene oxide. The flask was stoppered and the mixture was stirred at room temperature for 48 hr. The solution was evaporated *in vacuo* (60°/15 mm.) and three 125-ml. portions of toluene were successively added and evaporated (60°/0.15 mm.) to leave 84.9 g. (88%) of XXVI, a light yellow oil that was suitable for subsequent experiments without purification. A 2.5-g. portion of XXVI from a similar run was taken up in methylene chloride, washed with water, and dried. The methylene chloride solution was placed on a 2.5 × 13 cm. column of alumina (Merck 71707; pH 10) and eluted successively with methylene chloride, ether, ethyl acetate, and ethyl alcohol. From the methylene chloride fractions was recovered 0.18 g. of XX. The material from the central fractions of the product, the ethyl acetate fractions, amounted to 0.81 g. (23%) of XXVI as an analytically pure, hard, white gum; $\lambda_{max(\mu)}^{Nujol}$ 2.90 broad (OH), 5.72, 5.82 (C=O of esters) 9.20, 9.40, 9.50 (C—OH). It moved with R_f 0.45 in solvent F.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.7; H, 5.82; N, 4.26. Found: C, 65.7; H, 5.81; N, 4.19.

Methyl 4-[N-(2-Chloroethyl)-N-methylamino]salicylate

(**XXIX**).—A solution of 2.54 g. (7.72 mmoles) of crude XXVI and 15 ml. of phosphorus oxychloride was heated at reflux for 30 min., cooled slightly, poured onto crushed ice, and stirred for 30 min., by which time the ice had melted. The aqueous mixture was extracted with 100 ml. of methylene chloride. The organic extract was washed with 100-ml. portions of saturated sodium bicarbonate solution and water, dried, and evaporated *in vacuo* to leave 2.10 g. (78%) of an amber oil (XXVII), which moved in solvent B with R_f 0.93; in solvent F (Ederol acetylated paper), it showed a main spot (R_f 0.35) and a trace spot (R_f 0.10).

A solution of 1.96 g. of the above crude mustard (XXVII) in 60 ml. of methanol saturated (at 5°) with hydrogen chloride was heated at reflux for 23 hr. and then evaporated *in vacuo*. The residue was triturated with boiling ether (to remove methyl benzoate), and the ether was saturated with hydrogen chloride, then separated from the semisolids by filtration. The semisolid residue was dissolved in 50 ml. of methylene chloride; this solution was washed with saturated sodium bicarbonate solution, then water, and dried. Removal of the methylene chloride left 0.95 g. (70%) of broadly melting XXIX that was suitable for the next step.

Recrystallization from ether–petroleum ether, b.p. 60–110°, gave light pink needles of XXIX m.p. 82–83°; $\lambda_{max(\mu)}^{Nujol}$ 3.20, 7.80 (=C—OH), 6.00, 8.40, 8.60 (ester), 13.50 (C—Cl). It was not separable from XXVII in solvent systems tried. It gave a strong ferric chloride test.

Anal. Calcd. for $C_{11}H_{14}ClNO_3$: C, 54.2; H, 5.79; Cl, 14.6; N, 5.75. Found: C, 54.2; H, 5.74; Cl, 14.5; N, 5.84.

4-[N-(2-Chloroethyl)-N-methylamino]salicylic Acid (XXXIA). A. From XXVI.—A solution of 1.16 g. (3.53 mmoles) of the blocked hydroxyethyl compound (XXVI) in 25 ml. of methylene chloride was cooled in a Dry Ice–acetone bath while 6.0 ml. of thionyl chloride was added. The reaction mixture was heated at reflux for 1 hr. and evaporated *in vacuo*. To the residue of crude XXVII was added 15 ml. of concentrated hydrochloric acid and the mixture was heated at 85° for 45 min. The reaction mixture was cooled in an ice bath and extracted with ether (3 × 20 ml.) to remove benzoic acid. The acid solution was diluted tenfold with water and extracted with ether (3 × 50 ml.). The ether extract was dried and evaporated *in vacuo* to afford 0.27 g. (30%) of crude, white solid. One recrystallization from ether–Skellysolve B[38] afforded 0.10 g. (12%) of XXXIA, m.p. 128–131°. Further recrystallization from ether gave the analytical sample, m.p. 136–137°; $\lambda_{max(\mu)}^{Nujol}$ 3.20–4.20 (acidic OH), 6.12 (C=O of COOH); free of absorption at 3.0 and 9.3–9.8μ (C—OH). It moved with R_f 0.48 in solvent F (Ederol acetylated paper).

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.4; H, 5.26; Cl, 15.5; N, 6.10. Found: C, 52.9; H, 5.35; Cl, 15.3; N, 6.11.

B. From XXIX.—A solution of 20.0 g. (82 mmoles) of XXIX, 19.0 g. (91 mmoles) of phosphorus pentachloride, and 50 ml. of methylene chloride was heated on a steam bath until all the solvent had evaporated and then heated for 60 min. more. The amber oil was dissolved in 40 ml. of acetone, diluted with 40 ml. of benzene, and treated with 30 ml. of acetone containing 6.0 g. (0.33 mole) of water. After stirring at room temperature for 1 hr., the solution was evaporated *in vacuo* to leave 36.0 g. of pink foam whose infrared spectrum fitted that for XXX; $\lambda_{max(\mu)}^{film}$ 3.5–4.5, 8.0–8.9, 9.8–10.5 [—P(O)(OH)$_2$]. This foam was slurried with 200 ml. of water and 46.0 g. (0.172 mole) of dibasic sodium phosphate ($Na_2HPO_4 \cdot 7H_2O$) was added slowly, with warming until all of the base went into solution, to give a pink mixture of pH 5. The mixture was shaken with 400 ml. of methylene chloride and both layers were filtered to remove 8.0 g. (43%) of product, m.p. 149–150°. The liquid phases were acidified (pH 2) with concentrated hydrochloric acid and the organic layer was separated and extracted with 200 ml. of saturated sodium bicarbonate solution. The bicarbonate solution was washed with 50 ml. of methylene chloride, cooled in an ice bath, and acidified to pH 2, then extracted with 200 ml. of methylene chloride. This methylene chloride solution was dried and evaporated *in vacuo* to give an additional 2.5 g. (13.3%) of light pink, crystalline XXXIA, m.p. 148.5–149.5°, whose infrared spectrum and paper chromatographic behavior were identical to those of the sample of XXXIA above.

The combined products were dissolved in 150 ml. of hot absolute ethanol, treated with charcoal (Norit brand), filtered through a pad of diatomaceous earth (Celite brand), diluted with 1 l. of water, and cooled overnight. The precipitate was collected, washed, and dried to afford 8.1 g. (43%) of XXXIA, m.p. 156.5–157.0°, a light pink solid; its infrared spectrum and paper chromatographic behavior were identical to those of the previous sample of XXXIA.

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.4; H, 5.26; Cl, 15.5; N, 6.10. Found: C, 52.4; H, 5.13; Cl, 15.6; N, 6.10.

O-Acetyl-4-[N-(2-chloroethyl)-N-methylamino]salicylic Acid (XXXIB).—A solution of 0.50 g. (2.2 mmoles) of XXXIA in 25 ml. of acetic anhydride was heated at *ca.* 85° for 50 min., evaporated *in vacuo*, and the residue was taken up in 20 ml. of acetone. Water was added to incipient turbidity, and the solution was heated at 50° for 30 min., then allowed to stand at room temperature for 5 days in order to hydrolyze completely all anhydride material. The acetone was removed *in vacuo*, the aqueous residue was extracted with methylene chloride, and the organic layer was dried and evaporated to leave 0.55 g. of oil. This was redissolved in 10 ml. of methylene chloride, diluted with Skellysolve B,[38] and allowed to stand overnight to yield 0.31 g. (53%) of XXXIB as white needles, m.p. 118–119°, homogeneous on paper. Recrystallization from ether–petroleum ether gave the analytically pure XXXIB, m.p. 119.5–120.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.70–4.20, 6.00 (acid), 5.69 (C=O of ester). It had R_f 0.83 in solvent B.

Anal. Calcd. for $C_{12}H_{14}ClNO_4$: C, 53.1; H, 5.20; Cl, 13.1; N, 5.16. Found: C, 53.4; H, 5.41; Cl, 12.8; N, 5.12.

Methyl O-Benzoyl-4-aminosalicylate (XXVIII). A. Hydrogen Bromide in Acetic Acid.—A mixture of 8.5 g. (21 mmoles) of the N-carbobenzoxy ester (XXI) in 150 ml. of glacial acetic acid saturated with hydrogen bromide was treated by the procedure used for XX to give 5.03 g. (89%) of XXVIII, m.p. 168–169° (from ether–Skellysolve B[38]); the infrared spectrum and paper chromatographic behavior were like those of the analytical sample below.

B. Hydrogenolysis.—Hydrogen was passed through a stirred mixture of 0.50 g. (1.23 mmoles) of XXI, 0.10 g. of 5% palladium on charcoal, 0.5 ml. of acetic acid, 1.5 ml. of water, and 10 ml. of 2-methoxyethanol at 70–75° for 1 hr. (carbon dioxide evolution in the exit gases ceased after *ca.* 0.5 hr.). The catalyst was removed by filtration and the solvents by evaporation *in vacuo* to afford 0.34 g. (100%) of crystalline XXVIII, m.p. 167–169°, not increased by recrystallization from ethanol–water; $\lambda_{max(\mu)}^{Nujol}$ 2.89, 2.98, 3.12 (NH_2), 5.74, 5.89 (C=O of esters). It moved with R_f 0.28 in solvent F.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.5; H, 4.84; N, 5.17. Found: C, 66.1; H, 4.83; N, 5.18.

Methyl 4-[Bis(2-hydroxyethyl)amino]salicylate (XXXIII).—The reaction of 16.7 g. (0.10 mole) of methyl 4-aminosalicylate (XVIII)[14] and 10 ml. of ethylene oxide in glacial acetic acid by the procedure used for XXVI gave, after crystallization from toluene, 13.2 g. (60%) of XXXIII, m.p. 97–98°. Recrystallization from benzene gave 0.95 g. (43%) of the analytical sample, m.p. 103.0–103.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.0–3.1 (OH), 3.6–4.0 (acidic OH), 5.99 (C=O of ester), 9.30, 9.45, 9.65 (OH). It moved with R_f 0.69 in solvent F (Ederol acetylated paper).

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.5; H, 6.72; N, 5.49. Found: C, 56.5; H, 6.78; N, 5.50.

Methyl O-Benzoyl-4-[bis(2-hydroxyethyl)amino]salicylate (XXXV). A. From XXXIII.—A solution of 12.3 g. (48

mmoles) of the methyl ester (XXXIII) in 145 ml. of 1,2-dimethoxyethane was treated with 2.64 g. (49 mmoles) of sodium methoxide. The mixture was stirred at 50° for 1 hr., removed from the water bath, and treated over a period of 30 min. with a 15-ml. solution of 1,2-dimethoxyethane containing 6.75 g. (48 mmoles) of benzoyl chloride. Stirring was continued for 1 hr. more, then the reaction mixture was evaporated to dryness at 60°/15 mm. The residue was dissolved in 200 ml. of methylene chloride and washed successively with three 50-ml. portions of 1 *N* sodium hydroxide solution and 100 ml. of water. The organic solution was dried and evaporated to give an oil that crystallized from 125 ml. of toluene to give 7.26 g. (42%) of XXXV as needles, m.p. 120–121°, homogeneous by paper chromatography and negative to the ferric chloride test.

Recrystallization from ether gave the analytical sample of XXV, m.p. 122–123°; $\lambda_{max(\mu)}^{Nujol}$ 3.15 (OH), 5.74, 5.85 (C=O of esters), 9.25, 9.35, 9.45 (OH). It moved in solvents B and I with R_f values of 0.80 and 0.48, respectively.

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.5; H, 5.89; N, 3.90. Found: C, 63.3; H, 6.15; N, 3.67.

B. From XXVIII.—A cold mixture of 69.0 g. (0.254 mole) of the O-benzoylamine (XXVIII), 350 ml. of glacial acetic acid, and 72 ml. of ethylene oxide was allowed to react by the procedure used for XXVI to afford 73.2 g. (80%) of a white solid, m.p. 121–122°. Examination of the infrared spectrum before and after reaction with acetic anhydride indicated that there was essentially no monohydroxyethyl compound (XXXIV) present (lack of amide C=O). This product is suitable for subsequent reactions.

Methyl 4-(2-Hydroxyethylamino)salicylate (XXXII).—A solution of 13.2 g. (0.30 mole) of ethylene oxide and 45.3 g. (0.271 mole) of XVIII in 25 ml. of acetic acid was allowed to react at 20° for 3 hr., then worked up as for XXXIII to give 46.4 g. (81%) of crude XXXII, m.p. 70–74°. This crude product contained small amounts of the bishydroxyethyl compound (XXXIII), but was suitable for subsequent reactions.

Recrystallization from 500 ml. of toluene gave two crops. The first crop of 19.8 g. (35%) had m.p. 75–76° and consisted of mainly XXXII with some XXXIII. The second crop of 23.2 g. (41%), m.p. 86–88° (softens, 80–84°), was essentially all XXXII, as indicated by infrared spectra and nitrogen analysis (found: 6.39%; theory, 6.64%; theory for bis, 5.49%).

The second crop was recrystallized once more from toluene to obtain 11.6 g. (20%) of XXXII, m.p. 85–87°; $\lambda_{max(\mu)}^{Nujol}$ 2.95, 2.99 (OH, NH), 6.03 (ester C=O), 9.42, 9.64 (C — OH). It gave a main spot, R_f 0.55. with a trace spot, R_f 0.65, in solvent F (Ederol acetylated paper).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.20; N, 6.64. Found: C, 57.2; H, 6.44; N, 6.35.

Methyl O-Benzoyl-4-(2-hydroxyethylamino)salicylate (XXXIV). A. From XXVIII.—A mixture of 10.0 g. (37 mmoles) of XXVIII, 200 ml. of acetic acid, 100 ml. of water, and 30 ml. (0.60 mole) of ethylene oxide was allowed to react and was worked up as before (see preparation of XXXIII) to afford an oil which, on crystallization from ether, gave 4.6 g. (40%) of XXXIV as white needles, m.p. 127–129°.

Recrystallization from ether afforded the analytical sample of XXXIV, m.p. 130.5–131.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.87, 2.94 (OH, NH), 5.81, 5.90 (C=O of esters), 9.60 (C — OH). It moved in solvent F with R_f 0.40.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.7; H, 5.44; N, 4.44. Found: C, 64.3; H, 5.54; N, 4.15.

B. From XXXII.—Reaction of 2.50 g. (13.7 mmoles) of XXXII, m.p. 86–88°, with equimolar quantities of sodium methoxide and benzoyl chloride in 1,2-dimethoxyethane by the procedure used above for XXXV, gave, after crystallization from ether, 1.62 g. (52%) of XXXIV in two crops: 1.12 g. (36%), m.p. 127–129°, and 0.56 g. (16%), m.p. 125–127°. Both of these crops were identical by infrared spectra comparison and were not contaminated by any of the bishydroxyethyl compound (XXXV).

Methyl O-Benzoyl-4-[bis(2-chloroethyl)amino]salicylate (XXXVII).—Reaction of a solution of 0.72 g. (2.0 mmoles) of XXXV in 5 ml. of phosphorus oxychloride by the procedure used for XXIX gave, after crystallization from ether, 0.59 g. (74%) of XXXVII as light tan crystals, m.p. 104.5–105.5°; $\lambda_{max(\mu)}^{Nujol}$ 5.77, 5.89 (C=O of ester); no C—OH absorption in 9.2–9.5-μ region. It moved with R_f 0.95 in solvent B.

Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.6; H, 4.83; Cl, 17.9; N, 3.53. Found: C, 57.9; H, 4.90; Cl, 17.6; N, 3.64.

Reaction with thionyl chloride in refluxing chloroform for 4 hr. gave mainly starting material and intractable gum. However, reaction for 16 hr. gave some of the above mustard (XXXVII).

Methyl O-Benzoyl-4-(5,6,7,8-tetrahydro-4-H-1,3,2,6-dioxathiazocin-6-yl)-salicylate S-Oxide (XLV).—A solution of 3.0 g. (8.3 mmoles) of XXXV in 60 ml. of methylene chloride was chilled in a Dry Ice–acetone bath and treated with 20 ml. of thionyl chloride. After warming to room temperature, the reaction solution was heated at reflux for 4 hr. and evaporated *in vacuo* to leave a green residue that was taken up in 50 ml. of methylene chloride, washed with 50 ml. of half-saturated sodium acetate solution, then water, dried, and evaporated to dryness. The residue was dissolved in a minimum amount of methylene chloride and 5.0 g. of diatomaceous earth (Celite) was added. This mixture was triturated with 150 ml. of ether, the ether was evaporated to 75 ml., then allowed to stand at room temperature. The white crystals that precipitated were collected and dried to afford 0.75 g. (22%) of XLV, m.p. 155–156°; $\lambda_{max(\mu)}^{Nujol}$ 5.85, 5.87 (C=O of esters), 7.6–8.0 (sulfite); free of OH and NH absorption in 2.5–3.3-μ region. In solvent I, it had R_f 0.20, main spot, and a minor spot at origin.

Anal. Calcd. for $C_{19}H_{19}NO_7S$: C, 56.4; H, 4.73; N, 3.46; S, 7.91. Found: C, 56.5; H, 4.80; N, 3.73; S, 7.47.

Methyl 4-[Bis(2-chloroethyl)amino]salicylate (XL).—Treatment of 6.10 g. (15.4 mmoles) of XXXVII with methanolic hydrogen chloride by the procedure used above for XXIX gave, after crystallization from petroleum ether, b.p. 60–110°, 3.62 g. (80%) of XL as white needles, m.p. 60.5–61.0°; $\lambda_{max(\mu)}^{Nujol}$ 5.99, 8.38, 8.58 (ester); 13.5–13.9 (C—Cl). It moved in solvent system B with R_f 0.91.

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_3$: C, 49.3; H, 5.17; Cl, 24.3; N, 4.79. Found: C, 49.2; H, 5.13; Cl, 24.2; N, 4.89.

4-[Bis(2-chloroethyl)amino]salicylic Acid (XLIVA). A. From XL.—By the procedure used for XXXIA (part B), there was obtained from a mixture of 0.63 g. (2.2 mmoles) of XL and 0.47 g. (2.2 mmoles) of phosphorus pentachloride, 0.15 g. of white crystals (48% from XL) of XLIVA, m.p. 149–150°; $\lambda_{max(\mu)}^{Nujol}$ 3.6–4.1 (acidic OH), 6.05 (C=O of CO-OH). The compound moved in solvents F (R_f 0.46) and B (R_f 0.68).

Anal. Calcd. for $C_{11}H_{13}Cl_2NO_3$: C, 47.5; H, 4.71; Cl, 25.5; N, 5.04. Found: C, 47.6; H, 4.66; Cl, 25.4; N, 5.03.

B. From XXXIII.—A solution of 2.55 g. (10 mmoles) of XXXIII in 20 ml. of phosphoryl chloride was heated at reflux for 6 hr. The dark solution was cooled, poured over excess crushed ice, and stirred vigorously for 15 min. The acidic mixture was extracted with a total of 100 ml. of methylene chloride. The methylene chloride was extracted with a total of 200 ml. of water. The water extracts, after 4 days at room temperature, deposited a precipitate. This was dissolved in 50 ml. of methylene chloride and extracted with 50 ml. of saturated aqueous bicarbonate. The aqueous layer was acidified to pH 1 and extracted with 50 ml. of ether. Evaporation of the dried ether solution afforded 0.72 g. of a yellow solid. This crude product was again dissolved in ether, treated with charcoal, and the ether was evaporated to leave 0.29 g. (11%) of white, crystalline product, m.p. 148–

152°, whose infrared spectrum and paper chromatographic behavior indicated it to be XLIVA.

O-Acetyl-4-[bis(2-chloroethyl)amino]salicylic Acid (XLIVB).—A solution of 0.50 g. (1.8 mmoles) of XLIVA in 25 ml. of acetic anhydride was heated and worked up by the procedure used for the preparation of XXXIB to give, after recrystallization from ether–petroleum ether, 0.30 g. (53%) of XLIVB as white crystals, m.p. 141–142°; $\lambda_{max(\mu)}^{Nujol}$ 3.70–4.20, 5.99 (COOH), 5.67 (C=O of ester). It moved with R_f 0.84 in solvent B.

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_4$: C, 48.8; H, 4.73; Cl, 22.2; N, 4.38. Found: C, 48.8; H, 4.61; Cl, 22.3; N, 4.36.

Methyl 4-[(2-Chloroethyl)amino]salicylate (XLII).—A solution of 4.34 g. (13.8 mmoles) of XXXIV in 20 ml. of phosphorus oxychloride was refluxed for 15 min., then worked up as for XXXVII to afford a quantitative yield of XXXVI as a light yellow oil that could not be induced to crystallize. It was homogeneous on paper chromatography in solvent A (R_f 0.41; starting material R_f 0.68) and showed no infrared —OH absorption.

Treatment of 3.54 g. (10.6 mmoles) of crude XXXVI with methanolic hydrogen chloride for 5.5 hr. by the procedure used for XXIX gave 1.41 g. (61%) of broadly melting XLII. This was suitable for use in the next experiment.

Recrystallization from ether–petroleum ether with the aid of charcoal (Norit brand) gave XLII as white needles, m.p. 87–88°; $\lambda_{max(\mu)}^{Nujol}$ 2.95 (NH), 3.2–4.0, 7.85 (=C—OH), 6.08, 8.40, 8.60 (ester). It gave two spots in solvent H, with R_f 0.14 and R_f 0.43; the latter being the more intense. The R_f 0.43 spot may be due to hydrolysis to the acid, XLVI.

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.4; H, 5.26; Cl, 15.5; N, 6.10. Found: C, 52.3; H, 5.20; Cl, 15.7; N, 6.21.

4-[(2-Chloroethyl)amino]salicylic Acid (XLVI).—A solution of 0.49 g. (2.13 mmoles) of XLII in 5 ml. of concentrated hydrochloric acid was heated at 75° for 55 min., diluted with 100 ml. of cold water, chilled, and extracted with two 25-ml. portions of methylene chloride. This organic solution was extracted with two 25-ml. portions of saturated aqueous sodium bicarbonate, the bicarbonate extracts were washed with 25 ml. of methylene chloride and acidified to pH 2 with hydrochloric acid. The white precipitate was collected on a filter, washed with 25 ml. of water, and dried to give 0.11 g. (24%) of XLVI as white plates, m.p. 142.5–143.0°. Recrystallization from ether with essentially no losses gave XLVI, m.p. 143.0–143.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.95 (NH); 3.5–4.2 (acidic OH); 6.10 (C=O of acid). It moved in solvents F (Ederol acetylated paper), B, and H with R_f values of 0.59, 0.59 and 0.45, respectively.

Anal. Calcd. for $C_9H_{10}ClNO_3$: C, 50.1; H, 4.67; Cl, 16.5; N, 6.51. Found: C, 50.2; H, 4.88; Cl, 16.4; N, 6.57.

4-Bis(2-hydroxyethyl)salicylic Acid (XXXIX). A. Acid Hydrolysis.—The methyl ester (XXXIII) (0.10 g., 0.39 mmole) in 5 ml. of concentrated hydrochloric acid was hydrolyzed (4 hr.) and worked up as in the preparation of XLVI to afford 0.05 g. (54%) of XXXIX, m.p. 146–147°; $\lambda_{max(\mu)}^{Nujol}$ 3.00 (OH), 3.6–4.2 (acidic OH); 6.10 (C=O of COOH). It moved in solvent I with R_f 0.30.

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.8; H, 6.27; N, 5.81. Found: C, 54.8; H, 6.23; N, 5.75.

B. Saponification.—A solution of 4.00 g. (15.7 mmoles) XXXIII in 32 ml. of 1 *N* sodium hydroxide solution (32 mmoles) was heated on a steam bath for 60 min. The solution was cooled in ice and acidified with 32 ml. of 1 *N* hydrochloric acid to precipitate the product. This was collected on a filter, washed, and dried to yield 3.15 g. (83%) of XXXIX, m.p. 140–141°. This was identical to product above by infrared spectra and paper chromatographic behavior.

3-(4-Carbomethoxy-3-hydroxyphenyl)-2-chloro-1,3,2-oxazaphospholidine 2-Oxide (XLIXA).—A mixture of 0.80 g. (3.78 mmoles) of methyl 4-(2-hydroxyethylamino)salicylate (XXXII) and 5.0 ml. of phosphorus oxychloride was heated, with stirring, at 80–85° for 1.5 hr. The light amber solution was poured over 50 ml. of crushed ice and water and stirred for 15 min. until a white semisolid formed. This was extracted with 50 ml. of methylene chloride, the extract was washed with 50 ml. of saturated aqueous sodium bicarbonate, then water, dried, and evaporated at 60°/15 mm. to afford 0.95 g. of light yellow oil. Recrystallization from anhydrous ether gave 0.45 g. (41%) of XLIXA as white crystals, m.p. 151.0–152.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.20 (phenolic OH), 5.96 (ester C=O), 7.75–7.85 (ester C—O—C, P → O); no absorption at 3.0 μ. It had R_f 0.20 (streaky) and R_f 0.84 in solvents F and B, respectively. It gave a strong ferric chloride test.

Anal. Calcd. for $C_{10}H_{11}ClPO_5$: C, 41.3; H, 3.80; Cl, 12.2; N, 4.81. P, 10.6. Found: C, 41.5; H, 3.88; Cl, 12.3; N, 4.68; P, 10.5.

Reaction of XXXII with phosphorus oxychloride in hot benzene gave the same product with the same analysis.

2-(1-Aziridinyl)-3-(4-carbomethoxy-3-hydroxyphenyl)-1,3,2-oxazaphospholidine 2-Oxide (XLIXB).—A solution of 0.45 g. (1.55 mmoles) of XLIXA in 40 ml. of chloroform was stirred and treated with 4 ml. of ethylenimine. The resultant solution was heated at reflux for 60 min. and evaporated *in vacuo* at 40°, and the residue was dissolved in 50 ml. of methylene chloride. The organic layer was washed with three 50-ml. portions of water, dried, filtered through diatomaceous earth (Celite), and allowed to stand overnight to afford 0.32 g. (69%) of XLIXB as white crystals, m.p. 137–138°, homogeneous on paper. A portion of product from a previous run was recrystallized from ether to yield the analytical sample of XLIXB, m.p. 137–138°; $\lambda_{max(\mu)}^{Nujol}$ 6.00 (C=O), 7.80, 7.89 (P=O and Ar—OH), 10.68 (CH_2 of ethylenimine). It had R_f 0.74 in solvent B.

Anal. Calcd. for $C_{12}H_{15}N_2O_5P$: C, 48.3; H, 5.07; N, 9.39; P, 10.4. Found: C, 48.3; H, 5.10; N, 9.20; P, 10.4.

Ethyl *m*-Nitroöxanilate (L).—A solution of 1.37 g. (0.01 mole) of ethyl oxalyl chloride in 20 ml. of methylene chloride was added rapidly to a refluxing solution of 2.76 g. (0.02 mole) of *m*-nitroaniline in 50 ml. of methylene chloride. After heating for 5 min. more at reflux, the reaction mixture was cooled and filtered to remove the precipitated *m*-nitroaniline hydrochloride in quantitative yield. The filtrate was diluted four fold with petroleum ether, chilled, and the white crystals which formed were collected, washed with some more of the cold solvent mixture, and dried *in vacuo* to give 2.20 g. (92%) of ethyl *m*-nitroöxanilate, m.p. 147.0–149.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.03 (amide NH), 5.82 (ester and amide C=O), 6.50 (amide II, NO_2), 7.37 (NO_2); it had R_f 0.85 in solvent B.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.5; H, 4.23; N, 11.78. Found: C, 50.7; H, 4.49; N, 11.65.

Ethyl *m*-Aminoöxanilate (LI).—A mixture of 1.19 g. (5 mmoles) of ethyl *m*-nitroöxanilate (L) 75 mg. of 5% palladium on charcoal, and 25 ml. of ethanol was hydrogenated at room temperature and 50 p.s.i.g. A rapid hydrogen uptake of 12 mmoles (120%) took place during 10 min.; no further uptake was noted during the next hr. The catalyst was removed by filtration and the solvent was stripped *in vacuo* (bath, 50°). The residue was crystallized from methylene chloride–petroleum ether, to give 0.75 g. (76%) of white crystals, m.p. 112–113°; $\lambda_{max(\mu)}^{Nujol}$ 2.91, 3.02, 3.12 (NH), 5.76, 5.88 (amide and ester C=O); 6.40 (amide II), 8.12 (ester C—O—C). It had R_f 0.72, 0.82 and 0.62 in solvents B, C and F, respectively.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.87; N, 13.5. Found: C, 57.7; H, 5.95; N, 13.2.

Ethyl *m*-[Bis(2-hydroxyethyl)amino]oxanilate (LIV).—A mixture of 11.5 g. (0.055 mole) of LI, 40 ml. of acetic acid, 120 ml. of water, and 20 ml. of ethylene oxide was allowed to react as in the preparation of XXVI to yield 13.8 g. (84%) of yellow, crystalline product, m.p. 99.0–99.5° (from methylene chloride–petroleum ether).

The analytical sample was obtained by one recrystalliza-

tion from the same solvents with no increase in melting point. It had $\lambda_{max(\mu)}^{Nujol}$ 2.99 (OH, NH), 5.79, 5.89 (ester, amide C=O), 6.40 (amide II), 9.30 (C — OH). It had R_f 0.78 and 0.75 in solvents B and F, respectively.

Anal. Calcd. for $C_{14}H_{20}N_2O_5$: C, 56.8; H, 6.79; N, 9.45. Found: C, 56.7; H, 6.87; N, 9.57.

Ethyl *m*-[Bis(2-chloroethyl)amino]oxanilate (LV).—Reaction of 5 ml. of cold phosphorus oxychloride and 2.0 g. (6.7 mmoles) of LIV for 10 min. by the procedure for XXIX afforded 1.50 g. (67%) of product as white needles, m.p. 70–71°; $\lambda_{max(\mu)}^{Nujol}$ 3.01 (NH), 5.84 (ester, amide C=O), 6.49 (amide II), 8.42 (ester C—O—C); free of absorption at 9.30 μ (OH). It moved in solvents B with R_f 0.89 and F with R_f 0.94.

Anal. Calcd. for $C_{14}H_{18}Cl_2N_2O_3$: C, 50.5; H, 5.44; Cl, 21.3; N, 8.42. Found: C, 50.3; H, 5.69; Cl, 21.3; N, 8.58.

***m*-[Bis(2-chloroethyl)aminoöxanilic Acid (LIII).**—A mixture of 0.40 g. (1.2 mmoles) of LV and 10 ml. of 12 *N* hydrochloric acid was stirred at room temperature for 3 hr., the now homogeneous solution was diluted threefold with water and extracted with two 50-ml. portions of methylene chloride. The undried[40] extracts were evaporated at 40°/0.5 mm. to a gum which, on trituration with 10 ml. of ethylene dichloride, afforded 0.19 g. (55%) of bright yellow product, m.p. 160–161°, that was homogeneous in paper chromatography. Recrystallization from methylene chloride–petroleum ether, yielded 0.18 g. (50%) of analytically pure product, m.p. 161–162°; $\lambda_{max(\mu)}^{Nujol}$ 3.05, 3.15 (NH), 5.70 (C=O of acid), 5.92 (C=O of amide), 6.40 (amide II). It moved in solvents B and F, with R_f values of 0.33 and 0.53, respectively.

Anal. Calcd. for $C_{12}H_{14}Cl_2N_2O_3$: C, 47.3; H, 4.62; Cl, 23.2, N, 9.19. Found: C, 47.3; H, 4.51; Cl, 23.3; N, 9.18.

***m*-Aminoöxanilic Acid (LII).**—A mixture of 8.0 g. (39 mmoles) of the ester LI and 70 ml. of concentrated hydrochloric acid was heated at *ca.* 85°. The starting material dissolved initially and then the product precipitated. After 15 min. of heating, the precipitated hydrochloride salt was collected on a filter, washed, and dried to give 7.8 g. (94%) of product, m.p. over 200°; $\lambda_{max(\mu)}^{Nujol}$ 3.05 (NH), 3.85 ($NH^{\oplus}$), 5.78 (C=O of acid), 5.90, 6.42 (amide).

Recrystallization of 4.5 g. from N,N-dimethylformamide gave 3.1 g. (78% from the ester) of product as the zwitterion, which decomposed gradually above 200° without melting; $\lambda_{max(\mu)}^{Nujol}$ 3.00 (NH), 3.50–4.20 ($NH^{\oplus}$), 5.90, 6.50 (amide), 6.32, 7.30 ($COO^{\ominus}$); no absorption at 5.78 μ. It moved with R_f values of 0.07 and 0.60 in solvents G and F (Whatman No. 1 paper), respectively.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.2; H, 4.47; N, 15.6. Found: C, 53.2; H, 4.28; N, 15.7.

***m*-(Chloroacetamido)oxanilic Acid (LVI).**—The procedure used for preparing iodoacetamidosalicylic acids was followed for the reaction between chloroacetyl chloride and LII to give a 64% yield of LVI, m.p. 198–199°. Three recrystallizations from ethanol–petroleum ether gave the analytical sample, m.p. 199.0–199.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.10, 3.12, (NH), 3.60–4.30 (weak acidic OH), 5.78, 5.95 (C=O), 6.45 (amide II). It moved with R_f 0.30 in solvent J.

Anal. Calcd. for $C_{10}H_9ClN_2O_4$: C, 46.8; H, 3.53; Cl, 13.8; N, 10.9. Found: C, 46.9; H, 3.68; Cl, 13.6; N, 10.9.

***m*-(Iodoacetamido)oxanilic Acid (LVII).**—The reaction of iodoacetyl chloride and *m*-aminoöxanilic acid (LII) using the procedure for the preparation of VI gave LVII, m.p. 197–198° dec., in 23% yield. Recrystallization from ethanol–petroleum ether did not change the melting point; $\lambda_{max(\mu)}^{Nujol}$ 3.10 (NH), 5.75, 5.87, 6.09 (C=O), 6.40 (amide II). It moved with R_f 0.73 and 0.36 in solvents D and G, respectively.

Anal. Calcd. for $C_{10}H_9IN_2O_4$: C, 34.5; H, 2.60; I, 36.4; N, 8.05. Found: C, 34.4; H, 2.83; I, 37.1, N, 8.16.

Ethyl *m*-Acetyloxanilate (LVIII).—The reaction of 5.40 g. (0.040 mole) of *m*-aminoacetophenone and 2.74 g. (0.020 mole) of ethyl oxalyl chloride by the procedure used for L above afforded 4.3 g. of white product, m.p. 105–107°. Recrystallization from Skellysolve B[38] gave 4.0 g. (85% yield) of analytically pure product, m.p. 106–107°; $\lambda_{max(\mu)}^{Nujol}$ 3.01, 3.06 (NH), 5.72, 5.82, 5.90 (C=O). It had R_f 0.85 in solvent B.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.58; N, 5.96. Found: C, 61.4, H, 5.53; N, 6.10.

***m*-Acetyloxanilic Acid (LIX).**—To 90 ml. of 2.5% sodium hydroxide, vigorously stirred, and maintained at 80°, was added 2.35 g. (10 mmoles) of LVIII, which rapidly dissolved. As soon as complete solution was obtained, the solution was chilled in ice and acidified with 25% hydrochloric acid to give 1.8 g. (87% yield) of LIX, m.p. 187–188°, which was homogeneous by chromatography. Recrystallization from absolute ethanol gave the analytical sample, m.p. 187–188°; $\lambda_{max(\mu)}^{Nujol}$ 3.08 (NH), 5.67, 5.90, 5.95 (C=O); 6.40 (amide II); lacking in the customary carboxylic acid absorptions at 3.5–4.0 μ, but readily soluble in sodium bicarbonate; the product had R_f 0.19 in solvent system B.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.9; H, 4.37; N, 6.75. Found: C, 57.9; H, 4.50; N, 6.57.

***m*-[Bromoacetyl]oxanilic Acid (LX).**—A suspension of 4.10 g. (0.020 mole) of LIX in 200 ml. of ether was heated at reflux, stirred, and illuminated[41] while a solution of 3.2 g. (0.020 mole) of bromine in 20 ml. of ether was added dropwise over a period of 15 min. The reaction mixture was heated and stirred for 10 min. more and then evaporated to half its volume. After being chilled in a Dry Ice–acetone bath, the crystals that had precipitated were collected by filtration, washed with cold ether, and dried *in vacuo* to afford 4.71 g. (84%) of LX, m.p. 163–164°.

Product from a similar run was recrystallized from absolute ethanol to give the analytical sample, m.p. 167–168°; $\lambda_{max(\mu)}^{Nujol}$ 3.02 (NH), 5.62, 5.94 (C=O), 6.40 (amide II). It moved with R_f 0.15 in solvent B and R_f 0.69 in D.

Anal. Calcd. for $C_{10}H_8BrNO_4$: C, 41.9; H, 2.81; Br, 27.9; N, 4.89. Found: C, 42.0; H, 2.96; Br, 28.2; N, 5.18.

Ethyl *m*-(Bromoacetyl)oxanilate (LXI).—Bromination of 2.35 g. (0.010 mole) of LVIII with 1.7 g. (0.011 mole) of bromine by the same procedure used for the acid (LX) gave a yield of 2.75 g. (88%) of product, m.p. 124.0–124.5°, unchanged by recrystallization from absolute ethanol. The product had $\lambda_{max(\mu)}^{Nujol}$ 3.04 (NH), 5.90 (C=O), 6.45 (amide II); it was not separable from starting material by paper chromatography in the solvent systems that were tried.

Anal. Calcd. for $C_{12}H_{12}BrNO_4$: C, 45.8; H, 3.85; Br, 25.4; N, 4.46. Found: C, 45.7; H, 3.78; Br, 25.1; N, 4.31.

***m*-[α-(Pyridinium)acetyl]oxanilate (LXIV).**—A solution of 0.50 g. of *m*-(bromoacetyl)oxanilic acid (LX) in 10 ml. of pyridine was heated on a steam bath for 30 min. The mixture was chilled and the precipitate was collected on a filter and washed with cold water to afford, after drying, 0.45 g. (91%) of product, m.p. > 300°. Recrystallization from aqueous ethanol gave an 80% recovery of product, m.p. >300°; $\lambda_{max(\mu)}^{Nujol}$ 3.06, 3.17 (NH), 5.86, 5.92 (C=O), 6.15 ($COO^{\ominus}$), 6.40 (amide II). It moved in solvent F (Whatman No. 1 paper) with R_f 0.52 and in D with R_f 0.44.

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 63.2; H, 4.22; N, 9.87. Found: C, 63.6; H, 4.12; N, 9.76.

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(39) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **72**, 833 (1950), reported the preparation of α-chlorophenylacetyl chloride by the action of either thionyl chloride or phosphorus pentachloride on mandelic acid. In our hands, phosphorus pentachloride gave much better yields. With thionyl chloride, the formation of much benzaldehyde was observed, as noted by H. Meyer, *Monatsh. Chem.*, **22**, 441 (1901).

(40) In one experiment where the extracts were dried over anhydrous magnesium sulfate, the product was lost, presumably by adsorption on the drying agent.

(41) Infrared lamp, 115 v., 250 w., manufactured by Sylvania.

Ethyl *m*-[α-Pyridinium) acetyl]oxanilate Bromide (LXII).—Ethyl *m*-(bromoacetyl)oxanilate (LXI), 1.0 g., treated with pyridine by the procedure used for the acid, gave 1.21 g. (97%) of product, m.p. 170–172° dec. Recrystallization from absolute ethanol gave 1.1 g. (88%) of analytically pure product, m.p. 172–173° dec., $\lambda_{max(\mu)}^{Nujol}$ 2.92, 3.12 (NH), 5.82 (C=O), 6.09, 6.67 (C_5H_5N—$^{\oplus}$). It moved in solvent G with R_f 0.64.

Anal. Calcd. for $C_{17}H_{17}BrN_2O_4$: C, 51.9; H, 4.36; Br, 20.3; N, 7.13. Found: C, 51.5; H, 4.15; Br, 20.1; N, 7.30.

Degradation of LXIV to *m*-Aminobenzoic Acid (LIII).—A mixture of 0.40 g. of LXIV in 10 ml. of 1 *N* sodium hydroxide solution was heated on a steam bath for 0.75 hr. The resultant solution was cooled in ice, acidified to pH 1 with hydrochloric acid, then evaporated to dryness. The residue was dissolved in 20 ml. of saturated sodium acetate solution and extracted with ethyl acetate (2 × 20 ml.). The extracts were combined, washed, dried, and evaporated to afford 0.10 g. (51%) of *m*-aminobenzoic acid as a light pink solid, m.p. 168–170°; m.p. 170–172° when mixed with authentic *m*-aminobenzoic acid of m.p. 172–173°. The infrared spectra and paper chromatographic behavior in several solvent systems were identical to those of the authentic *m*-aminobenzoic acid.

Degradation of Ethyl *m*-[α-(Pyridinium)acetyl]oxanilate Bromide (LXII) to *m*-Aminobenzoic Acid (LXIII).—A mixture of 0.50 g. of the ester LXII in 10 ml. of 1 *N* sodium hydroxide solution was heated for 5 hr. on a steam bath. The reaction was worked up as above to give 0.10 g. (59%) of product, m.p. 167–169°, which was established as *m*-aminobenzoic acid by mixed melting point and comparison of infrared spectrum and paper chromatographic behavior with those of an authentic sample.

Dibromination of Ethyl *m*-Acetyloxanilate (LVIII).—A mixture of 0.24 g. (1 mmole) of LVIII and 0.70 g. (2 mmoles) of tribromoacetophenone[32] was heated in an oil bath at 110° for 3 hr. The resulting amber oil was crystallized from absolute ethanol to give 0.26 g. (67%) of a dibromo derivative of ethyl *m*-acetyloxanilate, m.p. 104–105°; $\lambda_{max(\mu)}^{Nujol}$ 3.05 (NH); 5.85, 5.92 (C=O); 6.45 (amide II). It moved in solvent F with R_f 0.46 (LVIII, R_f 0.52).

Anal. Calcd. for $C_{12}H_{11}Br_2NO_4$: C, 36.7; H, 3.82; Br, 40.1; N, 3.56. Found: C, 36.7; H, 3.82; Br, 40.1, N, 3.53.

On the basis of its preparation, this dibromo derivative is presumed to be ethyl *m*-(α,α-dibromoacetyl)oxanilate. However, this was not established.

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Polymers. IV. Polymeric Diels-Alder Reactions[1,2]

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Polymeric Diels-Alder adducts were prepared from 2-vinyl-1,3-butadiene and *p*-benzoquinone, *m*-phenylenebismaleimide, ethylene diacrylate, and N,N′-methylenediacrylamide. The first two polymers were insoluble and melted above 500°. Diels-Alder polymers were also prepared from three derivatives of 2-hydroxy-1,3-butadiene, bis(2-butadienylmethyl) acetal, bis(2-butadienylmethyl) hexamethylenedicarbamate, and bis(2-butadienylmethyl) *m*-xylylenedicarbamate. Various combinations of these bifunctional dienes with *p*-benzoquinone, *p*-phenylenebismaleimide, and benzidinebismaleimide produced a series of polymers in yields varying from 53 to 99% with intrinsic viscosities from 0.05 to 0.28 and softening points from 74 to 194°.

Theoretically, any reaction that proceeds in high yields can be somehow adapted for use in a polymerization reaction. Although the Diels-Alder reaction has been used extensively in organic chemistry and very often gives very high yields, very little work has been carried out to adapt this interesting reaction to the production of polymers. One of the few reactions that has been studied is the self-condensation of cyclopentadiene.[5] In this reaction the double bond remaining after the reaction of the diene in a Diels-Alder reaction becomes the dienophile for the next condensation step. However, since this double bond is a poor dienophile, very vigorous conditions are required and the reaction proceeds to give only tetramers, pentamers, and hexamers.

A simpler procedure appeared to be the preparation of a bi- or polyfunctional diene which could be made to react with a polyfunctional dienophile. While a number of bifunctional dienophiles, such as benzoquinone and the bismaleimides, are available, reactive bifunctional dienes are not readily available. This scarcity stems from the fact that a simple diene, such as butadiene, is bifunctional with respect to many reactions but in the Diels-Alder reaction it is only monofunctional. Therefore, in order for a compound to be bifunctional with respect to the Diels-Alder reaction, it must contain two diene systems. The simplest compound containing two diene systems is 2-vinylbutadiene (I).

Since the pyrolysis of esters had been shown in

(1) Previous paper in this series, *J. Org. Chem.*, **25**, 1800 (1960).

(2) Presented in part before the Division of Polymer Chemistry at the 126th Meeting of the American Chemical Society, New York, N. Y., September, 1954, and in part at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(3) Office of Naval Research Fellow, 1953–1954.

(4) Office of Naval Research Fellow, 1956–1957; National Science Foundation Predoctoral Fellow, 1957–1959.

(5) H. Staudinger and H. A. Bruson, *Ann.*, **447**, 97 (1926); K. Alder and G. Stein, *ibid.*, **496**, 204 (1932); K. Alder and G. Stein, *Ber.*, **67**, 613 (1934).