N-Methyl-α-(2-thienyl)-β-phenylethylamine hydrochloride (XIII). (*a*) A mixture of 20.2 g. (0.10 mole) of benzyl 2-thienyl ketone (I) and 23.6 g. (0.40 mole) of *N*-methylformamide was refluxed for 12 hr. Two volumes of water were added, the organic layer was separated and refluxed for 2 hr. with 30 ml. of concentrated hydrochloric acid. Water (50 ml.) was added and the mixture extracted with two 75-ml. portions of ether. After drying, the extracts were saturated with hydrogen chloride. An oil which separated was dissolved in absolute alcohol and ether was added to precipitate the product; yield 1.1 g.

(*b*) α-(2-Thienyl)-β-phenylethylamine (22 g., 0.108 mole) and 11.5 g. (0.108 mole) of benzaldehyde were warmed for 15 min. on a steam bath. Water which was liberated was removed under vacuum. Then 15.3 g. (0.108 mole) of methyl iodide was added. The resulting solution was heated at 100° for 12 hr. in a sealed tube. The reaction mass was boiled for 30 min. with 50 ml. of 95% alcohol, the alcohol was removed, and 100 ml. of water was added. This solution was filtered, treated with 2 g. of activated charcoal, filtered, and cooled. The addition of sodium hydroxide caused an oil to separate which was extracted with 100 ml. of ether. The extract was dried and mixed with 50 ml. of anhydrous ether saturated with hydrogen chloride. A precipitate which formed was dissolved in a minimum of absolute alcohol and reprecipitated with ether; yield 9 g.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DOW CHEMICAL CO., EASTERN RESEARCH LABORATORY]

Aminophenols. I. The Reaction of *o*-Aminophenol with Chloracetic Acid and Some Comments on the Formation of Phenmorpholones[1]

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Received November 25, 1957

The reaction between *o*-aminophenol and chloroacetic acid has been reinvestigated; the products obtained have been identified, their structures proved, and optimum conditions of formation established. A number of examples are presented of the ring-closure of *o*-hydroxyphenylglycines and *o*-aminophenoxyacetic acids to 2- and 3-phenmorpholones, respectively, and the similarity to the ring-chain tautomerism of α-(β-hydroxyethylamino)ketones is noted.

Vater[2] reported that *N*-(*o*-hydroxyphenyl)glycine (I) may be prepared by the alkylation of *o*-aminophenol with chloroacetic acid. Repetition of his work yielded an entirely different product and, inasmuch as no published account more recent than Vater's[2] is available, we investigated the reaction in some detail. We now find that by varying the experimental conditions there may be isolated at least five major products (I–V), all in yields of 60% or better.

Though the reaction of mono- or disubstituted amines with chloroacetic acid in the presence of a suitable acid acceptor is a well known method for the preparation of *N*-mono- and disubstituted glycines,[3] it is usually difficult to stop the reaction at the introduction of a single acetic acid group, and separation of the mono- from the diproduct can be tedious.[4] In general, the formation of the monoglycine is favored by an excess of amine,[5] while the diglycine is usually obtained in good yield when excess chloroacetic acid is used.[6] When no added base is present (hydroxide, acetate, etc.) then the amine itself acts as acceptor of the acid liberated and, to avoid decreasing the yield, must be present in excess. These principles are demonstrated amply in the discussion which follows.

The introduction of a mono- or dicarboxymethyl group in *o*-aminophenol (as in I or IIa) offers a favorable opportunity for intramolecular lactonization of the carboxyl with the *o*-phenolic function to form the stable six membered phenmorpholone ring. However, the fact that we found this condensation to be remarkably facile in specific cases only, prompted us to extend our investigations to related systems and to correlate these with some previously reported ring closures. Thus, the formation of 2- and 3-phenmorpholones from *o*-hydroxyphenylglycines and *o*-aminophenoxyacetic acids is presented as a logical adjunct to our study of the reaction of *o*-aminophenol with chloroacetic acid.

Formation of the products. Table I represents a summary of the products obtained from over 20 runs in which the experimental conditions and ratio of reagents were varied systematically. The products, or mixtures, obtained from this reaction are controlled largely by two factors: (1) the ratio of the reactants, *o*-aminophenol and chloroacetic acid, and (2) the *p*H of the solution. That both these factors are equally important can be seen from a casual inspection of Table I. Thus, for example, maintaining the ratio of reactants constant and changing the *p*H slightly, as in runs 3 and 4, give different products, and this is equally true of runs 6 and 8 where the *p*H is constant and the ratio is changed.

Since chloroacetic acid is a strong acid, the *p*H

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(1) Presented in part before the Organic Section of the 131st Meeting of the American Chemical Society, Miami, Fla. April 1957.

(2) H. Vater, *J. prakt. Chem.*, **29**, 289 (1884).

(3) M. Sahyun, *Outline of Amino Acids and Proteins*, Reinhold Publishing Co., N. Y., 1944, p. 95.

(4) P. J. Meyer, *Ber.*, **14**, 1325 (1881); *Ber.*, **35**, 580 (1902).

(5) Rebuffat, *Gazz. chim. ital.*, **17**, 234 (1888), **20**, 122 (1891).

(6) *Org. Syntheses*, **Coll. Vol. II**, 2nd ed., 397 (1943).

TABLE I

Run No.	o-Aminophenol, Mol.	Chloroacetic Acid, Mol.	NaOH, Mol.	Approx. pH	Product[a] I	II	III	IV	Total[b] o-Aminophenol Accounted for, %
1	1	1	0	4	..	..	..	60	90
2	1	2	0	3	..	..	..	90	90
3	1	1	1	7	20	..	50	..	80
4	1	1	2	8[c]	20	20	..	..	90
5	1	4	4	7	..	50	45	..	95
6	1	4	6	8[c]	..	80	..	..	80
7	2	1	0	6	[d]	..	50	..	70
8	2	1	2	8[c]	60	..	..	..	90
9	4	1	..	6	20	..	..	..	85
10	1	4	6	10		(50% of V)			

[a] Based on reactant present in least amount. [b] The difference between this figure and the o-aminophenol converted to product represents o-aminophenol actually isolated as such. [c] Excess base added dropwise so as to maintain the pH at 7–8. [d] I is present in filtrate, but was not isolated.

will not rise significantly above 7 until more than one mole of strong base (sodium hydroxide in this case) is present per mole of acid. Thus at a low pH; *i.e.*, when no excess of acid acceptor over chloroacetic acid is present (runs 1 and 2), no alkylation occurs, but it is possible to isolate the salt. o-aminochloracetate (IV). This compound is entirely dissociated into its components at pH <2 and >7, but is stable and is obtained in optimum yield at pH 3. On the other hand, when the pH is high enough to dissociate the phenolic protons, *O*-alkylation as well as *N*-alkylation will take place, this being a common method for the preparation of aryloxyacetic acids.[7] Therefore, when conditions called for a large excess of base (runs 4 and 6), *O*-alkylation was avoided by maintaining the pH at 7–8 by addition of the hydroxide solution as needed. In the one case where the pH was allowed to reach 10 (run 10) reaction occurred rapidly at both the amino and phenolic functions, and the major product was the disodium salt of [o-(carboxymethoxy)phenyl]iminodiacetic acid (V).

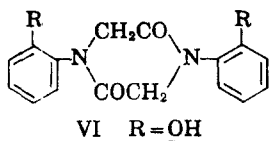
The monosubstituted glycine (I) was obtained in good yield only with a twofold excess of o-aminophenol at a pH of 7–8 (run 8). This is interpreted as a mass action effect wherein the excess phenol represses the formation of the disubstituted glycine, IIa. Conversely, with an excess of chloracetic acid, as in runs 5 and 6, the (ring-closed) dialkylated II, rather than I, is obtained. The situation is further complicated by the strong tendency for II to condense with unreacted aminophenol to give III. However, this occurs only in neutral or slightly acid solution and at a pH of 8, III is rapidly hydrolyzed back to II. This explains why in run 5 at a neutral pH, a mixture of both II and III is obtained, whereas in run 6, where the pH is maintained at 8, only II was realized. Finally, with equimolar amounts of reagents on the neutral or slightly acid side (runs 3 and 7) there was obtained a mixture of I and III with, the latter predominating. We may assume that here the initial mixture consisted of I and II, the latter being converted to the insoluble III by condensation with excess o-aminophenol.

Structure of the products. *N*-(o-hydroxyphenyl) glycine (I), which crystallized from water as the monohydrate, existed entirely as the Zwitterion in analogy to *N*-phenylglycine. According to Vater,[2] I loses water on heating to form an "anhydride" and Beilstein[8] erroneously concludes that the structure of this product is the lactone VII. We now find that though quantitative dehydration of I at 140° under vacuum does indeed show that two moles of water are lost (including one mole of water

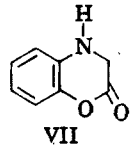
(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc. N. Y., 4th Ed., p. 263.

(8) *Beilstein*, Vol. 27 (Hauptwerk), p. 190.

of hydration), the actual dehydration product is not VII, but 2,5-dioxo-1,4-di-(*o*-hydroxylphenyl)-piperazine (VI). An analogous bimolecular con-



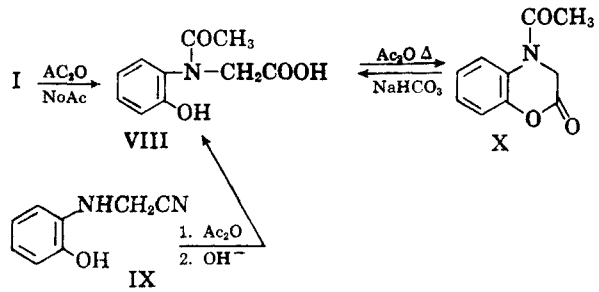
VI R=OH
VI-a R=H



VII

densation occurs with *N*-phenylglycine which on heating to 150° forms VIa.[9] The absence of a lactone carbonyl band and its insolubility in bicarbonate rule out VII as the dehydration product, while supporting evidence for VI is obtained from the strong amide-I band at 6.08μ in its spectrum. An attempt to prepare VII by treating I with hydrochloric acid yielded only *N*-(*o*-hydroxyphenyl)-glycine hydrochloride, and it was concluded that in this case lactonization does not readily take place.[9a]

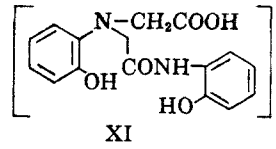
When I was treated with acetic anhydride–sodium acetate, *N*-acetylation occurred to yield the water-insoluble sodium salt of VIII, which was converted to pure VIII on acidification. This compound has been prepared by Shimo[10] by the acetylation of *N*-(*o*-hydroxyphenyl)glycinonitrile (IX) and subsequent hydrolysis of the nitrile. He does not mention the hydrolysis of IX to I. We found



that no acetylation of the phenolic function of VIII took place under mild conditions, while in boiling acetic anhydride ring closure occurred to yield *N*-acetylphenmorpholone-2 (X). Unlike compounds such as II, and others discussed below, which are not isolatable in the open-chain form, X is readily saponified back to VIII by bicarbonate and VIII does not lactonize even in warm 6*N* hydrochloric acid.

All attempts to isolate *N*-(*o*-hydroxyphenyl)-iminodiacetic acid (IIa) led only to the lactone, 2-phenmorpholone-4-acetic acid (II). Thus, when the aqueous alkaline reaction mixture from run 6 was made strongly acid and warmed, it at once deposited II in good yield. The lactone II was soluble in bicarbonate and required approximately two equivalents of base for titration in aqueous alcohol. However, acidification of an alkaline solution of II to *p*H 4 (the estimated *p*H of the free acid IIa) and extraction with ether afforded only unchanged II, again indicating that the free acid is not capable of isolation. In contrast to the *N*-monosubstituted glycine (I), II is insoluble in strong acid and does not form a stable hydrochloride. In addition, its infrared spectrum shows a normal carboxyl band (~5.84μ) and, therefore, it does not exist as a Zwitterion.

When II[11] was refluxed with aqueous *o*-aminophenol it was converted almost quantitatively to III, thus providing evidence for the structure of the latter. This amide formation in aqueous solution would seem to be highly unusual, if not unique, were it occurring by the elimination of water between the amine and carboxyl groups, a reaction which is usually conducted at high temperatures under dehydrating conditions.[12] It is more likely that amide formation occurs by attack of the amino group on the lactone function to yield the nonisolatable intermediate XI which spontaneously



XI

lactonizes to give III. The fact that I, in which the lactone function is absent, does not react further with *o*-aminophenol lends support to this argument. The ready formation of the amide bond of III is paralleled by its rapid hydrolysis in base; by merely dissolving III in warm bicarbonate, *o*-aminophenol precipitates on cooling. The structure of III is supported also by its infrared spectrum which contains absorptions characteristic of a phenol, γ,δ-unsaturated δ-lactone and secondary amide.

Treatment of III with excess acetic anhydride in the presence of sodium acetate yielded the monoacetyl derivative, XII, which on hydrolysis with cold, dilute base afforded not the expected *o*-aminophenol or *o*-aminophenylacetate, but only *o*-hydroxyacetanilide. This conflicting piece of evidence was resolved by the realization that after hydrolysis at the amide function, an oxygen to nitrogen rearrangement had taken place. Such re-

(9) P. J. Meyer, *Ber.*, **10**, 1967 (1877).

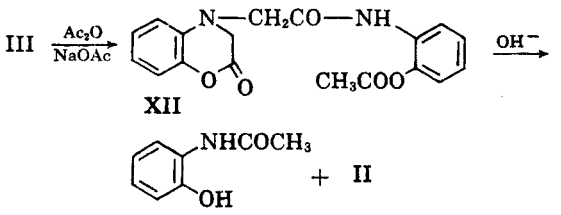
(9a) Subsequent to the completion of this work, a paper appeared by D. G. O'Sullivan and P. W. Sadler (*J. Chem. Soc.*, 2916 (1957)) in which VII was mentioned as having been prepared by Vater's[2] method from I. Drs. O'Sullivan and Sadler very kindly supplied a sample of their compound which we found to be identical to our compound III both from comparison of their infrared spectra and m.p.'s. Thus it appears that to date VII has not been successfully prepared.

(10) K. Shimo, *Bull. Chem. Soc. Japan*, **1**, 206 (1926).

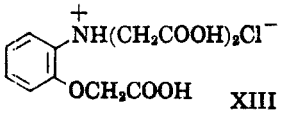
(11) The authors are grateful to B. M. Williams of the Edgar C. Britton Laboratory, The Dow Chemical Co., Midland, Mich., for a sample of II, submitted in the very early states of this work, and for his directions for preparing same.

(12) For example see, C. N. Webb, *Org. Syntheses*, **Coll. Vol. I**, 82 (1943).

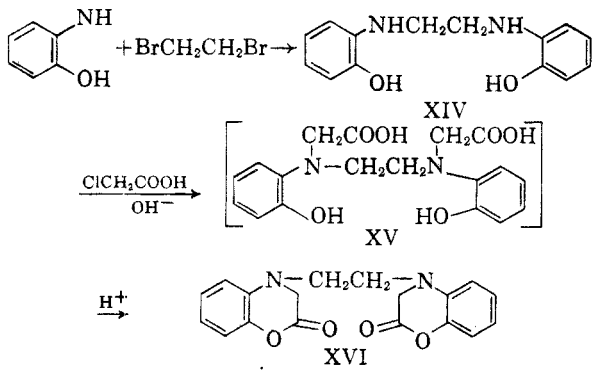
arrangements are common with the *o*-aminophenols and have been extensively investigated.[13]



The *O*-alkylated product V was isolated only as its disodium salt and it was not possible to convert the salt to the free tri- acid even by carefully controlled acidification or ion-exchange methods.[13a] However, no difficulty was experienced in obtaining the hydrochloride (XIII), though neutralization of XIII again gave impure material. The structures of V and XIII were confirmed by their ultraviolet and infrared spectra and by titration data, as well as by the usual elemental analyses.

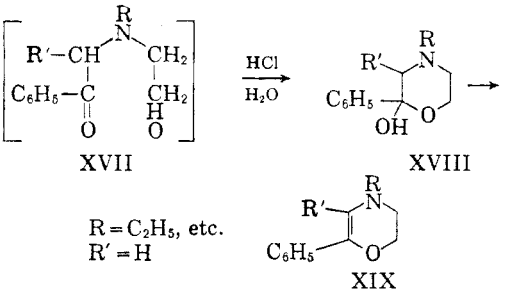


Formation of 2- and 3-phenmorpholones. Our interest in these compounds arose from the observation that *N*-(*o*-hydroxyphenyl)glycine (I) could not be induced to lactonize even by boiling in strong acid while the corresponding iminodiacetic acid (IIa) could be isolated only as the lactone (II).

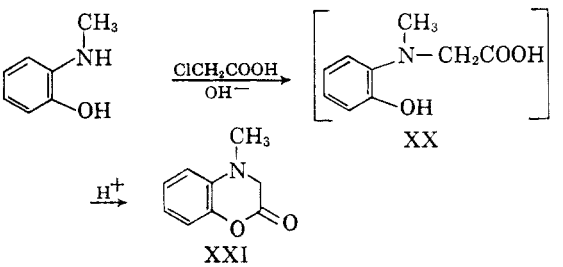


This same phenomenon was encountered in an attempted preparation of *N*,*N*′-ethylenebis(*N*-*o*-hydroxyphenyl)glycine (XV) by the action of chloroacetic acid on *o*,*o*′-ethylenediiminodiphenol (XIV). On acidification of the alkaline reaction mixture, only the dilactone, XVI, was obtained. Whereas neither II nor XVI were acid-soluble, the nonlactonizable I formed a stable hydrochloride.

Though the data presented above is far from conclusive, it strongly suggests that the formation of the morpholone ring is spontaneous when the nitrogen is tertiary but ring closure does not occur when the nitrogen is secondary. We were, therefore, interested to learn that this same phenomena has been observed with a related system. Thus, Lutz and co-workers[14,15] and Cromwell and Tsou[16] report that the α-(β-hydroxyethylamino)ketones exist in the chain form when the nitrogen is secondary (XVIII, R equals H) and in the ring form when the nitrogen is tertiary (XVIII and XIX, R equals alkyl). Further, a recent study[17] of the factors which control this cyclization reports that in the absence of secondary steric and electronic effects, the dominant factor in the equilibrium distribution of chain and cyclic forms is the presence or absence of an alkyl group on nitrogen.[18]



To obtain additional information about the spontaneous formation of *N*-alkyl-2-phenmorpholones, an attempt was made to isolate *N*-methyl-*N*-(*o*-hydroxyphenyl)glycine (XX) from the chloro,



(13) For the most recent work, see A. L. LeRosen and E. D. Smith, *J. Am. Chem. Soc.*, **70**, 2705 (1948); **71**, 2815 (1949).

(13a) Some time after the completion of this work, the authors received a private communication from L. F. Berhenke of the Edgar C. Britton Laboratory, The Dow Chemical Co., Midland, Mich., to the effect that the free acid (of V or XIII) had been successfully prepared in their laboratory. The isolation was accomplished in approximately 25% yield by repeated extraction of an aqueous solution of V (acidified to its isoelectric point) with methyl isobutyl ketone and repeated recrystallizations from this solvent. The product, which was estimated to be 99.3% pure by analysis and titration, had an indefinite m.p. and was found to readily decarboxylate with the loss of two moles of CO_2 when allowed to stand in aqueous solution. This latter observation undoubtedly explains our difficulties, inasmuch as we attempted purification from aqueous media.

(14) R. E. Lutz, J. A. Freek, and R. S. Murphey, *J. Am. Chem. Soc.*, **70**, 2015 (1948).

(15) R. E. Lutz and R. H. Jordan, *J. Am. Chem. Soc.*, **71**, 996 (1949).

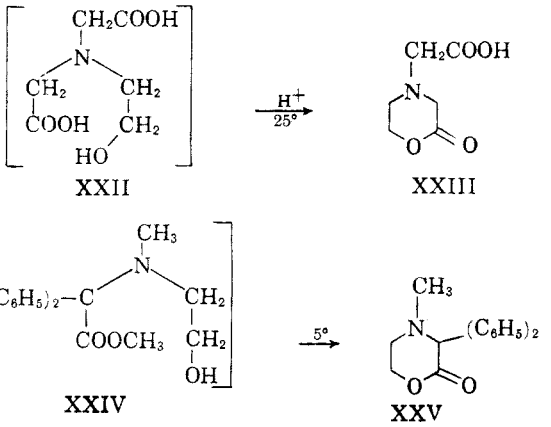
(16) N. J. Cromwell and Kwan-Chung Tsou, *J. Am. Chem. Soc.*, **71**, 993 (1949).

(17) C. E. Griffin and R. E. Lutz, *J. Org. Chem.*, **21**, 1131 (1956).

(18) The non-spontaneous lactonization of VIII must be attributed to the presence of a tertiary amide in place of a tertiary amine group.

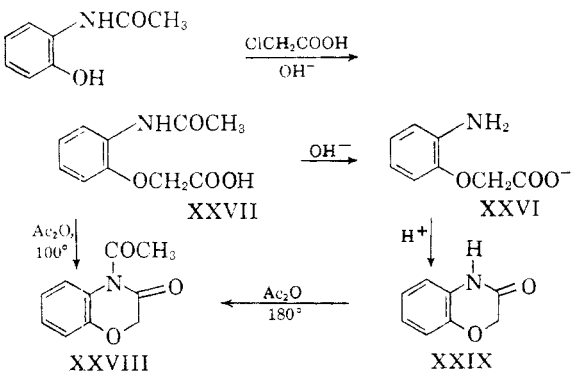
acetic acid alkylation of *N*-methyl-*o*-aminophenol.

As expected on the basis of the previous discussion, however, the sole product of the reaction was the lactone XXI. Other isolated examples have been previously reported, two of which are noted here. When an alkaline solution of *N*-(2-hydroxyethyl)iminodiacetic acid (XXII) is acidified, a quantitative yield of the lactone (XXIII) is obtained,[19] and *N*-methyl-3,3-diphenyl-2-morpholone (XXV) is obtained from the nonisolable ester

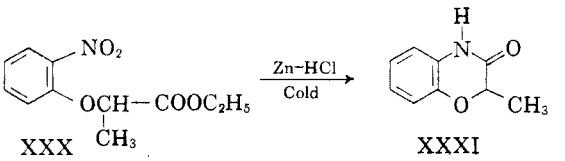


XXIV.[20] In this connection, it has been reported that the secondary amine, *N*-hydroxyethylglycine is not lactonized, but is converted to its hydrochloride on treatment with acid.[21]

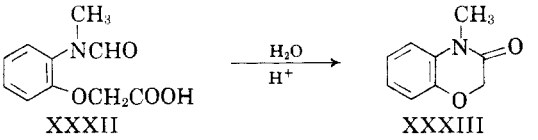
As a logical adjunct to the formation of the 2-morpholones, the analogous lactamization of *o*-aminophenoxyacetic acids to 3-phenmorpholones was briefly investigated. An attempt to prepare *o*-aminophenoxyacetic acid by the hydrolysis of *o*-acetylaminophenoxyacetic acid (XXVII) yielded the salt (XXVI) of the desired product, but acidification of XXVI gave only the lactam XXIX, in agreement with the work of Jacobs and Heidelberger.[22] Other workers[23,24] have attempted to prepare the free amino acid by the reduction of *o*-nitrophenoxyacetic but again obtained only the salt (XXVI) or the lactone (XXIX). Further, we have found that XXVII ring-closes to *N*-acetylphenmorpholone-3 (XXVIII) under the vigorous dehydrating conditions of hot acetic anhydride while Wheeler and Barnes[23] who prepared XXVIII by the action of acetyl chloride on the silver salt of XXIX, report that XXVIII could not be prepared by acetylation of XXIX with acetic anhydride even at 180°. We interpret these data as indicating that, although acetylation of the free amino group (as in XXVII) greatly reduces the tendency for lactamization, the tendency toward formation of the morpholone ring does exert some driving force toward acylation of the *N*, which is completely inhibited once the ring is formed (as in XXIX).



An additional example of the spontaneous lactonization of an *o*-aminophenoxyacetic acid derivative is available in the observation[25] that XXX on reduction affords only the phenmorpholone XXXI. However, no examples concerning the corresponding secondary amine compounds are available and



we, therefore, investigated the acid hydrolysis of the previously unreported *N*-methyl-*N*-formyl-*o*-phenoxyacetic acid (XXXII), which gave as the only isolatable product, *N*-methylphenmorpholone-3 (XXXIII).



In the light of the above, it would seem that in the case of the *o*-aminophenoxyacetic acids, spontaneous lactamization takes place with both primary and secondary amino groups. Further elucidation of the driving force in these and related ring closures must await additional data.

EXPERIMENTAL

General. All melting points are uncorrected. The analyses were carried out by Dr. C. K. Fitz, Needham Heights, Mass. Infrared spectra were obtained as split mulls in Fluorolube and Nujol on a Baird Associates Model 4-55 Recording Spectrophotometer equipped with sodium chloride optics and the ultraviolet spectra on a Cary Model 14 Spectrophotometer. Potentiometric titration curves were

(19) L. W. Ziemlak, J. L. Bullock, F. C. Bersworth, and A. E. Martell, *J. Org. Chem.*, **15**, 255 (1950).

(20) H. S. Mosher, M. B. Frankel, and M. Gregory, *J. Am. Chem. Soc.*, **75**, 5326 (1953).

(21) A. I. Kipriyanov and G. I. Kipriyanov, *J. Gen. Chem. (U.S.S.R.)* **2**, 585 (1932); *Chem. Abstr.*, **27**, 1619 (1933).

(22) W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, **39**, 2188 (1917).

(23) H. L. Wheeler and B. Barnes, *Amer. Chem. J.*, **20**, 560 (1898).

(24) A. Thate, *J. pract. Chem.*, [2], **29**, 146 (1884).

(25) C. A. Bischoff, *Ber.*, **33**, 1591 (1900).

obtained directly from the Precision-Dow Recording Titrator.

o-Aminophenol was Eastman or Fisher Practical grade, recrystallized from alcohol (charcoal). It was usually light tan in color and had m.p. 165–170° (subl. and dec.). Chloroacetic acid was Fisher Reagent grade, used as received.

o-Aminophenolchloracetate (IV). *o*-aminophenol (0.1 mol.) and chloroacetic acid (0.2 mol.) in 100 ml. of water was stirred at room temperature for 2 hr. The undissolved solid was collected, washed with cold water, dried, and washed with ether to remove traces of unreacted amine. The yield of white-tan powder, m.p. 148–149°, was 90%. IV may be obtained as large white crystals from hot water or from ether-benzene. $\lambda_{max.}^{Nujol}$ 3.62, 2.78ms (NH_3^+); 6.33vs (COO^-).

Anal. Calcd. for $C_8H_{10}NO_3Cl$: C, 47.2; H, 4.9; N, 6.9; Cl, 17.2. Found: C, 47.8; H, 5.0; N, 7.1; Cl, 17.1.

N-(o-Hydroxyphenyl)glycine (I). A mixture of 10.9 g. (0.1 mol.) of *o*-aminophenol and 4.7 g. (0.05 mol.) of chloroacetic acid in 50 ml. of water was neutralized with 0.05 mol. of 10% sodium hydroxide solution and the mixture brought to reflux under a nitrogen atmosphere. The *p*H was maintained at about 8 by dropwise addition of 10% base, and the reaction was discontinued when 0.1 mol. (total) base had been added. The average reaction time was 1 hr. The solution was chilled and the insoluble unreacted *o*-aminophenol was collected; 6 g. (55%). Acidification of the filtrate to *p*H 4 and prolonged chilling afforded 5.5 g. (60%) of tan-brown prisms, m.p. about 140°, with resolidification to yellowish plates and final m.p. of about 270° (dec.). An analytical sample was obtained as light tan crystals from water. It is readily subject to air oxidation and, in fact, a colorless, dry sample becomes brown in color after a few days in a tightly stoppered vial. $\lambda_{max.}^{Nujol}$ 3.18s (OH); 3.65, 3.82m (NH_2^+); 6.13s (COO^-).

Anal. Calcd. for $C_8H_9NO_3 \cdot H_2O$: C, 51.9; H, 6.0; N, 7.6. Found: C, 51.8; H, 6.1; N, 7.6.

The *hydrochloride* was obtained as a grey to white powder from concentrated hydrochloric acid; after washing with acetone and ether it melted at 162–165°. $\lambda_{max.}^{Nujol}$ 3.09s (OH); 3.63, 3.84w (NH_2^+); 5.74s (COOH).

Anal. Calcd. for $C_8H_9NO_3 \cdot HCl$: C, 47.2; H, 4.9; N, 6.9; Cl, 17.2. Found: C, 46.7; H, 5.0; N, 6.8; Cl, 16.9.

I was converted to *2,5-dioxo-1,4-di-(o-hydroxyphenyl)-piperazine* (VI) by dehydration at 140° under vacuum. The yellow solid was purified by washing with acetone and precipitating from an aqueous, basic solution by acidification; white powder, m.p. 273–274° (dec.). $\lambda_{max.}^{Nujol}$ 3.17m (OH); 6.08s (amide I), no amide II.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.5; H, 4.7; N, 9.2.

2-Phenmorpholone-4-acetic acid (II). The procedure given for I was repeated with 0.1 mol. *o*-aminophenol, 0.4 mol. chloroacetic acid and 0.6 mol. of base. When the clear solution was made strongly acid and warmed on the steam bath, it deposited a solid. After chilling there was obtained 16.5 g. (80%) of tan plates, m.p. 178–180°. An analytical sample was obtained as white plates from water (charcoal), m.p. 180–182°. $\lambda_{max.}^{Nujol}$ 5.65s (δ-lactone, γ,δ-unsatd.); 6.03s (amide I); 6.43s (amide II).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.5; H, 4.6; N, 9.4.

2-Phenmorpholone-4-(2'-hydroxy)acetanilide (III). Nine g. (0.008 mol.) of *o*-aminophenol and 3.8 g. (0.045 mol.) of chloroacetic acid in 50 ml. of water were refluxed for 30 min. under nitrogen. The solid, which did not dissolve on prolonged reflux, was collected, washed with water, and dried; 3.0 g. (50%) of dark brown powder, m.p. 220–230°. Purification was effected by recrystallization from aqueous acetone (charcoal) and an analytical sample was obtained from alcohol as large, almost-white plates, m.p. 236–238°. $\lambda_{max.}^{Nujol}$ 3.01m (NH), 3.27s (OH), 5.67s (δ-lactone C=O, γ, δ-unsatd.), 6.07s, 6.45s (amide I and II).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.5; H, 4.6; N, 9.4. Neutral. Equiv., 298.3. Found: 290, 305.

III was also prepared by refluxing a mixture of 1.04 g. (0.005 mol.) of II and 0.55 g. (0.005 mol.) of *o*-aminophenol in 40 ml. of water under a nitrogen atmosphere. The clear solution deposited a solid which was collected after 30 min. of reflux. There was obtained 1.2 g. (80%) of tan powder, whose infrared spectrum and melting point were identical to that of III, prepared as described above.

Acetylation of III: 2-phenmorpholone-4-(o-acetoxy)acetanilide (XII). A mixture of 1 g. of III, 1 g. of anhydrous sodium acetate, and 2 ml. of acetic anhydride was warmed until most of the solid had dissolved. Trituration with water followed by addition of alcohol gave 0.7 g. of white solid, m.p. 173–175°. Recrystallization from aqueous alcohol did not raise the m.p. but afforded fine white needles. $\lambda_{max.}^{Nujol}$ 3.02m (NH); no OH; 5.68s, br. (δ-lactone and acetoxy; γ,δ-unsatd.); 5.96s, 6.55s (amide I and II).

Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.6; H, 4.7; N, 8.2. Found: C, 63.6; H, 4.6; N, 8.3.

[o-(Carboxymethoxy)-phenyl]imino-diacetic acid, disodium salt (V). The procedure given for II was repeated with the exception that the solution was allowed to occasionally reach a *p*H of 10. The cooled, clear solution was acidified to about *p*H 5 with 3*N* hydrochloric acid and the precipitated solid collected; 17 g. (50%) of tan powder which did not melt up to 285°. An analytical sample was obtained as white crystals from aqueous alcohol. $\lambda_{max.}^{Nujol}$ 2.92m, br (H_2O); 5.83m (COOH); 6.20s, br (COO^-).

Anal. Calcd. for $C_{12}H_{11}NO_7Na_2 \cdot H_2O$: C, 41.8; H, 3.8; N, 4.05; Na, 13.3. Found: C, 41.3; H, 4.3; N, 4.1; Na, 13.1.

V was converted to the free acid *hydrochloride* (XIII) by dissolving 1 g. in 3 ml. of concentrated hydrochloric acid, filtering the precipitated sodium chloride, and evaporating the filtrate to dryness.

Anal. Calcd. for $C_{12}H_{14}NO_7Cl \cdot H_2O$: C, 42.8; H, 4.8; N, 4.1; Cl, 10.6; neut. eq., 86.3. Found: C, 43.0; N, 4.6; N, 4.0; Cl, 11.0; neut. eq. 88.3.

A pure sample of the free amino acid was not obtained.[13a]

N-Acetyl-N-(o-hydroxyphenyl)glycine (VIII). One g. each of I, anhydrous sodium acetate, and acetic anhydride were warmed until a clear melt was obtained. After cooling, the mixture was dissolved in 20 ml. of hot water, charcoaled, and concentrated to one half its volume. At this point there may be isolated by chilling, the monosodium salt monohydrate of VIII as lustrous plates, m.p. 276–278°. On acidification the salt was converted to the free anhydrous acid which was recrystallized from boiling water to yield 0.8 g. of white, rod-like crystals, m.p. 190–192° (lit.[10] 201–202°) $\lambda_{max.}^{Nujol}$ 2.97s (OH); 5.84s (COOH); 6.22s (amide I); 6.30s (?).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7; neut. eq. 209.2. Found: C, 57.1; H, 5.2; N, 6.9; neut. eq. 212.1.

VIII gave no color with ferric chloride and was recovered unchanged after brief boiling in 6*N* hydrochloric acid.

N-Acetyl-phenmorpholone-2 (X). This was prepared by brief reflux of 0.1 g. of VIII in 2 ml. of acetic anhydride. Addition of 5 ml. of water gave 0.06 g. of a white powder, m.p. 171–3°. It was insoluble in water, ligroin and ether and was obtained as white prismatic rods, m.p. 176–7°, from alcohol. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.60 (δ-lactone; γ,δ-unsatd.); 6.02 (amide I).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.9; H, 4.7; N, 7.3. Found: C, 62.6; H, 4.8; N, 7.4.

X was soluble in dilute bicarbonate and on acidification was quantitatively converted back to VIII.

o,o'-Ethylenediiminodiphenol (XIV). A mixture of 25 g. (0.23 mol.) of *o*-aminophenol and 50 g. (0.23 mol.) of ethylenebromide in 650 ml. of water was refluxed under nitrogen for 2 hr. The clear yellow solution was decanted and the dark oily solid converted to a tan solid by washing with ether. There was obtained 12 g. of product, m.p. 214–217° (dec.), soluble in hot alcohol, strong acid, and base, and insoluble in water, ether, benzene, and ligroin. It gave a dark brown color with ferric chloride. An analytical sample, obtained as fine white needles from alcohol, melted

at 215° (dec.) $\lambda_{max.}^{Nujol}$ 3.04w (NH); 3.75br (OH); 6.28s, 6.62s, 13.54vs (*o*-disubst. phenyl).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6; N, 11.5. Found: C, 68.8; H, 6.2; N, 11.6.

XIV was converted to *N,N'-ethylenebis(2'-hydroxyacetanilide), diacetate*, by warming with an excess of acetate-acetic anhydride. The solid, obtained by extraction with water, was recrystallized from benzene to give colorless prisms, m.p. 171–173°.

Anal. Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.1; H, 5.9; N, 6.8. Found: C, 63.9; H, 6.2; N, 6.9.

Treatment of XIV with 2 mols. of acetate-acetic anhydride gave *N,N'-ethylenebis-o-hydroxyacetanilide*, m.p. 242–243° (dec.), as tan crystals from alcohol. This same product could be obtained by careful alkaline hydrolysis of the diacetate.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.8; H, 6.1; N, 8.5. Found: C, 65.5; H, 6.3; N, 8.6.

N,N'-Ethylenebis-(N-o-hydroxyphenyl)glycine, di-δ-lactone (XVI). An alkaline solution of 1 g. of XIV was refluxed with an excess of sodium chloroacetate under nitrogen for 2 hr. until the *p*H was about 7. The solution was cooled, the *p*H adjusted to 5 with hydrochloric acid, and the solid collected and combined with an additional crop obtained on concentrating the filtrate; total yield 1.2 g. of buff powder, m.p. 160–170°. An analytical sample, obtained as very fine white needles from alcohol, melted at 176–178°. It was insoluble in water and acid and slowly soluble in dilute base. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.66s (δ-lactone-γ,δ-unsatd.).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6. Found: C, 66.5; H, 5.2; N, 8.8.

N-Methyl-phenmorpholone-2 (XXI). A solution of 0.5 g. (0.004 mol.) of *N*-methyl-*o*-aminophenol (prepared by the method of Clark[26]) and 0.5 g. (0.005 mol.) of chloroacetic acid was maintained at *p*H 8 by the addition of 10% sodium hydroxide solution, while refluxed under nitrogen. After 1 hr. the clear solution was cooled, acidified, and refrigerated overnight. The precipitated tan plates weighed 0.2 g. and melted at 51–52°. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.62s (δ-lactone, γ,δ-unsatd.).

Anal. Calcd. for $C_9H_9NO_2$: N, 8.6. Found: N, 8.4.

N-Methyl-N-formyl-o-aminophenoxyacetic acid (XXXII). This was prepared by the usual procedure from 1.5 g. (0.01 mol.) of *N*-methyl-*o*-hydroxyformanilide (m.p. 108–109°, lit.,[26] 103–104°), 0.94 g. (0.01 mol.) of chloroacetic acid and 0.08 g. (0.02 mol.) of caustic in 20 ml. of water. Acidification yielded 0.8 g. of crude product, m.p. 157–163°, and 0.5 g. of starting material was isolated from the filtrate. Recrystallization from 25 ml. of boiling water (charcoal) gave 0.5 g. (*ca.* 30%) of white microcrystalline powder, m.p. 174–174.5°. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.72s (COOH); 6.16s (amide I); 6.30s (?).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 57.6; H, 5.4; N, 6.6.

XXXII was converted to *N-methyl-phenmorpholone-3* (XXXIII) by dissolving in warm 1*N* hydrochloric acid and allowing the product to crystallize. The white needles had m.p. 59.5–60° (lit.[23] 58–59°).

N-Acetyl-phenmorpholone-3 (XXVIII). One g. of *N*-acetyl-*o*-aminophenoxyacetic acid[24] (XXVII) was boiled briefly with 2 g. of acetic anhydride, cooled, and treated with 15 ml. of water. The oily product crystallized on standing and after recrystallization from 50 ml. of alcohol consisted of 0.7 g. (80%) of fine white needles, m.p. 79–79.5° (lit.[23] 77°).

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Substituted Aryl Phosphonic and Phosphinic Acids[1,2]

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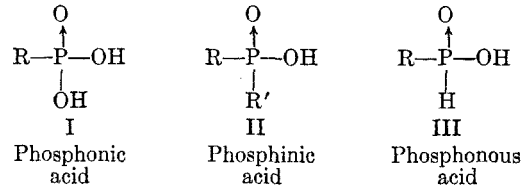
A number of new, substituted arylphosphonic and phosphinic acids have been prepared from the corresponding anilines. These include the 2,5-dibromophenyl-, 2-bromo-3-nitrophenyl-, 2,3-dichlorophenyl-, 3,5-dichlorophenyl-, 2,3,6-trichlorophenyl-, and 2,4,5-trichlorophenylphosphonic and phosphinic acids. Ethyl esters of several such acids are also reported. These compounds are being tested for plant-growth activity.

Halogen-substituted benzoic acids have been examined in detail as plant growth substances and factors relating structure and growth activity have been suggested.[3–5] It was of interest to prepare and test the phosphonic and phosphinic acid analogs of the active benzoic acids; the present paper reports initial investigations of this problem.



To date, there has been no report of the testing of halogen-substituted arylphosphorus acids as plant growth substances. Maguire and Shaw have reported the preparation and testing of 2,4-dichloro-

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