when 200 cc. of sulfuric acid were added to 200 cc. of hydrochloric acid only 49 g. were liberated. If each experiment had been given ample time to reach equilibrium the two values would, of course, be the same. In the former case equilibrium was reached very much sooner than in the latter, and it is due principally to this fact that the first method is so much superior to the second.

It has been observed[1] that dry hydrogen chloride acts strongly upon rubber, producing, among other things, various sulfur compounds. After the rubber has been exposed for some time, however, it is only slightly attacked. For accurate work, nevertheless, the rubber stopper should be replaced with a glass part.

O. R. SWEENEY.

CHEMICAL LABORATORY,
OHIO STATE UNIVERSITY.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

ON NITRO- AND AMINOPHENOXYACETIC ACIDS.

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER.

Received June 27, 1917.

In the course of synthetic work which was undertaken in connection with investigations to be published later, it was found necessary to prepare a large number of substituted aminophenoxyacetic acids and their derivatives. A perusal of the literature showed that only a few of the simpler members of this series had been described, so that the preparation and study of these substances became a separate undertaking. We wish, therefore, to present the results of this work in the present communication.

At first we adopted the procedure of starting with the appropriate nitrophenol, converting this into the nitrophenoxyacetic acid, and then into the desired amino derivative. In preparing the nitrophenoxyacetic acids it was found most satisfactory to employ the method used by Kym[2] for the preparation of *p*-nitrophenoxyacetic acid. This involves heating the dried sodium salt of the nitrophenol with ethyl chloroacetate and saponifying the nitro ester so obtained. Although this method is somewhat more time-consuming than the reaction between the nitrophenol and chloroacetic acid in boiling alkaline solution it proved to be more economical in the case of the less easily accessible nitrophenols, since the yields of the esters were practically quantitative.

Later in the work an attempt was made to prepare the nitrophenoxyacetic acid from 4-nitroguaiacol, but no reaction took place between the dried sodium salt and ethyl chloroacetate. It was found, however, that.

[1] THIS JOURNAL, 36, 2366 (1914).

[2] Kym, *J. prakt. Chem.*, [2] 55, 113 (1897).

the method used by Howard[1] for the preparation of *p*-aminophenoxyacetic acid was applicable in this case. In this method the acetaminophenol and chloroacetic acid are allowed to react in boiling aqueous solution with two molecular equivalents of sodium hydroxide. This method was also used for the preparation of a number of the aminophenoxy acetic acids which had already been prepared over the nitro compounds, and in these cases also not only gave excellent results but seemed even better suited for large-scale work than that involving the use of the nitrophenol sodium salts. The method was accordingly adopted with equal success in all subsequent work in which accessible aminophenols were in question. In the preparation of acetaminophenoxyacetic acids by this method we have found it advantageous, after the first reaction between the acetaminophenol, chloroacetic acid, and alkali, to add again one-half the amounts of chloroacetic acid, alkali and water, and again boil to neutral reaction. The yields then obtained were usually excellent.

The acetaminophenols necessary in this investigation were easily prepared from the aminophenols according to the method of Lumière and Barbier,[2] in which the aminophenol and acetic anhydride are made to react in aqueous solution. For the preparation of such *p*-aminophenols as were used as starting materials we have adopted with excellent results the rapid and convenient method used by Henderson and Sutherland[3] for the preparation of *p*-aminothymol, consisting in the reduction of the nitrosophenol in ammoniacal solution with hydrogen sulfide. In all cases in which a phenol can be easily converted into its nitroso derivative (or quinoneoxime) we regard this method as the most convenient for quickly preparing the corresponding *p*-aminophenol in large amounts.

At the end of the paper we have appended a number of closely related substances, such as naphthoxy- and quinolyloxyacetic acids and two aminophenoxybutyric acids. These last were prepared by converting the bromopropyl ethers of the acetaminophenols into the nitriles and then saponifying. Although the reaction between the bromopropyl ethers and potassium cyanide proceeded normally, our attempts to prepare the corresponding amino-β-phenoxypropionic acids failed, owing to the fact that the acetaminophenyl bromoethyl ethers react with potassium cyanide in a different sense, recalling a similar failure to obtain nitrile formation reported by Schreiber[4] in attempting to react potassium cyanide with *p*-cresoxyethyl bromide. The substitution of β-iodo- or bromopropionic acid or ester for chloroacetic acid or ester in the methods given above also proved unsatisfactory.

[1] Howard, *Ber.*, **30**, 546 (1897).

[2] Lumière and Barbier, *Bull. soc. chim.*, [3] **33**, 783 (1905).

[3] Henderson and Sutherland, *J. Chem. Soc.*, **97**, 1617 (1910).

[4] Schreiber, *Ber.*, **24**, 196 (1891).

In general, the aminophenoxyacetic acids described in this paper are difficultly soluble in cold water, more or less readily in hot, and sparingly soluble in the neutral organic solvents. Aqueous suspensions dissolve on adding either mineral acid, alkali, carbonate, or ammonia. Practically all of the aminophenoxyacetic acids and their esters give colors with ferric chloride, and those containing primary amino groups are readily diazotizable, coupling with R-salt to give soluble dyes of varying shades of red. The amino acids also form hydrochlorides which crystallize readily but are very easily hydrolyzed. Finally, several of the acids showed the property of retaining one molecule of water, even at 100° *in vacuo*.

As in our previous papers, all substances were dried to constant weight *in vacuo* over a suitable drying agent, at 100° whenever possible, before analyses or melting-point determinations were made.

(*A*) *o*-Aminophenoxyacetic Derivatives.

The Acid, o-$CH_3CONHC_6H_4OCH_2CO_2H$.—*o*-Aminophenol was prepared from the nitrophenol by means of sodium sulfide and converted into the acetyl derivative by dissolving in one mol. of dilute sodium hydroxide, adding 1.1 mols acetic anhydride, and then acidifying, according to Lumière and Barbier.[1] 40 g. *o*-acetaminophenol, 25 g. chloroacetic acid (1 mol), 42.6 g. 50% sodium hydroxide solution (2 mols), and about 200 cc. water were boiled down to small volume in an open flask. One-half the above quantities of chloroacetic acid, alkali, and water were then added and the solution once more boiled down to small volume. After diluting with water, hydrochloric acid was added in excess, the acetamino acid separating as a thick slurry. This was filtered off, washed with water and dried in the air. The yield was 50 g. Recrystallized from water it forms large, faintly pinkish spears which contain one molecule of water of crystallization and which melt with gas evolution when plunged into a bath at a temperature above 100°. When anhydrous and recrystallized again from boiling xylene, in which it is very difficultly soluble, it melts at 153–4° (cor.) with preliminary softening. The compound is very easily soluble in cold acetic acid when not anhydrous, and sparingly soluble after its water of crystallization is driven off.

1.1467 g. subst.: 0.0904 g. loss *in vacuo*, finally at 100°. H_2O, 7.88%. 1 H_2O, 7.93%.

Anhydrous: Kjeldahl: 0.3190 g. subst.; 15.30 cc. 0.1 *N* HCl.

Calc. for $C_{10}H_{11}O_4N$: N, 6.70%. Found: N, 6.72%.

***o*-Aminophenoxyacetic Anhydride.**—This substance is obtained by boiling the acetamino acid with 1 : 1 hydrochloric acid, the anhydride separating after a few minutes. The anhydride may also be prepared from *o*-nitrophenoxyacetic acid by the usual methods of reduction, including that involving ferrous sulfate and ammonia. We have found it

[1] *Loc. cit.*

advantageous, however, to substitute sodium hydroxide for the ammonia in the case of this particular substance, owing to the sparing solubility of the anhydride in boiling, dilute ammonia and its ready solubility, on the other hand, in boiling dilute sodium hydroxide. By adopting this modification, yields as high as 78% of the theory could be obtained, or about 10% in excess of the amounts recovered when ammonia was used. The rapidity and convenience of the procedure here outlined would make this appear to be the most satisfactory method for the preparation of the anhydride, especially as the necessary *o*-nitrophenoxyacetic acid may be easily obtained as follows: 139 g. *o*-nitrophenol are suspended in 800 cc. water, 160 g. 50% sodium hydroxide solution (2 mols) added, and the mixture warmed until the phenol dissolves. A solution of 95 g. (1 mol) of chloroacetic acid in 200 cc. water is then added and the whole boiled under a reflux condenser for 1.5 hours. The unchanged nitrophenol is then distilled off with steam and the residual solution cooled, filtered, and acidified to Congo red with hydrochloric acid. A number of preparations, carried out as above, gave yields of from 55 to 60 g. of *o*-nitrophenoxyacetic acid.

o-Aminophenoxyacetic anhydride was first satisfactorily isolated by Thate,[1] who reduced the nitro acid with iron filings and acetic acid and reported the melting point as 166–7°. Our samples of the anhydride showed all the properties described by Thate, except the melting point, which was found to be 173–3.5 °(cor.) after recrystallization from water.

(*B*) *m*-Aminophenoxyacetic Acids.

m-Nitrophenoxyacetic Acid, $m\text{-}O_2NC_6H_4OCH_2CO_2H$.—35.9 g. of the anhydrous sodium salt of *m*-nitrophenol and 27.4 g. chloroacetic ethyl ester were heated in an oil bath under an air condenser, first at 130–40° until a clear melt was obtained, and finally for 2 hours at 175°. After cooling, the melt was taken up in alcohol and the ester saponified by adding an excess of aqueous sodium hydroxide and heating the mixture on the water bath for 15 minutes. On acidifying with hydrochloric acid, the *m*-nitrophenoxyacetic acid separated in a yield of 46 g. Recrystallized from water, the acid forms brilliant, slightly brownish needles which melt constantly at 154–5° (cor.) with preliminary softening, resolidifying when the temperature of the bath drops a few degrees below the melting point. The acid dissolves readily in water only at the boiling point, is easily soluble in acetic acid and difficultly in toluene, benzene or chloroform. Bischoff,[2] who obtained the compound by the hydrolysis of the corresponding malonic ester, gives 152–3° as the melting point, while Hewitt, Johnson, and Pope,[3] who obtained the ester in 40% yield by heating

[1] Thate, *J. prakt. Chem.*, [2] **29**, 178 (1884).

[2] Bischoff, *Ber.*, 40, 3143 (1907).

[3] Hewitt, Johnson and Pope, *J. Chem. Soc.*, 103, 1626 (1913).

m-nitrophenol and chloroacetic ester in alcohol in the presence of sodium, give 151° as the point of fusion.

0.1982 g. subst.; 12.4 cc. moist N, 766 mm., 22°.
Calc. for $C_8H_7O_5N$: N, 7.11%. Found: N, 7.11%.

***m*-Aminophenoxyacetic Acid.**—41.4 g. *m*-nitrophenoxyacetic acid were dissolved in warm alcohol and treated first with 112 cc. concentrated hydrochloric acid and then with 37.6 g. tin, added in small portions to the warm solution. When a drop of the mixture gave a clear solution on dilution with water, the liquid was decanted off, evaporated to dryness, taken up in water, and the tin precipitated with hydrogen sulfide. The filtrate from the tin sulfide was evaporated to dryness, yielding 37.5 g. of the crude amino acid hydrochloride. A portion of this was dissolved in water, boiled with bone-black, filtered, cooled, and the free amino acid precipitated by the addition of sodium acetate solution. Recrystallized first from water, then by dissolving in dilute hydrochloric acid and precipitating with sodium acetate, it forms colorless, lenticular platelets which dissolve only sparingly in the usual neutral solvents. Rapidly heated to 205°, then slowly, it melts at 207–8° with decomposition. The aqueous suspension of the amino acid gives a dull brown color with ferric chloride on warming.

0.1574 g. subst.; 11.85 cc. moist N, 748 mm., 24°.
Calc. for $C_8H_9O_3N$: N, 8.38%. Found: N, 8.27%.

***m*-Aminophenoxyacetic Ethyl Ester Hydrochloride.**—The crude amino acid hydrochloride obtained above was suspended in about 10 parts of absolute alcohol and treated with a stream of dry hydrochloric acid gas, without cooling. The mixture was concentrated *in vacuo* and the salt, which had separated partially, was completely precipitated with dry ether. A portion was recrystallized from a small volume of absolute alcohol, using bone-black, and letting the filtered solution stand at 0°. The salt separates as colorless plates and flat needles, which melt at 135–6.5° with slight preliminary softening and evolve gas above 200°. It is very readily soluble in water, the free oily ester separating from the solution on adding sodium carbonate.

0.1353 g. subst.; 0.0837 g. AgCl.
Calc. for $C_{10}H_{13}O_3N.HCl$: Cl, 15.31%. Found: Cl, 15.31%.

2-Methyl-5-nitrophenoxyacetic Acid.—The dry sodium salt of 2-methyl-5-nitrophenol was prepared from equimolecular amounts of the nitrocresol and alcoholic sodium hydroxide by evaporating to dryness *in vacuo*, then in a desiccator, and finally in an air bath at 140°. 55.2 g. of the salt thus obtained were heated in an oil bath under an air condenser with 38.7 g. chloroacetic ester (1 mol) until clear at 130–40° and finally for 2 hours at 175°. The melt was taken up in alcohol, diluted with an equal volume of water, and the ester saponified by warming with an ex-

cess of sodium hydroxide. The nitro acid, precipitated by means of sulfuric acid, weighed 49.8 g. Recrystallized first from acetic acid, then water, it forms delicate, drab-colored needles which melt at 177–7.5° (cor.) with preliminary softening. It dissolves sparingly in cold water, acetic acid, or benzene, and readily in alcohol or acetone.

0.1617 g. subst.; 9.6 cc. moist N, 756 mm., 21.5°.
Calc. for $C_9H_9O_5N$: N, 6.64%. Found: N, 6.67%.

2-Methyl-5-aminophenoxyacetic Acid.—This substance is mentioned in Ger. pat. 230,592,[1] but we have been unable to find a description of its preparation or properties. 2-Methyl-5-nitrophenoxyacetic acid was reduced with tin and hydrochloric acid and the amino acid hydrochloride isolated exactly as in the case of *m*-aminophenoxyacetic acid. The salt was taken up with water, filtered, and the free acid precipitated by addition of sodium acetate solution. Recrystallized by dissolving in dilute hydrochloric acid and precipitating with sodium acetate, it forms sheaves of minute spindles which decompose at about 232° with preliminary softening. It is difficultly soluble in the usual neutral solvents and gives no color with ferric chloride.

0.1444 g. subst.; 9.8 cc. N, 761 mm., 21.0°.
Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.70%.

4-Methyl-5-nitrophenoxyacetic Acid.—The sodium salt of 4-methyl-5-nitrophenol was prepared by dissolving the nitrocresol in the theoretical amount of 2 *N* sodium hydroxide solution and salting out with sodium chloride. The phenoxyacetic acid was prepared from the dried salt exactly as in the two preceding cases. The yield was practically theoretical. Recrystallized first from water, using bone-black, then from acetic acid, the compound melts at 151–4° (cor.) with preliminary softening. It separates from toluene in feathery aggregates of very faintly yellow crystals which melt as above. The acid dissolves in acetic acid or hot toluene, giving colorless solutions, while the solution in boiling water is yellow.

0.1680 g. subst.; 10.1 cc. N, 760 mm., 21.0°.
Calc. for $C_9H_9O_5N$: N, 6.64%. Found: N, 6.81%.

4-Methyl-5-aminophenoxyacetic Acid.—The nitro acid was reduced as in previous examples. The amino acid was isolated from the crude hydrochloride by taking this up in water, filtering, and adding sodium acetate. Recrystallized from water, it forms long, narrow, slightly brownish leaflets which soften above 200° and melt with decomposition at 235–40°. It is very difficultly soluble in the usual neutral solvents. A solution in hot water gives, with ferric chloride, a purplish color, changing through brown to green and depositing dark green flocks.

[1] Friedländer, *Fortschr. Teerfarbenfabrik.*, 10, 880.

0.1403 g. subst.; 9.3 cc. N, 763 mm., 25.5°.
Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.61%.

3-Nitro-6-methoxyphenoxyacetic Ethyl Ester.—The sodium salt of 5-nitroguaiacol was prepared from 5-nitroguaiacol and alcoholic sodium hydroxide. Recrystallized from 85% alcohol, it forms orange-red, glistening needles which are easily soluble in water and burn explosively when placed in a flame. 28.7 g. of the dried salt were heated for about 1.5 hours in an oil bath at 150° with 18.4 g. chloroacetic ester (until the melt was clear) and then at 180° for about 2 hours. The melt was cooled, taken up with benzene, filtered from sodium chloride, and precipitated with ligroin. The yield of ester was 33 g. Recrystallized twice from 95% alcohol and twice from benzene it forms faintly yellow rhombs which melt at 84.5–5° (cor.) with slight preliminary softening. The ester is sparingly soluble in the cold in 95% alcohol or dry ether, and dissolves in benzene or toluene.

Kjeldahl: 0.2562 g. subst.; 9.9 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_6N$: N, 5.49%. Found: N, 5.41%.

3-Nitro-6-methoxyphenoxyacetic Acid.—The ester was dissolved in 50% alcohol and warmed on the water bath with an excess of sodium hydroxide for one-half hour. The solution was cooled, diluted with water, and the nitro acid precipitated with sulfuric acid. After filtering, washing with water, and drying, the yield was 37 g. from 35.5 g. of the dry sodium salt of 5-nitroguaiacol. Recrystallized successively from 85% alcohol, acetic acid, and 95% alcohol, the nitro acid forms glistening, cream-colored, microscopic prisms which sublime slightly above 150° and melt at 184.5–6° (cor.) with preliminary softening It is very difficultly soluble in the cold in water, alcohol, chloroform, benzene, or toluene.

Kjeldahl: 0.1899 g. subst.; 8.15 cc. 0.1 *N* HCl.
Calc. for $C_9H_9O_6N$: N, 6.17%. Found: N, 6.01%.

3-Amino-6-methoxyphenoxyacetic Acid.—10 g. of the nitro acid were dissolved in dilute aqueous ammonia, warmed, and added to a hot solution of 90 g. of crystallized ferrous sulfate in 230 cc. water. Ammonia was added in excess and the mixture heated for about 15 minutes before filtering. The filtrate was acidified with acetic acid and concentrated to small bulk. The amino acid separated in a yield of 6 g. Purified by dissolving in a little dilute hydrochloric acid, boiling with bone-black, filtering, and adding sodium acetate to the filtrate, then by recrystallization from water, the substance forms clusters of minute needles which contain between 0.5 and one molecule of water of crystallization. It is very difficultly soluble in the usual neutral solvents and, when anhydrous, melts with preliminary decomposition at 222–4°. In aqueous suspension the amino acid gives a deep violet color with ferric chloride, while it dissolves in concentrated sulfuric acid with an indigo color.

Kjeldahl: 0.1995 g. subst.; 9.4 cc. 0.1 *N* HCl.
Calc. for $C_9H_{11}O_4N$: N, 6.51%. Found: N, 6.60%.

The amino acid was also prepared through the acetamino derivative by the following series of reactions:

5-Acetaminoguaiacol(3-acetamino-6-methoxyphenol). — The hydrochloride of 5-aminoguaiacol was prepared by reduction of the nitro compound according to Mameli.[1] The acetamino derivative was obtained by dissolving the hydrochloride in water, adding an excess of sodium acetate, and then shaking with 1.1 mols of acetic anhydride, essentially as described by Jona and Pozzi.[2] The product obtained by us, however, differed in its properties from those recorded by these authors. Recrystallized twice from 95% alcohol it forms glistening, rhombic prisms, which melt at 169–72° with preliminary softening, instead of 116–9°. It is difficultly soluble in cold water, or hot benzene, but dissolves more readily in the cold in alcohol or acetone. An aqueous suspension gives a slowly developing olive-brown color with ferric chloride and dissolves with a pink color, changing to brown, when a drop of sodium hydroxide solution is added.

0.1333 g. subst.; 9.0 cc. N, 763 mm., 22.5°.
Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.83%.

3-Acetamino-6-methoxyphenoxyacetic Acid.—84 g. 5-acetaminoguaiacol and 44 g. chloroacetic acid were dissolved in 800 cc. water containing 37.2 g. sodium hydroxide (2 mols) and slowly boiled down to small volume in an open flask. The solution was cooled, acidified with acetic acid, filtered from any unchanged acetaminoguaiacol, and then acidified to Congo red with mineral acid. An excellent yield of the phenoxyacetic acid was obtained. Formed in this way, the acid separates as a hydrate which melts at about 110° and is easily soluble in acetic acid, but on rubbing the solution in this solvent or recrystallizing even from water an anhydrous form, crystallizing in rhombs, is obtained. A portion, recrystallized first from water, then from acetic acid, melted at 208–10° (cor.) with preliminary softening. The anhydrous acid is difficultly soluble in the cold in the usual neutral solvents. When boiled with 1:1 hydrochloric acid, it yields the above amino acid.

Kjeldahl: 0.2950 g. subst.; 12.10 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_5N$: N, 5.86%. Found: N, 5.75%.

(*C*) *p*-Nitro- and *p*-Aminophenoxyacetic Acids.

Especially in the case of the *p*-aminophenoxyacetic acids is it preferable, as stated in the introduction, to proceed over the corresponding acetamino compounds, owing to the ease with which the parent aminophenols may be prepared. Of the methods available, we have found it

[1] Mameli, *Chem. Zentr.*, 1908, I, 25.
[2] Jona and Pozzi, *Gaz. chim. ital.*, 41, I, 729 (1911).

very satisfactory, both from the standpoint of yield and of convenience, to nitrosate phenols containing a free *para* position and then reduce the nitrosophenols in ammoniacal solution with hydrogen sulfide, according to the method used by Henderson and Sutherland[1] in the case of *p*-nitrosothymol.

p-Aminophenoxyacetic Acid.—The *p*-aminophenol necessary for the preparation of this substance was prepared as above indicated and converted into the acetyl derivative by the method of Lumière and Barbier.[1] 177 g. *p*-acetaminophenol, 111 g. chloroacetic acid, 188 g. 50% sodium hydroxide solution, and 1700 cc. water were boiled down to somewhat less than one-half volume in an open flask. The solution was then treated with one-half the original amounts of chloroacetic acid, sodium hydroxide, and water, and again boiled down to small volume. The acetaminophenoxy acetic acid was precipitated by acidifying to Congo red and was washed with water. The yield was 205 g., corresponding in properties to those given by Howard,[1] who omitted the second treatment with chloroacetic acid and alkali, a procedure which, however, we regard as essential for attaining high yields. The crude hydrochloride of *p*-aminophenoxyacetic acid was obtained by boiling the acetamino compound with 1 : 1 hydrochloric acid. The amino acid itself melts with gas evolution and subsequent resolidification at about 220°.[2]

The Methyl Ester Hydrochloride.—217 g. of crude *p*-aminophenoxyacetic acid hydrochloride were treated in 2 liters of dry methyl alcohol with a rapid stream of dry hydrochloric acid gas, without cooling. The ester hydrochloride separated and was filtered off and washed with dry ether. Additional fractions were obtained on concentrating the alcoholic filtrate *in vacuo*, the total yield being 205 g. A portion was recrystallized from absolute alcohol, forming long, broad needles which melted with effervescence at 223–5° when rapidly heated. The salt dissolves readily in water or methyl alcohol and only sparingly in cold absolute alcohol.

0.2803 g. subst.; 0.1852 g. AgCl.
Calc. for $C_9H_{11}O_3N.HCl$: Cl, 16.30%. Found: Cl, 16.34%.

The Methyl Ester.—A portion of the crude ester hydrochloride was dissolved in a little water and decomposed with sodium carbonate solution. The ester separated as an oil which rapidly crystallized. Recrystallized from water, it forms long needles which soften above 63° and melt at 65–6° (cor.). It is difficultly soluble in cold water and readily in cold alcohol or benzene. The aqueous solution gives a purple color with ferric chloride.

Kjeldahl: 0.3226 g. subst.; 17.7 cc. 0.1 *N* HCl.
Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.69%.

[1] *Loc. cit.*

[2] Cf. THIS JOURNAL.

p-Acetylmethylaminophenoxyacetic Acid, p-$CH_3CON(CH_3)C_6H_4OCH_2CO_2H$.—$p$-Acetylmethylaminophenol was prepared by dissolving "metol" in water, adding 1.1 mols of acetic anhydride, turbining, and adding an excess of sodium acetate. Equimolecular amounts of the phenol and chloroacetic acid and 2 mols of sodium hydroxide were boiled in 10 parts of water under a reflux condenser until neutral, about 2 hours being required. The solution was cooled, filtered from a small amount of unchanged phenol, and acidified to Congo red with hydrochloric acid. The phenoxyacetic acid, obtained in excellent yield, was filtered off and washed with water. Recrystallized twice from water, it forms almost colorless prisms which melt at 151–2° (cor.) with slight preliminary softening. The acid dissolves in ethyl acetate or absolute alcohol, but is only sparingly soluble in the cold in water or acetic acid, and practically insoluble in toluene or chloroform.

Kjeldahl: 0.3300 g. subst.; 14.55 cc. 0.1 N HCl.
Calc. for $C_{11}H_{13}O_4N$: N, 6.28%. Found: N, 6.17%.

p-Methylaminophenoxyacetic Acid.—The acetyl compound was boiled several hours with 5 parts 1 : 1 hydrochloric acid, concentrated *in vacuo* to a syrup, taken up with water, and treated with an excess of sodium acetate solution. The amino acid separated at once and was washed with water and alcohol and dried. In one series of experiments 70 g. p-methylaminophenol sulfate ("metol"), carried through the steps described above, yielded 60 g. of the amino acid. Recrystallized twice from water, it forms almost colorless, glistening scales which soften above 200° and melt at 213–4° with gas evolution. The substance is very difficultly soluble in the usual neutral solvents. An aqueous suspension gives a deep lilac color with ferric chloride, while a solution in dilute hydrochloric acid deposits glistening needles of a nitroso compound when treated with sodium nitrite solution.

Kjeldahl: 0.3108 g. subst.; 17.0 cc. 0.1 N HCl.
Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.66%.

p-Glycine Ethyl Ester Phenoxyacetic Acid, p-$H_5C_2O_2CCH_2NHC_6H_4OCH_2CO_2H$.—12 g. of air-dry p-aminophenoxy acetic acid were dissolved in 67 cc. of normal sodium hydroxide and boiled under a reflux condenser with 8.2 g. chloroacetic ethyl ester and 70 cc. alcohol for 1.5 hours. After cooling the ester separated on rubbing and was filtered off and washed with a little alcohol. Recrystallized twice from 85% alcohol, using bone-black, it forms almost colorless, radiating masses of hair-like needles which melt and decompose at 173–6° with preliminary softening. The ester gives a strong iodoform test and dissolves readily in water, the solution giving a violet color with ferric chloride.

Kjeldahl: 0.2117 g. subst.; 8.8 cc. 0.1 N HCl.
Calc. for $C_{12}H_{15}O_5N$: N, 5.53%. Found: N, 5.82%.

p-**Glycinephenoxyacetic Acid.**—The ethyl ester was warmed on the water bath for 10 minutes with a slight excess of double normal sodium hydroxide solution, cooled, acidified to Congo red with hydrochloric acid and concentrated *in vacuo*. The addition of strong hydrochloric acid caused a precipitate of the hydrochloride of the amino acid to separate on scratching. This was filtered off, dissolved in a small volume of hot water, and treated with saturated sodium acetate solution. The precipitate was filtered off and recrystallized from water, using bone-black, forming crusts consisting of spherules of micro-crystals. When rapidly heated to 175° and then slowly, the acid melts at 177–80° with gas evolution, a mixture with the ester melting at about 160°. When pure, the acid is rather difficultly soluble in cold water, acetic acid, or 95% alcohol. The aqueous solution gives a deep violet color with ferric chloride.

Kjeldahl: 0.2294 g. subst.; 14.3 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{11}O_5N$: N, 6.22%. Found: N, 6.23%.

The glycinephenoxyacetic acid was also prepared directly from *p*-aminophenoxyacetic acid, chloroacetic acid, and alkali, but, as made by this method, it could not be obtained analytically pure by recrystallization from water or 50% alcohol, probably owing to the presence of a more difficultly soluble diglycinephenoxyacetic acid. For synthetic purposes, however, the acid was sufficiently pure, as was shown by its conversion into the dimethyl ester.

The Dimethyl Ester.—10.6 g. of the crude acid were treated in 100 cc. of dry methyl alcohol with a stream of dry hydrochloric acid gas. The ester hydrochloride separated on cooling, the process being completed by the addition of dry ether. The yield was 10 g. A portion of the salt was decomposed with sodium carbonate solution, the gummy precipitate solidifying on rubbing. Recrystallized twice from methyl alcohol, it forms almost colorless, transparent prisms which melt at 63.5–4° (cor.) with slight preliminary softening. The ester is rather sparingly soluble in the cold in alcohol, methyl alcohol, or ether, but dissolves readily in benzene or acetone. The aqueous suspension gives a slowly developing violet color with ferric chloride, while a solution in acid yields an orange-colored precipitate with sodium nitrite.

0.1819 g. subst.; 8.8 cc. N, 766 mm., 26.5°.
Calc. for $C_{12}H_{15}O_5N$: N, 5.53%. Found: N, 5.37%.

2-Methyl-4-acetaminophenoxyacetic Acid.—*o*-Cresol was nitrosated in aqueous solution by means of sulfuric acid and sodium nitrite and the nitroso compound reduced in 10% ammoniacal solution with hydrogen sulfide. The resulting *p*-amino-*o*-cresol was acetylated as in previous examples. 62.5 g. *p*-acetamino-*o*-cresol, 40 g. chloroacetic acid, and 33.7 g. sodium hydroxide were dissolved in 500 cc. water, boiled down in an open flask to a volume of about 200 cc., and then boiled under a reflux con-

denser until neutral. The solution was cooled and acidified with hydrochloric acid. The yield of acetamino acid was 75% of the theory. Recrystallized twice from acetic acid, it melts with preliminary softening at 202–4.5°. It is very difficultly soluble in the cold in the usual solvents.

Kjeldahl: 0.3071 g. subst.; 13.05 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_4N$: N, 6.28%. Found: N, 5.95%.

2-Methyl-4-nitrophenoxyacetic Acid.—Equimolecular amounts of the dried sodium salt of *p*-nitro-*o*-cresol and ethyl chloroacetate were heated as in previous examples and the crude ester saponified in the usual way. Recrystallized twice from 50% acetic acid, then from toluene, the nitro acid forms practically colorless, felted needles which melt with preliminary softening at 127.5–30.5° to a liquid which clears completely at 135.5°. It is easily soluble in alcohol, hot 50% acetic acid, or hot toluene.

0.1369 g. subst.; 8.15 cc. moist N, 774 mm., 21.7°.
Calc. for $C_9H_9O_5N$: N, 6.64%. Found: N, 6.85%.

2-Methyl-4-aminophenoxyacetic Acid.—This substance was obtained both by reduction of the nitro acid in aqueous-alcoholic hydrochloric acid by means of tin, and by saponification of the acetyl derivative with 1 : 1 hydrochloric acid. The acid was separated from the solution of its hydrochloride by means of sodium acetate and purified by taking up in dilute hydrochloric acid and again adding sodium acetate solution. The amino acid forms almost colorless needles which sinter at about 230° and then darken, but do not melt up to 285°. It is difficultly soluble in the usual neutral solvents, and, in aqueous suspension, gives a deep violet color with ferric chloride. The substance apparently separates with one molecule of water of crystallization which is not lost at 100° *in vacuo*.

0.1254 g. subst.; 7.6 cc. N, 760 mm., 19.5°.
Calc. for $C_9H_{11}O_3N.H_2O$: N, 7.04%. Found: N, 7.08%.

The Methyl Ester Hydrochloride.—The salt was prepared in the same way as in previous cases, completing the precipitation by the addition of dry ether. Recrystallized from absolute alcohol, it forms minute needles which melt and decompose at 195–200° with preliminary softening. The salt is readily soluble in water, the solution giving a gradually deepening purple color with ferric chloride.

0.2748 g. subst.; 0.1679 g. AgCl.
Calc. for $C_{10}H_{13}O_3N.HCl$: Cl, 15.31%. Found: Cl, 15.12%.

The Methyl Ester.—Sodium carbonate separates the ester from the salt as an oil which solidifies on scratching. Dried and recrystallized from ligroin, the only one of the usual organic solvents in which it is difficultly soluble, it forms colorless needles which melt at 59.5–60° (cor.) with slight preliminary softening.

Kjeldahl: 0.3077 g. subst.; 0.1525 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{13}O_3N$: N, 7.18%. Found: N, 6.92%.

The Ethyl Ester Hydrochloride.—This was prepared in the same way as the methyl esters, concentrating the solution to small bulk *in vacuo* and precipitating the salt with dry ether. Recrystallized by dissolving in absolute alcohol and precipitating with dry ether, it forms colorless, glistening needles and plates, which melt at about 185–93° with gas evolution and preliminary softening.

0.1540 g. subst.; 11.63 cc. $AgNO_3$ soln.[1]
Calc. for $C_{11}H_{15}O_3N.HCl$: Cl, 14.44%. Found: Cl, 14.01%.

The Ethyl Ester.—Sodium carbonate separates the ester from an aqueous solution of the salt as an oil which soon solidifies. Recrystallized first from ligroin, then by dissolving in a little hot benzene, adding ligroin cautiously, and cooling, the ester separates as pale brown prisms which melt at 43.4.5° (cor.) with preliminary softening. It is less easily soluble in ligroin than in the other organic solvents.

0.0793 g. subst.; 4.9 cc. N, 756 mm., 26.5°.
Calc. for $C_{11}H_{15}O_3N$: N, 6.70%. Found: N, 6.77%.

3-Methyl-4-acetaminophenoxyacetic Acid.—*p*-Acetamino-*m*-cresol was prepared through the nitroso compound of *m*-cresol by reduction with ammonia and hydrogen sulfide and acetylation of the aminophenol as in the preceding examples. 21 g. acetamino compound, 13.3 g. chloroacetic acid, and 11.2 g. sodium hydroxide were dissolved in 300 cc. water and boiled down to about 100 cc., continuing the boiling under a reflux condenser until neutral. The solution was then cooled and the acetamino acid precipitated by adding hydrochloric acid. The yield was 21 g. Recrystallized from water, it forms aggregates of flat, glistening prisms, which, after a subsequent recrystallization from acetic acid, melt at 165–7.5° with preliminary softening. The acid is difficultly soluble in the cold in water or acetic acid.

0.3174 g. subst.; 13.70 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_4N$: N, 6.28%. Found: N, 6.05%.

3-Methyl-4-nitrophenoxyacetic Acid.—This substance was prepared in the usual way from the dried sodium salt of *p*-nitro-*m*-cresol and a slight excess of chloroacetic ester, followed by saponification. The yield was 87% of the theory. Recrystallized first from 50% alcohol, with boneblacking, then from acetic acid, the nitro acid forms faintly yellow needles which become opaque on drying and melt at 141–3°.

0.1124 g. subst.; 6.6 cc. N, 764 mm., 26.0°.
Calc. for $C_9H_9O_5N$: N, 6.64%. Found: N, 6.52%.

3-Methyl-4-aminophenoxyacetic Acid.—This substance was prepared as in the case of its isomer, both by reduction of the nitro acid with tin

[1] 1 cc. = 0.00186 g. Cl.

and aqueous alcoholic hydrochloric acid and, more conveniently, by hydrolysis of the acetamino acid.

Recrystallized from water it forms slightly brownish, hexagonal plates which contain one molecule of water of crystallization. The acid decomposes partially below the melting point, which lies at about 217–9°. In aqueous solution it gives a violet color with ferric chloride. The acid is very difficultly soluble in benzene or cold water.

1.2986 g. subst.; 0.1192 g. loss, 100° *in vacuo* H_2O, 9.18%. 1 H_2O, 9.05%.
Anhydrous: Kjeldahl: 0.2296 g. subst.; 13.0 cc. 0.1 *N* HCl.
Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.93%.

3-Methyl-4-aminophenoxyacetic Methyl Ester Hydrochloride.—On esterification of the acid in dry methyl alcohol saturated with hydrochloric acid the salt separated as large, glistening plates, more being obtained by addition of dry ether. Recrystallized by dissolving in dry methyl alcohol and precipitating with dry ether, it melts and effervesces at 195–200° with slight preliminary softening.

0.2410 g. subst.; 0.1504 g. AgCl.
Calc. for $C_{10}H_{13}O_3N.HCl$: Cl, 15.31%. Found: Cl, 15.43%.

The Methyl Ester.—The crude ester, precipitated from the salt by means of sodium carbonate, was recrystallized from 85% alcohol, forming rosets of glistening needles which soften above 104° and melt at 105–5.5° (cor.). The base is readily soluble in methyl alcohol, less easily in ether.

Kjeldahl: 0.2874 g. subst.; 14.25 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{13}O_3N$: N, 7.18%. Found: N, 6.95%.

The Ethyl Ester Hydrochloride.—This was prepared in the same way as its 2-methyl isomer. Recrystallized twice from absolute alcohol, in which it is rather difficultly soluble, it forms rhombic crystals, which melt at about 203–4° with gas evolution and preliminary softening.

0.2102 g. subst.; 0.1227 g. AgCl.
Calc. for $C_{11}H_{15}O_3N.HCl$: Cl, 14.44%. Found: Cl, 14.43%.

The Ethyl Ester.—Sodium carbonate deposited the ester from an aqueous solution of the salt as an oil which crystallized after several days in the ice box. The product was dried, taken up in alcohol-free ether, and the solution filtered and allowed to evaporate spontaneously in the ice box. The crystalline portion of the residue was freed from oil by pressing out on a porous plate and was recrystallized twice from alcohol-free ether with the aid of a freezing mixture. The ester forms pale brown needles which soften above 53.5° and melt at 55–5.5° (cor.). It dissolves readily at room temperature in the usual organic solvents except ligroin.

Kjeldahl: 0.2765 g. subst.: 12.85 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{15}O_3N$: N, 6.70%. Found: N, 6.51%.

3-Methyl-4-chloroacetylaminophenoxyacetic Acid.—6.25 g. of the

amino acid were suspended in water and dissolved by adding a solution of sodium hydroxide, drop by drop. An excess of sodium acetate was next added, followed by 5 cc. chloroacetyl chloride, with shaking and chilling. A thick paste of the sodium salt of the chloroacetyl compound resulted. This was dissolved by adding water and the solution neutralized with sodium hydroxide and again shaken with 3 cc. chloroacetyl chloride. The mixture was then made acid to Congo red, the chloroacetyl derivative separating as a voluminous mass of hair-like needles. After recrystallization from water the yield was 5.5 g. Recrystallized first from acetic acid, then from toluene, the substance forms rosets of delicate needles which melt at 159–60.5° (cor.) with slight preliminary softening. It is difficultly soluble in the cold in water, acetic acid, or toluene. When recrystallized from acetic acid it contains solvent of crystallization which is only slowly lost in the air, three weeks being required in one instance.

Kjeldahl: 0.2972 g. subst.; 11.50 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{12}O_4NCl$: N, 5.44%. Found: N, 5.42%.

o-Allylphenol, o-$H_2C : CHCH_2C_6H_4OH$.—This substance was encountered by Claisen[1] on decomposing 3-allylsalicylic acid by means of heat, but was not described in detail. The substance is easily obtained in good yield by the general method discovered by Claisen[2] for the conversion of the allylethers of phenols into their corresponding *o*-allylphenols. Owing to the comparatively low boiling point of phenyl allyl ether the isomerization takes somewhat longer than in most of the cases given by Claisen,[3] but is nevertheless practically quantitative. When the temperature of the boiling liquid no longer rises (219–20° is the maximum we observed) the product is dissolved in alkali, shaken out with ligroin if necessary, and the aqueous solution acidified with sulfuric acid. The allylphenol is taken up in ligroin, washed with water, filtered, dried over sodium sulfate, and evaporated. On fractionating *in vacuo* practically the entire amount boiled over at 109–10° at 22 mm. Claisen gives 96–100° at 12 mm. The phenol solidifies in a freezing mixture to a mass of crystals which melt at —6°. An aqueous suspension instantly reduces permanganate, and, with ferric chloride, gives a transitory dull blue color, changing to a muddy, greenish brown.

0.1031, 0.1062 g. subst.; 0.3040, 0.3138 g. CO_2; 0.0701, 0.0734 g. H_2O.
Calc. for $C_9H_{10}O$: C, 80.55%; H, 7.52%. Found: C, 80.42, 80.59%; H, 7.61, 7.74%.

p-Nitroso-o-allylphenol.—50 g. *o*-allylphenol were dissolved in 5 liters of water containing 375 cc. of normal sodium hydroxide solution and 170 g. sodium nitrite added. After adding ice, the mixture was vigorously

[1] Claisen, *Ann.*, 401, 73 (1913).
[2] *Ibid.*, p. 21.
[3] *Ibid.*, p. 49.

turbined while adding, drop by drop, a solution of 125 cc. acetic acid in 1250 cc. water, adding ice from time to time so as to keep the temperature below 5°. The nitroso compound separates at first as a dark tar which finally crystallizes. After stirring until the entire product is crystalline, the mixture is allowed to stand in the cold for about 2 hours. The supernatant liquid is then decanted off and the precipitate filtered, washed, and purified by taking up in 20% sodium carbonate solution, filtering from tar, and acidifying with sulfuric acid. As obtained in this way, the yield of nitroso compound was 35 g. Recrystallized from toluene, it forms yellow-brown crystalline aggregates which soften above 97.5° and melt with partial decomposition at 99.5–100°. The substance is very difficultly soluble in cold toluene, very easily in hot, and readily soluble in cold absolute alcohol. It dissolves in sodium hydroxide, sodium carbonate, or ammonia solutions with a brown-orange color, and in sulfuric acid-phenol (Liebermann test) with an olive green color.

0.1518 g. subst.; 11.4 cc. N, 761 mm., 24.0°.
Calc. for $C_9H_9O_2N$: N, 8.59%. Found: N, 8.39%.

2-Allyl-4-aminophenol.—34 g. *p*-nitroso-*o*-allylphenol were dissolved in 350 cc. dilute ammonia (1 part concentrated to 1.5 parts water) and saturated with hydrogen sulfide. The aminophenol was filtered off, washed with water, taken up in dilute hydrochloric acid, filtered from sulfur, and reprecipitated by means of ammonia. The yield was 25 g. Recrystallized from 50% alcohol, it forms delicate, slightly brownish leaflets which soften above 111° and melt at 112.5–13.5° (cor.). It dissolves readily in absolute alcohol or acetone and difficultly in cold benzene, readily on warming. An aqueous suspension gives a slowly developing purple color, followed by a brown precipitate, with ferric chloride. A solution in dilute alkali changes through green and violet to brown.

Kjeldahl: 0.1972 g. subst.; 13.35 cc. 0.1 *N* HCl.
Calc. for $C_9H_{11}ON$: N, 9.40%. Found: N, 9.48%.

2-Allyl-4-acetaminophenol.—25 cc. acetic anhydride were added to a solution of 25 g. of the aminophenol in 200 cc. of normal hydrochloric acid, followed, with vigorous stirring, by an excess of saturated sodium acetate solution. The acetamino compound separated as an oil which soon crystallized. The yield was 26 g. Recrystallized from a large volume of boiling benzene, it forms lenticular platelets which soften at 92° and melt at 93–3.5° (cor.). It is very easily soluble in acetic acid, alcohol, or ether. A solution in the first reduces permanganate instantly, while a suspension in water gives a momentary blue color with ferric chloride, changing to greenish gray.

Kjeldahl: 0.2999 g. subst.; 15.50 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_2N$: N, 7.33%. Found: N, 7.24%.

2-Allyl-4-acetaminophenoxyacetic Acid.—24 g. of the crude acet-

aminoallylphenol, 11.3 g. chloroacetic acid, 19.2 g. 50% sodium hydroxide solution, and 200 cc. water were boiled down to small bulk in an open flask. One-half of the above quantities of chloroacetic acid, alkali, and water were then added and the solution again boiled down to small volume. After dilution with warm water the solution was made just acid with acetic acid, bone-blacked, filtered, and made acid to Congo red. The acetamino acid separated as an oil which rapidly crystallized. The yield was 30 g. A small portion was recrystallized twice from acetic acid and then from xylene, forming almost colorless, wedge-shaped crystals which melted at 181–3° (cor.). The acid dissolves in acetone or acetic acid in the cold and is only very sparingly soluble in water or xylene at their boiling points. A solution in acetic acid reduces permanganate instantly, showing the allyl group to be still intact.

Kjeldahl: 0.2940 g. subst.; 11.70 cc. 0.1 *N* HCl.
Calc. for $C_{13}H_{15}O_4N$: N, 5.62%. Found: N, 5.58%.

2-Allyl-4-aminophenoxyacetic Acid.—10 g. of the crude acetamino acid were boiled for 20 minutes under an air condenser with 50 cc. 25% sulfuric acid, a clear solution being eventually obtained. This was cooled and treated with 20% sodium carbonate solution until most of the free acid was neutralized and a small amount of tar separated. Sodium acetate solution was then added in excess, the amino acid separating and rapidly crystallizing. The crude product was suspended in water, dissolved in a slight excess of hydrochloric acid, bone-blacked, and filtered. The amino acid separated from this solution on adding an excess of sodium acetate as spherules of microscopic leaflets which dissolved with difficulty in the usual neutral solvents. The yield was 4.7 g. When rapidly heated to 190°, then slowly, the acid softens and finally melts with gas evolution at 193.5–4° to a red liquid. An aqueous suspension gives a slowly-developing, deep violet color with ferric chloride. The diazonium solution couples with R-salt to yield a much deeper red than is obtained in the case of the other aminoalkylphenoxyacetic acids.

Kjeldahl: 0.1965 g. subst.; 9.5 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_3N$: N, 6.76%. Found: N, 6.77%.

***p*-Acetamino-*p*-xylenol(2,5-dimethyl-4-acetaminophenol).**—The necessary *p*-amino-*p*-xylenol was obtained in practically quantitative yield by the reduction of *p*-nitroso-*p*-xylenol in ammoniacal solution by means of hydrogen sulfide. The amino compound was converted into its acetyl derivative by dissolving in 1 mol hydrochloric acid, adding 1.25 mols acetic anhydride, turbining, and adding an excess of sodium acetate. The yield was almost quantitative. Recrystallized successively from water, acetic acid, and absolute alcohol, it forms transparent octahedra which soften at 178.5° and melt at 180–1.5° (cor.). The substance is practically insoluble in benzene, sparingly soluble in cold water, and

more readily in the cold in acetone, acetic acid, or alcohol. An aqueous solution gives a dull blue color with ferric chloride.

Kjeldahl: 0.3165 g. subst.; 17.50 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{13}O_2N$: N, 7.82%. Found: N, 7.75%.

2,5-Dimethyl-4-acetaminophenoxyacetic Acid.—This was prepared as in previous examples, adding additional amounts of chloroacetic acid, alkali, and water after the first heating. 37 g. were obtained from 33.6 g. of the acetaminoxylenol. Recrystallized first from water, then from acetic acid, the acetamino acid forms rosets of needles which melt, with preliminary softening, at 195–7° (cor.) to a yellow liquid. It is somewhat soluble in cold acetone, very sparingly in benzene or water.

Kjeldahl: 0.3119 g. subst.; 12.85 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{15}O_4N$: N, 5.91%. Found: N, 5.77%.

2,5-Dimethyl-4-aminophenoxyacetic Acid.—This substance was formed in quantitative yield on boiling the acetamino compound with 5 parts of 1 : 1 hydrochloric acid for 2 hours. The hydrochloride, which separated on cooling, yielded the free amino acid when dissolved in water and treated with sodium acetate. Recrystallized from water, the amino acid forms almost colorless, glistening scales which melt and decompose at 210–5° when rapidly heated, resolidifying and then not melting below 280°. It is very sparingly soluble in the usual neutral solvents, and, in aqueous suspension, gives an ultramarine color with ferric chloride.

Kjeldahl: 0.3798 g. subst.; 19.20 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{13}O_3N$: N, 7.18%. Found: N, 7.08%.

The Methyl Ester Hydrochloride.—The salt separated practically quantitatively on saturation of a methyl alcoholic suspension of the acid with hydrochloric acid gas. Recrystallized from dry methyl alcohol, it forms prismatic needles which darken and soften above 220° and melt with decomposition at 232–4°. It is quite soluble in water, difficultly in cold absolute alcohol.

0.2534 g. subst.; 0.1478 g. AgCl.
Calc. for $C_{11}H_{15}O_3N.HCl$: Cl, 14.44%. Found: Cl, 14.43%.

The Methyl Ester.—The ester separates as an oil which crystallizes on rubbing. Recrystallized twice from methyl alcohol it forms long, flat needles, which melt at 66.5–7° (cor.) with slight preliminary softening. It is readily soluble at room temperature in the usual organic solvents except ligroin, and only sparingly soluble in methyl alcohol at 0°.

Kjeldahl: 0.3050 g. subst.; 14.50 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{15}O_3N$: N, 6.70%. Found: N, 6.66%.

2,5-Dimethyl-4-aminophenoxyacetic Ethyl Ester Hydrochloride.—The salt separated from the ethyl alcoholic-hydrochloric acid reaction mixture on standing. Recrystallized from absolute alcohol, it forms long, glis-

tening needles which, when rapidly heated, melt at 205–15° with decomposition and preliminary softening.

0.3125 g. subst.; 0.1729 g. AgCl.
Calc. for $C_{12}H_{17}O_3N.HCl$: Cl, 13.66%. Found: Cl, 13.69%.

The Ethyl Ester.—The base separates as an oil which solidifies on rubbing. Recrystallized first from 50% alcohol, then twice from ligroin, it forms long needles which melt at 66–6.5° (cor.) with preliminary sintering, practically the same temperature as the melting point of the methyl ester. A mixture of the two substances melted at about 50°. The ethyl ester is readily soluble in the usual organic solvents at room temperature, with the exception of ligroin. Aqueous suspensions of both esters give violet colors with ferric chloride.

Kjeldahl: 0.3096 g. subst.; 13.15 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{17}O_3N$: N, 6.28%. Found: N, 5.95%.

Acetaminocarvacrol.—32 g. aminocarvacrol were suspended in 200 cc. water, 12 cc. acetic acid added, and the mixture then turbined and treated with 25 cc. acetic anhydride. The acetyl derivative separated as a thick oil which gradually crystallized and then showed the properties recorded in the literature. The yield was 38.5 g.

2-Methyl-4-acetamino-5-isopropylphenoxyacetic Acid.—This substance was obtained in practically quantitative yield by the method given in previous cases. The acid separated as an oil which rapidly crystallized. Recrystallized from much water it forms glistening needles with a faint pink tinge which are difficultly soluble in the cold in neutral solvents. The acid melts constantly at 190–1.5° (cor.) with preliminary softening.

Kjeldahl: 0.3899 g. subst.; 14.50 cc. 0.1 *N* HCl.
Calc. for $C_{14}H_{19}O_4N$: N, 5.28%. Found: N, 5.21%.

2-Methyl-4-amino-5-isopropylphenoxyacetic Acid.—This was obtained in quantitative yield by boiling the acetamino acid with 5 parts of 1 : 1 hydrochloric acid for 2 hours, cooling, filtering off the hydrochloride, and recovering the remainder from the filtrate by concentration. The acid was liberated from the salt as in previous examples and was purified by a repetition of the process. The amino acid forms faintly purplish prisms which soften above 215° and melt at 225–6° with effervescence. It is very difficultly soluble in the usual neutral solvents and, in aqueous suspension, gives an ultramarine color with ferric chloride.

Kjeldahl: 0.3178 g. subst.; 14.25 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{17}O_3N$: N, 6.28%. Found: N, 6.28%.

The Methyl Ester Hydrochloride.—This was prepared as in previous cases. A portion of the salt was dissolved in boiling absolute alcohol, cooled, and precipitated with dry ether, forming flat rods which softened above 180° and melted at 185–6° (cor.). It is rather sparingly soluble

in the cold in absolute alcohol or water, and in solution in the latter, gives a slowly-developing blue-violet color with ferric chloride.

0.3295 g. subst.; 0.1712 g. AgCl.
Calc. for $C_{13}H_{19}O_3N.HCl$: Cl, 12.96%. Found: Cl, 12.85%.

The Methyl Ester.—The base separated as an oil which crystallized on standing overnight in the ice box. Recrystallized from ligroin, it formed silky, hair-like needles which melted at 29–30° (cor.) and dissolved readily in the other organic solvents. The ester is strongly triboelectric.

0.0739 g. subst.; 4.0 cc. N, 763 mm., 24.5°.
Calc. for $C_{13}H_{19}O_3N$: N, 5.91%. Found: N, 6.05%.

***p*-Acetaminothymol.**—*p*-Aminothymol was prepared according to Henderson and Sutherland[1] and acetylated as described above in the case of its isomer, acetaminocarvacrol.

3-Methyl-4-acetamino-6-isopropylphenoxyacetic Acid.—The acid was obtained in the usual way, the yield being somewhat less than in the case of the isomeric 2,4,5-compound. Recrystallized from 50% acetic acid, it forms glistening needles which melt at 186.5–88° (cor.) with slight preliminary softening. It is difficultly soluble in water or toluene, easily in acetic acid or acetone.

Kjeldahl: 0.3457 g. subst.; 12.80 cc. 0.1 *N* HCl.
Calc. for $C_{14}H_{19}O_4N$: N, 5.28%. Found: N, 5.19%.

3-Methyl-4-amino-6-isopropylphenoxyacetic Acid.—The amino acid was prepared as in the case of the isomer. Recrystallized from ethyl acetate, it forms slightly brownish aggregates of rhombs which melted and decomposed at 204–6° when rapidly heated. It is very difficultly soluble in the usual neutral solvents and, in aqueous suspension, gives an ultramarine color with ferric chloride, as in the case of its isomer.

Kjeldahl: 0.3181 g. subst.; 14.10 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{17}O_3N$: N, 6.28%. Found: N, 6.21%.

The Methyl Ester Hydrochloride.—The salt was isolated in almost quantitative yield by evaporating to dryness *in vacuo* the methyl alcoholic-hydrochloric acid solution obtained in the esterification of the acid, taking up in a little hot absolute alcohol, and precipitating with dry ether. The salt separated slowly in sheaves and rosets of delicate needles which dissolved readily in methyl or ethyl alcohols and which, after purifying by a repetition of the final steps above, melted at 169–71° with slight preliminary softening. The aqueous solution, like the acid, gives an ultramarine color with ferric chloride. On addition of sodium carbonate the ester separated as an oil which did not crystallize.

0.2825 g. subst.; 0.1464 g. AgCl.
Calc. for $C_{13}H_{19}O_3N.HCl$: Cl, 12.96%. Found: Cl, 12.82%.

[1] *Loc. cit.*

2-Bromo-4-nitrophenol.—Van Erp[1] brominated *p*-nitrophenol in acetic acid solution, but obtained a pure product only after precipitating the accompanying dibromo compound by means of aniline. As will be seen below, removal of this substance can be readily accomplished simply by adding water. 97.3 g. *p*-nitrophenol were dissolved in about 250 cc. acetic acid and treated in several portions with a solution of 35 cc. bromine in 35 cc. acetic acid. The solution was then warmed on the water bath for several hours, until a test portion, when diluted with water, gave an oily precipitate which crystallized on cooling and scratching. An equal volume of water was next added, the solution cooled and allowed to stand for about 2 hours. The precipitated dibromo compound was filtered off and the filtrate diluted with a further quantity of water, precipitating the 2-bromo-4-nitrophenol. This was dried (yield, 83 g.) and recrystallized from toluene, then melting at 113–4°, as given for the product obtained by Diels and Bunzl[2] by hydrolysis of the ethyl ether.

2-Bromo-4-aminophenol Hydrochloride.—This substance was obtained by adding the nitrophenol in small portions to a solution of stannous chloride in concentrated hydrochloric acid. The double tin salt separated at once and was filtered off and decomposed in the usual manner. The yield of the aminophenol hydrochloride was excellent. When rapidly heated it darkens above 230° and decomposes to a purple tar at about 260–5°, corresponding in its other properties to those given by Hölz.[3]

2-Bromo-4-acetaminophenol.—This was prepared from the hydrochloride in aqueous solution with acetic anhydride and sodium acetate as in numerous previous examples, and showed the properties given by Hölz.

2-Bromo-4-acetaminophenoxyacetic Acid.—46.3 g. of the bromoacetaminophenol, 19 g. chloroacetic acid, 16.1 g. sodium hydroxide, and 400 cc. water, were boiled down to small bulk in an open flask, diluted with water, and made just acid with acetic acid. After filtering from traces of unchanged bromoacetaminophenol the phenoxyacetic acid was precipitated by acidification to Congo red. Recrystallized twice from acetic acid the compound forms slightly brownish aggregates of minute prisms which soften above 200° and melt to a brown liquid at 216–9.5° (cor.). It is somewhat less difficultly soluble at room temperature in absolute alcohol than in the other usual solvents.

Kjeldahl: 0.3784 g. subst.; 13.10 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{10}O_4NBr$: N, 4.86%. Found: N, 4.85%.

2-Bromo-4-aminophenoxyacetic Acid.—The acetamino acid was hydrolyzed with 1 : 1 hydrochloric acid, the amino acid hydrochloride separa-

[1] Van Erp, *Rec. trav. chim.*, **29**, 187 (1910).
[2] Diels and Bunzl, *Ber.*, **38**, 1491 (1905).
[3] Hölz, *J. prakt. Chem.*, [2] **32**, 65 (1885).

ting from the solution on cooling. This was converted into the free amino acid by treatment with sodium acetate in the usual way and the amino acid purified by a repetition of the process. The acid forms minute, almost colorless prisms which are very sparingly soluble in the usual neutral solvents. When rapidly heated it melts with effervescence at about 230–5°, resolidifying immediately to a mass which does not melt below 280°; if the heating is carried out slowly, the substance merely sinters above 215° and does not melt below 280°. An aqueous suspension gives a violet color with ferric chloride.

Kjeldahl: 0.3663 g. subst.; 14.60 cc. 0.1 *N* HCl.
Calc. for $C_8H_8O_3NBr$: N, 5.69%. Found: N, 5.58%.

The Methyl Ester Hydrochloride.—This salt was obtained from the amino acid hydrochloride by esterification in the usual way. Recrystallized from absolute alcohol, it forms glistening platelets which soften above 210° and melt with effervescence at 220–2°. The salt is quite readily soluble in water, the solution giving a slowly developing wine-red color with ferric chloride.

0.3173 g. subst.; 0.1540 g. AgCl.
Calc. for $C_9H_{10}O_3NBr.HCl$: Cl, 11.95%. Found: Cl, 12.01%.

The Methyl Ester.—The base, obtained by decomposition of the salt with dilute sodium carbonate, was recrystallized first from absolute alcohol, then from an insufficient amount of hot ligroin (b. p. 90–100°), the colored impurities remaining in the insoluble portion. The ester forms long, delicate, glistening needles which soften at 73.5° and melt at 74.5° (cor.). It is readily soluble in benzene, ether, or methyl alcohol.

0.1839 g. subst.; 8.6 cc. N, 761 mm., 20.0°.
Calc. for $C_9H_{10}O_3NBr$: N, 5.39%. Found: N, 5.33%.

2-Methyl-4-acetamino-6-bromophenol Hydrobromide.—This unusual salt was obtained as follows: 30 g. *p*-acetamino-*o*-cresol were dissolved in 300 cc. of hot acetic acid and cooled to about 35–40°. To the supersaturated solution was added, drop by drop, with constant stirring, a solution of 9.2 cc. bromine in 3 volumes of acetic acid. The hydrobromide separated when the solution was cooled and scratched, the yield being 44.5 g. Recrystallized from acetic acid containing a little hydrobromic acid the salt forms pale cream-colored crystalline aggregates which soften slightly above 180° and melt at 194–6° with effervescence.

0.1643 g. subst.; 9.6 cc. $AgNO_3$ soln.[1]
Calc. for $C_9H_{10}O_2NBr.HBr$: Br^-, 24.58%. Found: Br^-, 24.49%.

2-Methyl-4-acetamino-6-bromophenol(2-bromo-4-acetamino-*o*-cresol).—A portion of the salt was dissolved in a large volume of boiling water and treated with sodium acetate solution, whereupon the free acetamino-bromocresol separated. Recrystallized from toluene, it formed cream-

[1] 1 cc. = 0.004192 g. Br.

colored, woolly masses of delicate hairs which melted constantly at 155–6° (cor.), with preliminary softening. As Janney[1] reports, the melting point as 152°, and we were therefore in some doubt as to the position of the bromine on the nucleus, the compound was synthesized as follows:

2-Bromo-4-amino-*o*-cresol(2-methyl-4-amino-6-bromophenol) Hydrochloride.—4-Nitro-*o*-cresol was brominated in acetic acid solution according to Auwers[2] and the product reduced in the usual way with stannous chloride and hydrochloric acid, filtering off the sparingly soluble double tin salt which separated. The yield of the aminophenol hydrochloride was about 50% of the theory. Kehrmann, Mussmann, and Facchinetti[3] prepared the salt by reducing the bromoquinoneoxime but characterized it incompletely. Recrystallized from warm absolute alcohol by the addition of an equal volume of dry ether, the salt forms minute, flat needles which darken above 230° and decompose at 265–70°. It gives a purple color with ferric chloride.

Kjeldahl: 0.2048 g. subst.; 8.6 cc. 0.1 *N* HCl.
Calc. for $C_7H_8ONBr.HCl$: N, 5.87%. Found: N, 5.88%.

The free base obtained from the above salt melted at 146–8°, as found by Janney, and not as given by the above authors. When the amino hydrochloride is acetylated as in previous cases 2-methyl-4-acetamino-6-bromophenol is formed. The analysis, melting point, and mixed melting-point determinations showed it to be identical with the substance obtained by brominating *p*-acetamino-*o*-cresol as above.

Kjeldahl: 0.3701 g. subst.; 15.0 cc. 0.1 *N* HCl.
Carius: 0.1451 g. subst.; 0.1133 g. AgBr.
Calc. for $C_9H_{10}O_2NBr$: N, 5.74%; Br, 32.74%. Found: N, 5.68%; Br, 33.24%.

2-Methyl-4-acetamino-6-bromophenoxyacetic Acid.—The above 2-bromo-4-acetamino-*o*-cresol hydrobromide was used as starting material for this substance. One equivalent of the salt, one of chloroacetic acid, and three of sodium hydroxide were boiled in aqueous solution until neutral. The acetamino acid separated on acidifying to Congo red. Recrystallized twice from acetic acid, it forms minute, cream-colored, interlaced needles, which melt at 216–6.5° (cor.) with preliminary softening. It is somewhat less sparingly soluble in acetone or absolute alcohol than in the other usual solvents.

Kjeldahl: 0.3015 g. subst.; 10.15 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{12}O_4NBr$: N, 4.64%. Found: N, 4.72%.

The acid was also prepared from a portion of the bromoacetaminocresol obtained from the nitro compound and proved identical in every way to the substance just described.

[1] Janney, *Ann.*, **398**, 354 (1913).
[2] Auwers, *Ber.*, **39**, 3174 (1906).
[3] Kehrmann, Mussmann and Facchinetti, *Ber.*, **48**, 2021 (1915).

2-Methyl-4-amino-6-bromophenoxyacetic Acid.—The acetamino acid was boiled under a reflux condenser with 5 parts of 1 : 1 hydrochloric acid for about 15 minutes, until the amino acid hydrochloride began to separate from the boiling solution. The salt was converted into the free acid in the usual manner and this purified by a repetition of the process. The acid forms thin, almost colorless platelets, which melt with decomposition at 223°. It is very difficultly soluble in the usual solvents with the exception of boiling alcohol. An aqueous suspension gives no color with ferric chloride in the cold, but on boiling the liquid turns dark brown, soon changing to a lighter red brown.

Kjeldahl: 0.3058 g. subst.; 11.60 cc. 0.1 *N* HCl.
Calc. for $C_9H_{10}O_3NBr$: N, 5.39%. Found: N, 5.31%.

The Methyl Ester Hydrochloride.—The salt separated from the reaction mixture after saturating a suspension of the amino acid in dry methyl alcohol with hydrochloric acid gas and cooling the resulting solution. Recrystallized from methyl alcohol, it forms practically colorless, interlaced needles, which dissolve rather sparingly in water. When rapidly heated, the salt melts and decomposes at 245–50° with preliminary darkening and softening. Its aqueous solution gives a slowly-developing rose color with ferric chloride.

0.2758 g. subst.; 0.1270 g. AgCl.
Calc. for $C_{10}H_{12}O_3NBr.HCl$: Cl, 11.42%. Found: Cl, 11.39%.

The Methyl Ester.—The base separated as an oil which soon solidified. Recrystallized first from 50% alcohol, then from toluene by adding ligroin to the warm solution until just turbid, it forms sheaves of long needles which soften above 57° and melt at 59° (cor.). The ester is readily soluble in the usual organic solvents with the exception of ligroin.

Kjeldahl: 0.3395 g. subst.; 12.55 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{12}O_3NBr$: N, 5.11%. Found: N, 5.18%.

In our first efforts to prepare the 4-amino-6-methoxyphenoxyacetic acid recourse was had to the reaction between nitrophenol sodium salts and chloroacetic ethyl ester. Although no difficulty had been experienced in the case of the sodium salt of 5-nitroguaiacol it was found that the dried salt of the 4-nitro isomer failed to react, even in the presence of sodium iodide as catalyzer. The acetyl derivative of the desired amino acid was synthesized, however, by heating 4-acetaminoguaiacol[1] in aqueous solution with chloroacetic acid and alkali in the usual manner. The acetamino acid was then readily hydrolyzed to the amino compound.

4-Acetamino-6-methoxyphenoxyacetic Acid.—8 g. 4-acetaminoguaiacol, 4.2 g. chloroacetic acid, 3.6 g. sodium hydroxide, and 40 cc. water were boiled for about one hour. The sodium salt of the acid separated on cooling. The mixture was diluted with water and acidified with hydro-

[1] From the aminoguaiacol as in previous examples.

chloric acid. The yield of acetamino acid was about 85% of the theory. Recrystallized first from water, then acetic acid, it forms almost colorless nodules of microscopic crystals which melt at about 190–1°, the point of fusion depending somewhat on the rate of heating. The acid is sparingly soluble in the cold in the usual neutral solvents.

Kjeldahl: 0.3839 g. subst.; 15.9 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_5N$: N, 5.86%. Found: N, 5.80%.

4-Amino-6-methoxyphenoxyacetic Acid.—A batch of the acetamino acid obtained by working up to 60 g. 4-aminoguaiacol was boiled under a reflux condenser with about 500 cc. 1 : 1 hydrochloric acid for about one hour. The solution was evaporated *in vacuo*, taken up with water, and carefully neutralized with sodium carbonate solution, the amino acid separating on scratching. The yield was 60 g. Recrystallized from water it forms almost colorless, glistening plates which are less sparingly soluble in boiling water than in boiling alcohol or acetone. An aqueous suspension gives a deep purple color with ferric chloride. When rapidly heated the acid melts at 190° with decomposition.

0.1640 g. subst.; 10.8 cc. N, 761 mm., 21.5°.
Calc. for $C_9H_{11}O_4N$: N, 7.11%. Found: N, 7.45%.

The Ethyl Ester Hydrochloride.—The salt was prepared as in analogous cases already described, separated from the reaction mixture on cooling. Recrystallized from absolute alcohol it forms delicate, felted needles which melt at 180–6° with preliminary softening. It is readily soluble in the cold in water or methyl alcohol, less easily in absolute alcohol. The aqueous solution gives a purple color with ferric chloride and diazotizes readily, coupling with R-salt to give a dye of a deeper red shade than those obtained with most of the other aminophenoxyacetic acids. The free ester was obtained by adding aqueous sodium carbonate to the salt, but did not crystallize.

0.2549 g. subst.; 0.1415 g. AgCl.
Calc. for $C_{11}H_{15}O_4N.HCl$: Cl, 13.56%. Found: Cl, 13.73%.

In this case the synthesis of the 4-amino-6-carboxyphenoxyacetic acid was rendered difficult not only by the fact that the dried sodium salt of 5-nitrosalicylic methyl ester failed to react with ethyl chloroacetate, but also by the unsatisfactory result of an attempt to react 5-acetaminosalicylic acid with chloroacetic acid and alkali in aqueous solution. The amino acid was finally synthesized, however, by the following series of reactions:

4-Nitro-6-aldehydophenoxyacetic Acid.—5 g. *o*-aldehydophenoxyacetic acid were added in portions to 25 g. fuming nitric acid (d. 1.52), keeping the temperature below 5°. The clear, yellow solution was allowed to stand for 2–3 minutes and was then poured on to ice, precipitating the nitro derivative in excellent yield. Recrystallized first from acetic acid, then

ethyl acetate, it forms colorless, microscopic rhombs which melt at 190–2° (cor.) with preliminary softening. In the cold it is somewhat soluble in acetone or ethyl acetate, sparingly in alcohol or acetic acid, and almost insoluble in water. It dissolves sparingly in hot water to a colorless solution, which turns yellow on adding sodium hydroxide. The position of the nitro group was proven after oxidation to the corresponding carboxylic acid (see below).

0.1810 g. subst.; 9.6 cc. moist N, 756 mm., 19.4°.
Calc. for $C_9H_7O_6N$: N, 6.22%. Found: N, 6.02%.

The Acid Phenylhydrazone.—Equimolecular amounts of the acid and phenylhydrazine were warmed in 50% alcohol for one-half hour on the water bath. A yellow color developed immediately and the acid was converted into an orange precipitate. This was filtered off and recrystallized from 85% alcohol, forming glistening, brown-orange rhombs, which dissolved very sparingly in benzene, chloroform, or cold acetic acid, and more readily in acetone or ethyl acetate. When rapidly heated to about 220° and then slowly, it decomposes at 222°. The phenylhydrazone is very resistant to hydrolysis by boiling aqueous alcoholic hydrochloric acid, dissolves in sulfuric acid with an orange-red color, and yields a difficultly soluble, orange-red sodium salt with dilute aqueous sodium hydroxide or carbonate.

0.1375 g. subst.; 15.9 cc. moist N, 755 mm., 21.0°.
Calc. for $C_{15}H_{13}O_5N_3$: N, 13.33%. Found: N, 13.02%.

4-Nitro-6-carboxyphenoxyacetic Acid.—4.9 g. of the nitroaldehydo acid were dissolved in 60 cc. water containing 2.4 g. sodium carbonate and to the solution was slowly added a warm 4% solution of potassium permanganate until a permanent pink color was obtained. About 60 cc. of the permanganate solution were required. The mixture was decolorized with alcohol, filtered, and the filtrate acidified with sulfuric acid. The yield was excellent. Recrystallized from water, the acid forms warty aggregates of very faintly yellow, microscopic hairs which appear brownish under the microscope. When rapidly heated to 230° and then slowly, it turns yellow at about 235° and melts with decomposition at 238–40°. It is very sparingly soluble in the usual solvents, the solution in hot water having a light yellow color.

0.1519 g. subst.; 7.95 cc. moist N, 752 mm., 21.3°.
Calc. for $C_9H_7O_7N$: N, 5.81%. Found: N, 5.85%.

The position of the nitro group was determined by boiling a portion of the acid for one hour with a saturated solution of hydrobromic acid in acetic acid. The solution was evaporated to small bulk, taken up with water, and the precipitate twice recrystallized from water. In its properties it corresponded exactly with 5-nitrosalicylic acid, and its identity with

this was further shown by a mixed melting point with a sample prepared by nitration of salicylic acid, no depression being caused.

4-Nitro-6-carbethoxyphenoxyacetic Ethyl Ester.—3.4 g. of the above acid were suspended in 13.6 g. absolute alcohol and boiled 3.5–4 hours under a reflux condenser after adding 6.8 g. of concentrated sulfuric acid. The ester crystallized on cooling and was filtered off. Recrystallized from 95% alcohol it forms delicate, glistening, unctuous needles, which melt at 75–6° (cor.). It is sparingly soluble in the cold in 95% alcohol or ligroin, somewhat more soluble in absolute alcohol, and easily in the other organic solvents.

Kjeldahl: 0.3121 g. subst.; 9.6 cc. 0.1 *N* HCl.
Calc. for $C_{13}H_{15}O_7N$: N, 4.71%. Found: N, 4.31%.

4-Amino-6-carboxyphenoxyacetic Acid.—This was obtained by reduction of the nitro acid or nitro ester in alcoholic solution with tin and hydrochloric acid, the usual manipulations being followed. The amino acid was liberated from the hydrochloride in the usual way and purified by solution in dilute hydrochloric acid, precipitation with sodium acetate, and then dissolving in dilute sodium hydroxide and precipitating with acetic acid. The substance forms pale brown aggregates of plates which decompose slightly, but do not melt below 280°. It is very difficultly soluble in the usual neutral solvents and, in aqueous suspension, gives a light red-brown color with ferric chloride.

0.1617 g. subst.; 8.8 cc. N, 755 mm., 22.0°.
Calc. for $C_9H_9O_5N.H_2O$: N, 6.11%. Found: N, 6.09%.

The Ethyl Ester Hydrochloride.—One part of the amino acid hydrochloride, 2 parts of concentrated sulfuric acid, and 4 parts of absolute alcohol were heated under a reflux condenser for about 3.5 hours. Water and ice were then added and the solution made alkaline to phenolphthalein and immediately extracted with ether. The extract was dried over sodium sulfate, evaporated to dryness, and the residue taken up in absolute alcohol saturated with hydrochloric acid, precipitating the ester salt. After addition of dry ether the salt was filtered off. Recrystallized from absolute alcohol, it forms aggregates of delicate needles which soften at about 140°, become transparent at 146°, and are completely molten at 156–7°. The salt is slowly, although freely soluble in water, the solution giving a yellow brown color, darkening to red-brown, with ferric chloride.

0.2701 g. subst.; 16.45 cc. $AgNO_3$ soln.[1]
calc. for $C_{13}H_{17}O_5N.HCl$: Cl, 11.68%. Found: Cl, 11.33%.

The Ethyl Ester.—The ester was obtained from the hydrochloride as an oil which solidified in the ice box. It was recrystallized twice from absolute alcohol with the aid of a freezing mixture, forming slightly brownish crystals, which melted at 74–6° (cor.) with preliminary soften-

[1] 1 cc. = 0.00186 g. Cl.

ing and dissolved less readily in ligroin and ether than in the other usual organic solvents.

0.2002 g. subst.; 9.6 cc. N, 763 mm., 26.0°.
Calc. for $C_{13}H_{17}O_5N$: N, 5.24%. Found: N, 5.32%.

4-Acetamino-6-acetophenoxyacetic Acid.—22 g. 2-hydroxy-5-acetaminoacetophenone, 10.7 g. chloroacetic acid, 18.5 g. sodium hydroxide, and 200 cc. water were boiled down to small bulk in an open flask, repeating the process with one-half the amounts of chloroacetic acid, alkali, and water. After diluting and acidifying with acetic acid the mixture was allowed to stand overnight. A small amount of unchanged hydroxyacetaminoacetophenone was filtered off and the new acid precipitated from the filtrate by the addition of hydrochloric acid. The yield was 23.6 g. Recrystallized twice from acetic acid, the substance forms faintly greenish gray, woolly masses of delicate needles which are soluble in hot 95% alcohol or acetic acid and only sparingly soluble in hot water. When rapidly heated to 220° and then slowly the acid softens, then melts to a brown liquid and evolves gas at 223–6°. It dissolves in concentrated sulfuric acid with an olive-yellow color.

Kjeldahl: 0.3374 g. subst.; 13.40 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{13}O_5N$: N, 5.58%. Found: N, 5.56%.

4-Amino-6-acetophenoxyacetic Acid.—The acetamino acid was hydrolyzed by heating with 1 : 1 hydrochloric acid. The amino acid hydrochloride separated on cooling. A portion of this was dissolved in warm water and converted into the free acid by adding sodium acetate. Recrystallized from water, it forms long, pale brown, glistening needles, which contain between 1 and 1.5 molecules of water of crystallization. When anhydrous and rapidly heated, it darkens above 125° and gradually softens to a tar which decomposes at about 145°. The acid is soluble in hot water or hot absolute alcohol, and, in aqueous suspension, gives a slowly-developing purple color with ferric chloride. The diazonium solution couples with R-salt to give a deeper red color than the shades given by most of the other aminophenoxyacetic acids.

0.9402 g. subst., air-dry, lost 0.0860 g. H_2O, 9.15%. Calc.: 1 H_2O, 7.93%; 1.5 H_2O, 11.44%.
Recrystd.: 0.3551 g. subst., air-dry, lost 0.0359 g. H_2O, 10.11%.
Kjeldahl: 0.3107 g. subst., anhydrous; 15.0 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{11}O_4N$: N, 6.70%. Found: N, 6.76%.

4-Amino-6-acetophenoxyacetic Methyl Ester Hydrochloride.—This substance was prepared from the crude amino acid hydrochloride as in numerous preceding examples. Separation of the salt from the reaction mixture was completed by the addition of dry ether. Recrystallized from absolute alcohol containing a drop of concentrated hydrochloric acid, the hydrochloride forms nacreous, diamond-shaped plates which dissolve

readily in water, less easily in absolute alcohol. When rapidly heated to 190° and then slowly it darkens above this point and melts with decomposition at 204–7°.

0.3090 g. subst.; 0.1681 g. AgCl.
Calc. for $C_{11}H_{13}O_4N.HCl$: Cl, 13.67%. Found: Cl, 13.46%.

The Methyl Ester.—The free base was obtained by the action of sodium carbonate on an aqueous solution of the salt. Recrystallized from 95% alcohol, the ester forms flat, pale yellow needles, which melt at 141–2.5° (cor.) with slight preliminary softening. It is sparingly soluble in the cold in alcohol or benzene, soluble in acetone. An aqueous suspension gives a slowly-developing wine-red color with ferric chloride.

Kjeldahl: 0.2988 g. subst.; 13.35 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{13}O_4N$: N, 6.28%. Found: N, 6.26%.

Nitro-*o*-phenylenedi-[oxyacetic Acid].—40 g. *o*-phenylenedioxyacetic acid were added in portions to 160 cc. of concentrated nitric acid, keeping the temperature at about 25°. The phenoxyacetic acid slowly dissolved. After letting stand for about two hours the solution was poured into a large volume of water. The precipitated nitro acid was recrystallized from water, separating in a yield of 40.5 g. Recrystallized again from water, then from acetic acid, it forms practically colorless aggregates of minute crystals which melt at 181–3° (cor.) with preliminary softening. The acid separates from water with one molecule of water of crystallization and is sparingly soluble in the cold in the usual solvents.

2.4361 g. subst.; 0.1552 g. loss. H_2O, 6.37%. 1 H_2O, 6.23%.
Anydrous: 0.2053 g. subst.; 10.15 cc. N, 752 mm., 20.4°.
Calc. for $C_{10}H_9O_8N$: N, 5.17%. Found: N, 5.56%.

In attempts to fix the position of the nitro group the acid was boiled 1.5 hours with a saturated solution of hydrobromic acid in acetic acid, but was recovered unchanged. When heated in a sealed tube at 155–65° most of the substance was carbonized, only a small amount of a soluble hydrobromide being recovered. It seems reasonable to suppose, however, that the nitro group is in Position 4.

Amino-*o*-phenylenedi-[oxyacetic Acid].—The nitro acid was reduced in hot alcoholic solution with tin and concentrated hydrochloric acid until a test portion remained clear on diluting with water. The amino acid hydrochloride was isolated in the usual way and converted into the free acid by dissolving in water and adding sodium acetate. The acid separated on scratching, 17 g. being obtained from 40.5 g. of the nitro acid. Purified by dissolving in dilute hydrochloric acid and reprecipitating with sodium acetate the substance forms grayish microcrystals which, when rapidly heated, darken above 240° and decompose at 243–5°. It is sparingly soluble in the usual neutral solvents, and, in aqueous suspension, gives a violet color with ferric chloride.

Kjeldahl: 0.3209 g. subst.; 13.15 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{11}O_3N$: N, 5.81%. Found: N, 5.74%.

(*D*) Aminophenoxyacetic Acids with Condensed Nuclei.

4-Acetamino-1-naphthoxyacetic Acid. — 4-Acetamino-1-naphthol was prepared from the aminonaphthol hydrochloride by the action of acetic anhydride in aqueous solution, followed by sodium acetate, as in previous examples. When boiled in aqueous solution with chloroacetic acid and sodium hydroxide, repeating the treatment with one-half the original amounts, it gave a practically quantitative yield of the acetaminonaphthoxyacetic acid. Recrystallized twice from acetic acid, the substance formed practically colorless aggregates of spears which softened above 225° and melted at 233–4°. The acid is very difficultly soluble in the cold in the usual solvents, dissolving, however, in hot acetic acid or absolute alcohol, and slightly in hot acetone.

Kjeldahl: 0.3081 g. subst.; 11.70 cc. 0.1 *N* HCl.
Calc. for $C_{14}H_{13}O_4N$: N, 5.41%. Found: N, 5.32%.

4-Amino-1-naphthoxyacetic Acid.—The amino acid was obtained by boiling the acetamino compound with 1 : 1 hydrochloric acid as in previous examples and liberating the free acid from the salt by means of sodium acetate. Recrystallized from boiling amyl acetate, in which it is less sparingly soluble than in the other neutral solvents, the amino acid forms radiating masses of minute needles which turn purple above 215° and melt with decomposition at 220–4°. In aqueous suspension it gives a blue color with ferric chloride, and, in sodium carbonate solution, couples readily with benzenediazonium chloride, yielding a red precipitate. On adding sodium nitrite to a solution of the amino acid in dilute hydrochloric acid a blue color is produced owing to partial oxidation, but the diazonium solution formed couples readily with R-salt to give a purple color.

Kjeldahl: 0.2946 g. subst.; 13.40 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{11}O_3N$: N, 6.45%. Found: N, 6.37%.

8-Acetamino-5-hydroxyquinoline. — 8-Amino-5-hydroxyquinoline sulfate was prepared by the method of electrolytic reduction worked out by Gattermann.[1] The salt was suspended in 10 parts of water, treated with 1.1 mols of acetic anhydride, and rapidly turbined while adding strong sodium acetate solution. The salt quickly dissolved and the acetyl derivative separated in shining, greenish leaflets. In order to saponify any diacetyl compound that may have been formed sodium hydroxide was added to the mixture in slight excess, stirring until solution was complete. After reprecipitating the acetyl derivative with acetic acid, the mixture was cooled and the product filtered off and washed with water. The yield was practically quantitative. Recrystallized twice from 85% alcohol, the substance forms practically colorless leaflets that turn green

[1] Gattermann, *Ber.*, **27**, 1940 (1894).

on exposure to light and air. It decomposes partially above 190°, melting to a turbid, brown liquid at 221–3° and clearing completely at 227°. It is sparingly soluble in the cold in water or acetic acid, and very difficultly so in acetone or benzene. It dissolves with difficulty in dilute hydrochloric acid with an orange color, in dilute sodium hydroxide with an olive color. An aqueous suspension gives a deep olive color with ferric chloride.

0.1348 g. subst.; 16.2 cc. N, 767 mm., 25.0°.
Calc. for $C_{11}H_{10}O_2N_2$: N, 13.87%. Found: N, 13.89%.

8-Acetamino-5-quinolyloxyacetic Acid.—The acetaminohydroxyquinoline was condensed with chloroacetic acid in the same way as the preceding naphthyl compound. The new acid was isolated by adding concentrated hydrochloric acid to the reaction mixture, precipitating the hydrochloride as a thick mass of glistening needles. The mixture was cooled in ice-water and filtered, washing the salt with saturated sodium chloride solution. The product was then dissolved in water and treated with sodium acetate until neutral to Congo red. The yield of free acid obtained in this way from 30.3 g. of the acetaminohydroxyquinoline was 32 g. The acid separates from boiling water as brownish, glistening leaflets containing about one molecule of water of crystallizatio When rapidly heated it decomposes slightly and softens, finally me gas evolution at 255° It dissolves in dilute hydrochloric acid or green- ish yellow solutions.

1.0257 g. subst.; 0.0750 g. loss. H_2O, 7.31%. 1 H_2O, 6.47%.
Anhydrous: 0.1031 g. subst.; 9.7 cc. N, 751 mm., 21.0°.
Calc. for $C_{13}H_{12}O_4N_2$: N, 10.77%. Found: N, 10.80%.

8-Amino-5-quinolyloxyacetic Acid.—The acetamino acid was hydrolyzed as in previous cases, the amino acid hydrochloride separating on chilling. A further quantity was obtained by concentrating the filtrate *in vacuo*. When dissolved in water and neutralized with sodium acetate the salt yielded the free acid, 20 g. being obtained from 25 g. of the acetamino compound. A portion of the hydrochloride was recrystallized from 10% hydrochloric acid and the free acid liberated from this and recrystallized by dissolving in warm, very dilute hydrochloric acid and again adding sodium acetate solution. It forms brown, glistening crystals which soften above 190° when rapidly heated and melt and decompose at about 225°. When slowly heated the acid gradually softens above 190° to a tar which does not melt completely below 275°. It is readily diazotized, giving a purple color with R-salt, and, in aqueous suspension, gives a deep red-brown color with ferric chloride.

0.1028 g. subst.; 11.0 cc. N, 747 mm., 17.5°.
Calc. for $C_{11}H_{10}O_3N_2$: N, 12.84%. Found: N, 12.36%.

5-Amino-8-hydroxyquinoline Dihydrochloride.—Lippmann and Fleiss-

ner[1] reduced 5-nitroso-8-hydroxyquinoline hydrochloride with stannous chloride and hydrochloric acid, converting the amino hydrochloride into the free base. The nitroso compound may be very conveniently reduced by dissolving in ammonia and passing in hydrogen sulfide. 70 g. 5-nitroso-8-hydroxyquinoline hydrochloride were dissolved as well as possible in 1050 cc. of dilute ammonia (one part of concentrated to 1.5 parts of water) and the solution saturated with hydrogen sulfide. The precipitate of amino compound was filtered off, washed with water, suspended in a little water, treated with a slight excess of hydrochloric acid, and shaken until the base had dissolved. The solution was then filtered from the residue of sulfur and the dihydrochloride precipitated by the addition of concentrated hydrochloric acid or by passing in a stream of hydrochloric acid gas until saturated. After filtering off the first crop of crystals a further quantity was obtained by concentrating the filtrate to small bulk *in vacuo*. The total yield was 40 g. Recrystallized from 10% hydrochloric acid solution it forms crusts of brown plates which do not melt sharply when heated, but gradually soften and decompose, markedly at about 245°, but not melting completely below 280°. The salt dissolved in dilute hydrochloric acid with a yellow color, in water with an orange-red color, and in dilute sodium hydroxide with an olive color. The aqueous solution turns brown on adding ferric chloride.

Carius: 0.1171 g. subst.; 0.1414 g. AgCl.
Calc. for $C_9H_8ON_2.2HCl$: Cl, 30.41%. Found: Cl, 29.88%.

5-Acetamino-8-hydroxyquinoline.—38 g. of the above dihydrochloride were dissolved in 200 cc. water, treated with 25 cc. acetic anhydride, and then, with vigorous turbining, with an excess of sodium acetate. The reaction occurred at once, forming a dark-colored solution. The acetamino compound was precipitated from this by adding an excess of ammonia, separating gradually as greenish gray, lenticular plates. After recrystallizing from water the yield was 18.5 g. Recrystallized first from water, using bone-black, then from 95% alcohol, the substance forms almost colorless prisms which melt at 221–2° (cor.) with preliminary softening. It is insoluble in benzene, acetone, cold 95% alcohol or water, and dissolves in acetic acid with an orange-yellow color, in dilute alkalies and acids with a greenish yellow color, and in aqueous suspension gives a deep blue-green coloration with ferric chloride.

0.1381 g. subst.; 16.8 cc. N, 763 mm., 26.0°.
Calc. for $C_{11}H_{10}O_2N_2$: N, 13.87%. Found: N, 13.94%.

5-Acetamino-8-quinolyloxyacetic Acid.—17 g. 5-acetamino-8-hydroxyquinoline, 8 g. chloroacetic acid, 13.5 g. 50% aqueous sodium hydroxide, and about 170 cc. water were slowly boiled down to small volume. One-half of the above quantities of chloroacetic acid, alkali, and water were

[1] Lippmann and Fleissner, *Monatsh.*, **10**, 796 (1889).

then added and the solution again boiled down to small bulk. The resulting liquid was diluted with water and acidified faintly to Congo red with hydrochloric acid, the acetaminoquinolyloxyacetic acid separating on chilling as a voluminous mass of long, thin, yellow needles. On concentrating the filtrate a further crop was obtained, the total yield being 19.7 g. As isolated in this manner, the acid was sufficiently pure for conversion into the amino compound as described below, but could not be freed from its content of hydrochloric acid by simple recrystallization, even in the presence of sodium acetate. An analytically pure specimen was finally obtained as follows: A portion of the crude acid was dissolved in dilute sodium hydroxide and the solution treated with a slight excess of acetic acid. A product separated in which halogen still persisted. This was therefore dissolved in hot water, rapidly cooled, and treated with about one-half volume of 10% aqueous nitric acid. 5-Acetamino-8-quinolyloxyacetic acid nitrate soon separated in voluminous masses of yellow hairs. The salt was filtered off and dried *in vacuo* at room temperature over sulfuric acid, after which it darkened and softened at 150–5° and decomposed at 225–30°. It is soluble in water or hot 95% alcohol.

0.1052 g. subst.; 11.85 cc. N, 765 mm., 24.5°.
Calc. for $C_{13}H_{12}O_4N_2.HNO_3$: N, 13.00%. Found: N, 13.02%.

The nitrate was dissolved in a little hot water and the solution treated with an excess of sodium acetate. On standing in the ice box the free acid gradually separated as orange prisms and rhombs which were halogen-free and contained between two and two and half molecules of water of crystallization. On drying to constant weight at 100° *in vacuo* over sulfuric acid the substance lost its water and became straw-colored. When rapidly heated to 250°, then slowly, it softened and then melted with decomposition at 253–5°. The anhydrous acid is almost insoluble in dry acetone or absolute alcohol, and turns bright yellow under water, dissolving somewhat sparingly on heating.

Air-dry: 0.3392 g. lost 0.0467 g. H_2O, 13.77%. Calc.: 2 H_2O, 12.17%; 2.5 H_2O, 14.76%.
Anhydrous: 0.1468 g. subst.; 14.2 cc. N, 756 mm., 27.5°.
Calc. for $C_{13}H_{12}O_4N_2$: N, 10.77%. Found: N, 10.93%.

The Acid Dihydrochloride.—The crude acetamino acid was hydrolyzed by boiling with 5 parts of 1 : 1 hydrochloric acid for 2 hours. Most of the amino acid salt separated on cooling and scratching, a further quantity being obtained by concentrating the filtrate *in vacuo*. Recrystallized from a small volume of 10% aqueous hydrochloric acid, the salt formed long, narrow, brownish plates which turned slightly reddish in color when dried to constant weight *in vacuo* at room temperature over sulfuric acid. When rapidly heated to 150°, then slowly, the salt first reddens, then gradually softens, sinters, and darkens above 155°, and melts with gas evolution to

a bright red mass at 160–2°. It is readily diazotized, coupling with R-salt to give a dark purplish red color. It dissolves in water with an orange-red color, changing to deep red on adding ferric chloride. The solution of the salt in dilute hydrochloric acid is brownish yellow, while in dilute sodium hydroxide the color is pale yellow. When moistened with water the salt turns a deep brown-red, giving a solution of the same color on adding sodium acetate. The solution then gradually deposits a network of dark brown-red needles which dissolve very easily in water and probably consist of the free acid or its sodium salt.

0.1102 g. subst.; 0.1080 g. AgCl.
Calc. for $C_{11}H_{10}O_3N_2.2HCl$: Cl, 24.35%. Found: Cl, 24.25%.

The Methyl Ester.—14 g. of the crude hydrochloride were suspended in 140 cc. dry methyl alcohol and esterified by the action of dry hydrochloric acid gas. Separation of the ester dihydrochloride was completed by adding an equal volume of dry ether, the yield being 14 g. The salt forms slightly pinkish, glistening platelets which slowly lose hydrochloric acid and turn red on exposure to moist air. It dissolves in water with a red color which changes to brownish yellow on adding hydrochloric acid. The free ester separated from an aqueous solution of the salt on adding sodium carbonate and was recrystallized from 95% alcohol, forming lemon-yellow rhombs and flat needles which melted, with slight preliminary softening, at 176–7° (cor.). It is sparingly soluble in benzene or cold 95% alcohol but dissolves in acetone. An acetic acid solution of the ester has a red color, while an aqueous suspension gives an orange color with ferric chloride. It is readily diazotized, coupling with R-salt to form a dark red dye.

0.1171 g. subst.; 11.45 cc. N, 766 mm., 18.0°.
Calc. for $C_{12}H_{12}O_3N_2$: N, 12.07%. Found: N, 11.57%.

(*E*) Aminophenoxybutyric Acids.

o*-Acetaminophenoxypropyl Bromide** (o*-Acetaminophenyl-γ-bromopropyl Ether**), o-$CH_3CONHC_6H_4OCH_2CH_2CH_2Br$.—34 g. *o*-acetaminophenol were dissolved in 130 cc. alcohol and boiled on the water bath for 2.5 to 3 hours with 18 g. 50% sodium hydroxide solution and 350 g. trimethylene bromide. The alcohol and the excess of trimethylene bromide were then distilled off with steam. The mixture was cooled, made alkaline, and the residual heavy oil removed from the aqueous solution by shaking out with chloroform. The extract was dried and concentrated, and the oily residue taken up in alcohol. On scratching, a small amount of the propylene ether of *o*-acetaminophenol separated (see below). The amount of propylene ether formed is much larger if a smaller excess of trimethylene bromide is used. The filtrate from the propylene ether was concentrated and the residue treated with ligroin and chilled. The acetaminophenoxypropyl bromide crystallized on rubbing and was filtered

off, washed with ligroin, and sucked dry. The yield was 30 g. A portion was purified for analysis by dissolving in a small volume of absolute alcohol, bone-blacking, and filtering from a slight residue. The filtrate was diluted with water, giving an oily product which solidified when seeded. This was dried and recrystallized from a small volume of absolute alcohol with the aid of a freezing mixture. The bromide forms snowy, felted needles which soften above 60° and melt at 62–2.5° (cor.). It is readily soluble at room temperature in the usual organic solvents with the exception of ligroin.

0.1357 g. subst.; 6.3 cc. N, 762 mm., 25.5°.
Calc. for $C_{11}H_{14}O_2NBr$: N, 5.15%. Found: N, 5.16%.

Propylene bis-(*o*-Acetaminophenyl) Ether, o-$CH_3CONHC_6H_4OCH_2CH_2CH_2OC_6H_4NHCOCH_3$.—The alcohol-insoluble product obtained in the preparation of the acetaminophenoxypropyl bromide was recrystallized twice from acetic acid, forming rosettes of prismatic needles which soften at 192.5° and melt at 193.5–4.5° (cor.). The ether is sparingly soluble in the cold in the usual solvents, but is quite soluble in boiling alcohol or chloroform, and readily so in boiling acetic acid.

Kjeldahl: 0.3050 g. subst.; 17.65 cc. 0.1 *N* HCl.
Calc. for $C_{19}H_{22}O_4N_2$: N, 8.19%. Found: N, 8.11%.

***o*-Acetaminophenoxypropyl Cyanide (*o*-Acetaminophenyl-γ-cyanopropyl Ether, *o*-Acetaminophenoxybutyronitrile).**—40 g. of the crude bromide were dissolved in 200 cc. of absolute alcohol and heated to boiling on the water bath. To the boiling solution was added, drop by drop, a solution of 12 g. potassium cyanide in 25 cc. water. After 4 hours' boiling most of the alcohol was evaporated off and the residue treated with water. An oil separated, which soon crystallized. The substance was filtered off, washed with water, and taken up in a small volume of hot alcohol. On chilling, the solution set to a thick, crystalline mass, which was filtered off and washed with alcohol and ether. 20 g. of the cyanide were obtained in the main fraction, and a further quantity on concentrating the alcoholic filtrate and washings. Recrystallized from toluene, the nitrile forms thick, pale cream-colored, diamond-shaped plates which soften at 88° and melt at 89–90° (cor.). It is sparingly soluble in the cold in toluene or absolute alcohol and dissolves very readily in chloroform.

Kjeldahl: 0.2041 g. subst.; 18.6 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{14}O_2N_2$: N, 12.84%. Found: N, 12.77%.

***o*-Amino-γ-phenoxybutyric Acid Hydrochloride.**—15 g. *o*-acetaminophenoxypropyl cyanide were boiled for 2 hours with 75 cc. 1 : 1 hydrochloric acid. The amino acid hydrochloride separated as a thick mass on cooling. This was filtered off and washed first with a little 1 : 1 hydrochloric acid, then with dry acetone. The yield of salt was 12 g. A por-

tion was recrystallized by dissolving in the minimum amount of cold absolute alcohol, adding dry ether until just turbid, and seeding with a crystal. It separates in radiating masses of flat, pointed needles which melt at 180–2° with slight preliminary softening. The aqueous solution gives a slowly developing purple color with ferric chloride.

0.1596 g. subst.; 12.69 cc. $AgNO_3$ soln.[1]
Calc. for $C_{10}H_{13}O_3N.HCl$: Cl, 15.32%. Found: Cl, 14.79%.

o-Amino-γ-phenoxybutyric Acid.—A portion of the hydrochloride was dissolved in a small amount of water and the free acid precipitated as a gum by the addition of sodium acetate solution. The mixture was then shaken with benzene until this had taken up all of the acid. The benzene was dried over sodium sulfate and concentrated to small bulk, whereupon the amino acid gradually crystallized on rubbing and letting stand. It was purified by dissolving in hot benzene, carefully adding petroleum ether until a small fraction containing the colored impurities had separated, adding bone-black, filtering, and precipitating the remainder with petroleum ether as an almost colorless oil which solidified to a mass of microscopic platelets on seeding and rubbing. The acid melts at 54–7°, with preliminary softening, to a liquid containing bubbles. It dissolves with difficulty in the cold in ligroin or carbon tetrachloride, more easily in toluene or water, and readily in the other usual neutral organic solvents. An aqueous solution gives a slowly developing lilac color with ferric chloride. The acid is readily diazotized, coupling with R-salt to give a deep red dye.

0.1007 g. subst.; 6.6 cc. N, 751·mm., 22.5°.
Calc. for $C_{10}H_{13}O_3N$: N, 7.18%. Found: N, 7.48%.

o-Aminophenoxybutyric Methyl Ester.—15 g. of the amino acid hydrochloride in 130 cc. of dry methyl alcohol were saturated with dry hydrochloric acid gas and allowed to stand for 24 hours. The clear solution was concentrated to dryness *in vacuo* and the residue taken up in water. On adding sodium carbonate solution the ester separated as an oil which rapidly solidified. The yield was 10 g. Recrystallized from ligroin, it forms rectangular platelets which melt constantly at 45–5.5° with slight preliminary softening. It is readily soluble in the usual organic solvents with the exception of ligroin.

Kjeldahl: 0.3601 g. subst.; 16.8 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{15}O_3N$: N, 6.70%. Found: N, 6.54%.

p-Acetaminophenoxypropyl Bromide (p-Acetaminophenyl-γ-bromopropyl Ether).—This substance was prepared from *p*-acetaminophenol in the same way as the *ortho* isomer. After the steam distillation the residue crystallized on standing overnight, giving a yield of crude product equal to the weight of acetaminophenol used. Recrystallized successively

[1] 1 cc. = 0.00186 g. Cl.

from 95% alcohol, toluene and absolute alcohol, the bromide forms slightly brownish plates which soften above 129° and melt at 133–5°. It is soluble in the cold in acetone or chloroform and sparingly so in alcohol, toluene, or ether.

Kjeldahl: 0.3393 g. subst.; 12.7 cc. 0.1 *N* HCl.
Calc. for $C_{11}H_{14}O_2NBr$: N, 5.15%. Found: N, 5.24%.

p-Acetaminophenoxypropyl Cyanide (p-Acetaminophenyl-γ-cyanopropyl Ether, p-Acetaminophenoxybutyronitrile).—The cyanide was prepared as in the case of the *ortho* isomer, the yield from 27.3 g. of the bromide being 19.5 g. Recrystallized from absolute alcohol, it melts at 98–100° with preliminary softening. It dissolves readily in alcohol or acetic acid, difficultly in benzene.

Kjeldahl: 0.2957 g. subst.; 27.0 cc. 0.1 *N* HCl.
Calc. for $C_{12}H_{14}O_2N_2$: N, 12.84%. Found: N, 12.79%.

p-Amino-γ-phenoxybutyric Acid Hydrochloride.—After saponification of the nitrile the reaction mixture was cooled to 0° and the salt filtered off. 10 g. of the nitrile yielded 6.3 g. of the hydrochloride. Recrystallized twice from 1 : 1 hydrochloric acid, using bone-black, it forms flat, grayish prisms which darken above 180° and melt at 191–4° to a brown liquid. It is sparingly soluble in the cold in absolute alcohol and, in aqueous solution, gives a deep violet color with ferric chloride.

0.1828 g. subst.; 0.1125 g. AgCl.
Calc. for $C_{10}H_{13}O_3N.HCl$: Cl, 15.32%. Found: N, 15.22%.

p-Amino-γ-phenoxybutyric Acid.—The free acid crystallized from an aqueous solution of the salt on adding sodium acetate solution. Recrystallized from a small volume of water, using bone-black, the acid forms lustrous, slightly brownish scales which melt at 145.5–6° (corr.) to a brown liquid. It is sparingly soluble in cold alcohol and in hot benzene. The amino acid is readily diazotized, coupling with R-salt to give a deeper red dye than is formed from the simple aminophenoxyacetic acids.

Kjeldahl: 0.3215 g. subst.; 16.45 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{13}O_3N$: N, 7.18%. Found: N, 7.17%.

NEW YORK CITY.

[CONTRIBUTION FROM THE PHARMACOLOGICAL LABORATORY OF THE UNIVERSITY OF WISCONSIN.]

SOME OBSERVATIONS ON THE EFFECT OF THE PARTIAL PRESSURE OF OXYGEN ON COMBUSTION.

BY H. C. DOLLWIG, A. C. KOLLS AND A. S. LOEVENHART.

Received July 13, 1917.

The nature of combustion has aroused the curiosity of man from the earliest times and the fundamental theories of chemistry at different periods have centered around the views held regarding it. A large amount