tions. Conrad and Limpach[9] had previously prepared this acid by the hydrolysis of its ethyl ester.

2-Methyl-4-hydroxyquinoline, VI, was prepared in two ways: by the method of Conrad and Limpach from the acid described above, and by the method of McCluskey through the reduction of 2-methyl-4-hydroxyquinoline oxide.

2-Methyl-4-methoxyquinoline-3-carboxylic Acid Oxide, VIII.—Two g. of 2-methyl, 4-hydroxyquinoline-3-carboxylic acid oxide is mixed with 3.5 g. of pure dimethyl sulfate contained in a flask, and to this is carefully added the calculated amount of sodium methoxide. After the mixture has remained overnight at the ordinary temperature, a like amount of sodium methoxide is again added, the whole thoroughly mixed and 3.5 g. of dimethyl sulfate gradually added. After 24 hours the gelatinous mass is poured into an excess of water and the aqueous mass gently warmed on the water-bath for a few minutes. The insoluble compound is collected and may be purified by crystallization as fine, white needles from methyl alcohol. For analysis it is dried in a vacuum over sulfuric acid.

Anal. Subs., 0.1299: AgI, 0.1293, equivalent to (OCH_3) 0.01743. Calcd. for $C_{11}H_8O_3N(OCH_3)$: (OCH_3), 13.30. Found: 13.41.

2-Methyl-4-methoxyquinoline-3-carboxylic acid oxide is a white, crystalline compound that melts with decomposition at 190°. It is soluble in alcohol, sodium carbonate, sodium and ammonium hydroxide, rather difficultly soluble in acetone and insoluble in ligroin and ether. It does not reduce Fehling's solution. An alkaline solution quickly decolorizes potassium permanganate, forming an emerald-green solution. Its solution in methyl alcohol gives a red color to ferric chloride.

Summary

Several improvements have been made in the synthesis of indigo from *o*-nitrobenzoylacetic acid and in addition the constitution and properties of the reduction product, together with related compounds, obtained in the reduction of ethyl *o*-nitrobenzoylaceto-acetate have been established.

BROOKLINE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL]

DERIVATIVES OF PARA-CARBOXY-PHENOXYACETIC ACID

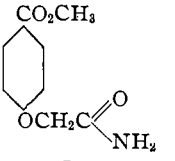
BY WALTER G. CHRISTIANSEN

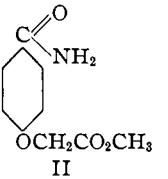
RECEIVED OCTOBER 5, 1925 PUBLISHED FEBRUARY 5, 1926

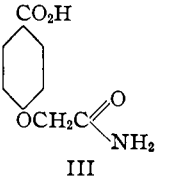
In connection with an investigation which is now in progress in this Laboratory, it became necessary to study some derivatives of *p*-carboxy-phenoxyacetic acid. The nitration of this acid was reported in a previous contribution.[1]

When methyl *p*-carbomethoxy-phenoxyacetate is treated with ammonia water under mild conditions, an amide-ester is obtained which is *p*-carbomethoxy-phenoxyacetamide I; the isomeric amide-ester II could not be isolated. By warming the reactants in a pressure bottle, the di-amide is produced. To prove that this half-amide is represented by I, *p*-hydroxy-

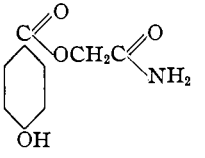
[1] Christiansen, THIS JOURNAL, **47**, 1158 (1925).

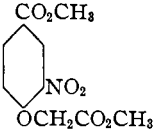

I

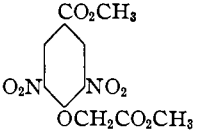

II


III

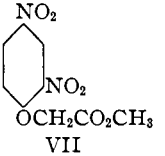
benzoic acid was converted into *p*-carboxy-phenoxyacetamide III and the latter compound was methylated. The amide-ester obtained in this way was found by the mixed-melting-point method to be identical with that secured from the dimethyl ester. *O*-*p*-hydroxybenzoyl-glycolamide IV is formed as a by-product, when *p*-hydroxybenzoic acid is treated with chloroacetamide in alkaline solution.

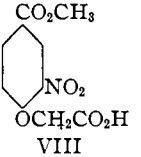

IV

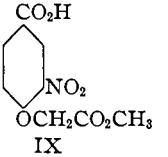

V


VI

Nitration of methyl *p*-carbomethoxy-phenoxyacetate with one molecular equivalent of nitric acid in sulfuric acid solution yields methyl 2-nitro-4-carbomethoxy-phenoxyacetate V as the main product and methyl 2,6-dinitro-4-carbomethoxy-phenoxyacetate VI, methyl 2,4-dinitrophenoxy-acetate VII, 2-nitro-4-carboxy-phenoxyacetic acid and a monomethyl ester of 2-nitro-4-carboxy-phenoxyacetic acid VIII or IX as by-products. These results are very interesting, because under similar conditions *p*-carboxy-

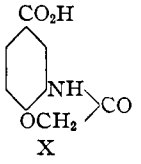

VII

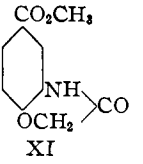

VIII

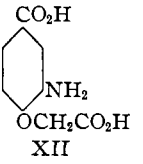

IX

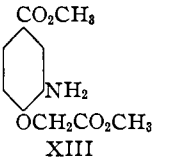
phenoxyacetic acid gives a practically quantitative yield of 2-nitro-4-carboxy-phenoxyacetic acid; only when two equivalents of nitric acid are used or when the mononitro derivative is nitrated does a nitro group replace the nuclear carboxyl group.[1] Also, in the previous study 3,5-dinitro-4-hydroxybenzoic acid was always obtained when attempts were made to prepare 2,6-dinitro-4-carboxy-phenoxyacetic acid. No indications of an analogous decomposition were found in the work reported herein.

Reduction of 2-nitro-4-carboxy-phenoxyacetic acid with ferrous hydroxide and methyl 2-nitro-4-carbomethoxy-phenoxyacetate V with iron and methyl alcoholic hydrochloric acid yields 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine X and 6-carbomethoxy-3-keto-3,4-dihydro-1,4-benzoxazine XI, respectively, instead of the two amino compounds XII and XIII. The formation of these internal anhydrides is an agreement with

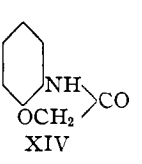

X

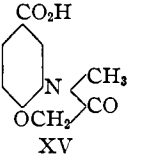

XI

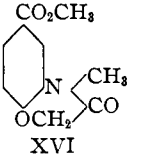

XII


XIII

the observation that attempts to prepare *o*-amino-phenoxyacetic acid always yield the internal anhydride XIV.


XIV


XV


XVI

The ester XI may also be prepared by methylation of X with methyl alcohol and hydrogen chloride. Reduction of the nitro-dimethyl ester V according to the method described below is accompanied by the formation of a monomethyl ester of 2-nitro-4-carboxy-phenoxyacetic acid, VIII or IX, as a by-product. This monomethyl ester is different from the one formed during nitration of methyl *p*-carbomethoxy-phenoxyacetate. Therefore, the two isomeric monomethyl esters which are represented by Formulas VIII and IX have been secured, but proof determining which is VIII and which is IX is still lacking; the melting points are 204–205° and 151–154°.

Methylation of X in alkaline solution with dimethyl sulfate yields products which are different from that obtained by means of methyl alcohol and hydrogen chloride. In this case the main product is one in which the imino hydrogen is replaced by a methyl group, that is 6-carboxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine XV. A more highly methylated product, 6-carbomethoxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine XVI, is also produced in which both the imino group and the carboxyl group have been methylated.

In the course of this research it has frequently been necessary to employ a known specimen of 3-nitro-4-hydroxybenzoic acid for mixed-melting-point determinations. The melting point of this substance has been recorded as 178°, 185° and 186–187°. Two specimens prepared in this Laboratory by nitration of *p*-hydroxybenzoic acid melt at 180–181° and three specimens secured by hydrolysis of 2-nitro-4-carboxy-phenoxyacetic acid and its mono- and dimethyl esters melt at 179–181°, 179–181° and 180–181.5°, respectively. In a previous communication,[1] attention was called to the various melting points which have been reported for 3,5-dinitro-4-hydroxybenzoic acid between the limits 235° and 249.5°, and two specimens were reported as melting at 240.5–243° and 241–245°. Another specimen of this substance is reported herein which was secured by

hydrolysis of methyl 2,6-dinitro-4-carbomethoxy-phenoxyacetate and which melts at 244–246°.

Experimental Part

Methyl *p*-Carbomethoxy-phenoxyacetate.—A suspension of 59.5 g. of *p*-carboxy-phenoxyacetic acid in 750 cc. of absolute methyl alcohol is stirred and treated with dry hydrogen chloride. After a short period the introduction of the gas is discontinued, and the suspension is warmed on a steam-bath. The addition of hydrogen chloride is resumed with slight external cooling. When the reaction mixture is reheated on the steam-bath, the solid dissolves completely. The clear alcoholic solution is treated with hydrogen chloride and cooled gradually; finally an ice-bath is used. After the cold solution has become saturated with the gas, it is left at room temperature overnight. The crude ester which is obtained by evaporating the alcoholic solution to dryness is dissolved in 3 liters of ether. This solution is extracted with 500 cc. of water, 600 cc. of 1.75 *N* sodium hydroxide and two 500cc. portions of water and dried with calcium chloride. When the ether is removed by evaporation, 49.7 g. of the dimethyl ester is obtained as a white, crystalline solid which melts at 92–92.7° and which is soluble in ether, alcohol, chloroform, benzene, ethyl acetate, acetone and carbon disulfide but insoluble in water and petroleum ether.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.9; H, 5.36. Found: C, 58.5; H, 5.54.

By acidification of the alkaline extract 10 g. of a mixture of partially methylated and unmethylated material is recovered.

***p*-Carbomethoxy-phenoxyacetamide. I. A.**—A suspension of 5 g. of methyl *p*-carbomethoxy-phenoxyacetate in 50 cc. of concd. ammonia water is warmed gently four times at 15-minute intervals; another 10 cc. of ammonia water is added at the time of the last heating. After the reaction mixture has remained at room temperature overnight, the white, crystalline solid is collected by filtration, washed with water and dried at 80°. The crude material (4 g.) is recrystallized from 220 cc. of water. *p*-Carbomethoxy-phenoxyacetamide (2.2 g.) is obtained as large, colorless, transparent needles; m. p., 164°. It is soluble in methyl and ethyl alcohols, chloroform and acetone but insoluble in benzene, ether, water and cold, dil. sodium hydroxide solution. When the solid is warmed with dil. sodium hydroxide solution, it dissolves and ammonia is evolved.

Anal. Calcd. for $C_{10}H_{11}O_4N$: N, 6.70. Found: 6.80.

B.—A solution of 1.1 g. of *p*-carboxy-phenoxyacetamide in 11 cc. of water and 0.8 cc. of 10.75 *N* sodium hydroxide is treated with 1.26 cc. of dimethyl sulfate during stirring at room temperature. The dimethyl sulfate is added in four portions with intervals of 15, 20 and 55 minutes between successive additions. After each portion of dimethyl sulfate is added, a white precipitate forms which is redissolved by adding, respectively, 0.1, 0.2, 0.4 and 0.4cc. portions of 10.75 *N* sodium hydroxide. After the third addition some crystalline material is present which is not redissolved by the alkali. Twenty minutes after the last addition, the reaction mixture is centrifuged, and the crystalline solid is washed thrice with water and dried at 80°; the yield is only 0.05 g. of slightly impure *p*-carbomethoxy-phenoxyacetamide. When the latter is recrystallized from water, 0.03 g. of stout, colorless needles is obtained; m. p., 162.5–164°; a mixture of this material with that obtained in **A** melts at 163–164°. The product is insoluble in cold, dil. sodium hydroxide solution, but dissolves and evolves ammonia when warmed. On account of the small quantity of material available (27 mg.) the analytical data could hardly be expected to agree closely with the calculated value.

Anal. Calcd. for $C_{10}H_{11}O_4N$: N, 6.70. Found: 7.42.

From the alkaline mother liquor, 0.94 g. of unchanged *p*-carboxy-phenoxyacetamide may be recovered.

***p*-Carboxy-phenoxyacetamide. III.**—A solution of 10 g. of *p*-hydroxybenzoic acid and 7.5 g. of chloro-acetamide in 73 cc. of 2 *N* sodium hydroxide solution is refluxed for three hours and acidified with 15 cc. of hydrochloric acid (d., 1.19); copious precipitation occurs immediately. After the mixture has been in the ice box overnight, the white solid is collected by filtration, washed and dried at 80°. The crude product (10 g.) is stirred with 75 cc. of water and treated with five 10cc. portions of saturated aqueous sodium bicarbonate; effervescence could not be detected when the fifth portion of bicarbonate was added. After 15 minutes the mixture is centrifuged, and the supernatant liquid is decanted through a gravity filter. The residue is re-extracted by stirring for 15 minutes with 40 cc. of water and 10 cc. of saturated bicarbonate solution. The insoluble material is again removed by centrifuging and the extract is poured through the same filter that was used for the first extract.

Acidification of the bicarbonate extract with hydrochloric acid yields a white precipitate which, after several hours in the ice box, is collected, washed and dried at 80°. The dried material (6.3 g.) is extracted by boiling with 800 cc. of water. By recrystallizing the insoluble residue and the first crop of material which separates from the aqueous extract several times from alcohol, 2.35 g. of *p*-carboxy-phenoxyacetamide is secured as a white, micro-crystalline powder; m. p., 282–282.5°. It is insoluble in water, ether, chloroform, benzene, acetone, methyl acetate and cold alcohol but soluble in dil. sodium bicarbonate solution and hot alcohol; when dissolved in warm aqueous sodium hydroxide it evolves ammonia.

Anal. Calcd. for $C_9H_9O_4N$: N, 7.18. Found: 7.11.

The dried insoluble residue (0.9 g.) after extraction of the original reaction product with bicarbonate is recrystallized from 200 cc. of water. *O*-*p*-hydroxybenzoylglycolamide (IV) is obtained as colorless, transparent, rectangular plates (0.1 g.); m. p., 257–258°. It is insoluble in sodium bicarbonate solution but soluble in cold, dil. sodium hydroxide solution; when this solution is warmed ammonia is evolved.

Anal. Calcd. for $C_9H_9O_4N$: N, 7.18. Found: 7.52.

***p*-Carbamido-phenoxyacetamide.**—Two g. of *p*-carbomethoxy-phenoxyacetamide is heated with 25 cc. of concd. ammonia water in a pressure bottle at 60–65° for 30 minutes. The reaction mixture is cooled, and after the addition of 20 cc. of ammonia water, it is reheated at 70–75° for one hour. On the following morning the reaction product is collected, washed and dried; the crude *p*-carbamido-phenoxyacetamide (0.7 g.) is recrystallized from 70 cc. of water. The fine, colorless needles, m. p. 261–264.5°, are insoluble in cold, dil. sodium hydroxide solution but dissolve readily and evolve ammonia when warmed.

Anal. Calcd. for $C_9H_{10}O_3N_2$: N, 14.44. Found: 14.47.

Methyl 2-Nitro-4-carbomethoxy-phenoxyacetate. V.—A solution of 40 g. of methyl *p*-carbomethoxy-phenoxyacetate in 160 cc. of sulfuric acid is treated dropwise during stirring at −3° to +3° with a mixture of 11.4 cc. of nitric acid (d., 1.42) and 11.4 cc. of sulfuric acid. The temperature is then allowed to rise to 10° and maintained at 9–10° for 45 minutes before the reaction mixture is diluted with 320 g. of ice and 320 cc. of water. After several hours, the slightly cream-colored solid is collected on a filter, washed and dried at 80°. The crude nitration product (33 g.) yields, when recrystallized several times from absolute methyl alcohol, 16.5 g. of methyl 2-nitro-4-carbomethoxy-phenoxyacetate as very slightly yellow needles; m. p., 125.5–127°. This substance is soluble in chloroform, acetone, ethyl and methyl acetates, benzene, nitrobenzene, glacial acetic acid and hot methyl, ethyl and *iso*propyl alcohols; it is slightly soluble in ether

and insoluble in water, carbon disulfide, cold aqueous sodium hydroxide and cold methyl, ethyl and *iso*propyl alcohols.

Anal. Calcd. for $C_{11}H_{11}O_7N$: C, 49.0; H, 4.12. Found: C, 48.5, 48.8; H, 4.38, 4.09.

HYDROLYSIS.—When a suspension of 3 g. of the nitro-dimethyl ester in 20 cc. of 5.4 *N* sodium hydroxide is heated, the solid gradually dissolves; the yellow solution changes to red and is evaporated to an orange paste. The latter is redissolved in water and the solution is re-evaporated; this process is repeated. A solution of the paste in 30 cc. of water is acidified with 10 cc. of hydrochloric acid. After standing in the ice box overnight, the precipitate is removed by filtration, washed and dried at 85°. Two g. (98%) of 3-nitro-4-hydroxybenzoic acid is obtained as a slightly buff-colored powder; m. p., 180–181.5°. A mixture of this material with a specimen melting at 180–181° prepared by nitration of *p*-hydroxybenzoic acid melts at 180–181.5°.

When the aqueous acid mother liquor and washings are left in an uncovered beaker at room temperature, coarse white crystals separate as evaporation occurs. After 13.5 weeks, the solution (about 500 cc.) is cooled in the ice box, and the crystals are collected on a filter, washed and dried. The material (1 g.) is 2-nitro-4-carboxy-phenoxyacetic acid.[1]

From the alcoholic mother liquors obtained in the purification of the nitro-dimethyl ester, an additional 1.3 g. of this substance, 0.62 g. of methyl 2,6-dinitro-4-carbomethoxy-phenoxyacetate, 3.3 g. of methyl 2,4-dinitrophenoxyacetate and 1.97 g. of a monomethyl ester of 2-nitro-4-carboxy-phenoxyacetic acid may be isolated. The nitro-monomethyl ester is evidently a product of partial hydrolysis of the main nitration product. Hydrolysis could not have occurred during the isolation processes, because all the fractionations were performed with organic solvents. The process by which these by-products were separated and purified is a long, tedious one involving about 80 fractionations and cannot be discussed here. Moreover, now that the nature of the by-products has been ascertained, a much shorter fractionation process could be developed. It will be sufficient to describe these by-products briefly.

Methyl 2,6-Dinitro-4-carbomethoxy-phenoxyacetate. VI.—Transparent, yellow plates, m. p. 118.5–119°, which are soluble in chloroform, acetone, benzene, glacial acetic acid and hot methyl, ethyl and *n* and *iso*propyl alcohols but insoluble in ether, cold alcohols, water and cold sodium hydroxide.

Anal. Calcd. for $C_{11}H_{10}O_9N_2$: C, 42.0; H, 3.21. Found: C, 41.7; H, 3.18.

By applying the method used for the mononitro-dimethyl ester, 0.11 g. of 3,5-dinitro-4-hydroxybenzoic acid is obtained as transparent, yellow plates from 0.2 g. of the dinitro compound described above; the yield is 76%. The hydrolysis product melts at 244–246°; a specimen of this dinitro-hydroxybenzoic acid prepared by nitration of *p*-hydroxybenzoic acid melts at 241–245°, and the melting point of the mixture is 240–244°.

Monomethyl Ester of 2-Nitro-4-carboxy-phenoxyacetic acid. VIII or IX.—This was obtained as broad, thin, nearly white needles, m. p. 204–205°, which are soluble in ethyl alcohol, glacial acetic acid, ethyl acetate, acetone, aqueous sodium bicarbonate and hot chloroform but insoluble in water, benzene, ether, carbon disulfide, petroleum ether and cold chloroform.

Anal. Calcd. for $C_{10}H_9O_7N$: C, 47.0; H, 3.56. Found: C, 46.9; H, 3.52.

When 0.5 g. of this substance is hydrolyzed with sodium hydroxide, it yields 0.25 g. (70%) of 3-nitro-4-hydroxybenzoic acid as slightly buff-colored needles, m. p. 179–181°; a mixture of this material with a known specimen (m. p., 180–181°) melts at 179–181°.

Methyl 2,4-Dinitro-phenoxyacetate. VII.—This fraction is obtained as a brownish-yellow oil which changes into a cream-colored solid, m. p. 53–58°, if it is rubbed and scratched vigorously. The material could not be purified readily; a pure specimen, prepared by methylation of 2,4-dinitro-phenoxyacetic acid, melts at 70–73°.[2]

The identity of this material is established by a determination of its hydrolysis and ammonolysis products. When 0.5 g. of this material is hydrolyzed with sodium hydroxide, 0.25 g. (66%) of crude 2,4-dinitrophenol is obtained which, when recrystallized from water, yields 0.11 g. of dinitrophenol; m. p., 110–113°. A mixture of the latter with a known specimen (m. p., 111–113.5°) melts at 111–113°. When 0.5 g. of the impure methyl dinitro-phenoxyacetate is suspended at room temperature in 5 cc. of concd. ammonia water for 24 hours, 0.4 g. (85%) of crude 2,4-dinitro-phenoxyacetamide is obtained which, when recrystallized twice from ethyl alcohol, yields 0.13 g. of the pure dinitro-amide as slightly brown needles; m. p., 181–184°. A known specimen of this amide, prepared from the methyl ester, melts at 183–188.5°,[3] and the mixture melts at 182–188°.

6-Carboxy-3-keto-3,4-dihydro-1,4-benzoxazine. X.—A solution of 4.8 g. of 2-nitro-4-carboxy-phenoxyacetic acid in 20 cc. of water and 8 cc. of concd. ammonia water is added to a boiling solution of 39 g. of ferrous sulfate heptahydrate in 85 cc. of water which is being stirred mechanically. Ammonia water is added until the reaction mixture is strongly alkaline to litmus; the boiling mass is stirred for five minutes, and after the addition of 5 cc. of ammonia water, it is filtered through a mat of vegetable carbon on a Büchner funnel. The slightly pink filtrate is acidified with 8 cc. of glacial acetic acid and cooled in the ice box for three hours. The curdy, white precipitate is collected on a filter, washed and dried in a vacuum over sodium hydroxide; the yield is 2.5 g. (70%). By recrystallizing this material from 270 cc. of 50% alcohol, 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine (1.6 g.) is obtained as white, minute needles; m. p., 310–314° with slight softening at 306–307°. This substance is soluble in aqueous sodium bicarbonate, concd. sulfuric acid, and hot alcohol but insoluble in water and aqueous hydrochloric and nitric acids.

Anal. Calcd. for $C_9H_7O_4N$: C, 55.9; H, 3.63; N, 7.25. Found: C, 55.1, 55.4; H, 3.73, 3.78; N, 7.36, 7.02, 7.22.

6-Carbomethoxy-3-keto-3,4-dihydro-1,4-benzoxazine. XI. A.—A solution of 8.6 g. of methyl 2-nitro-4-carbomethoxy-phenoxyacetate V in 200 cc. of methyl alcohol containing 4 cc. of hydrochloric acid (d., 1.19) is boiled under a reflux condenser and treated with four 1.35g. portions of iron filings with 15, 18 and 22 minute intervals between successive additions. When the reaction mixture has refluxed for three hours after the last addition of iron filings, 4.5 cc. of 12.5 *N* sodium hydroxide solution is added and the hot mixture is filtered through a gravity funnel; the gelatinous residue is washed thoroughly with three 100cc. portions of hot methyl alcohol. The filtrate is evaporated to dryness on a steam-bath.

The powdered, crude reaction product (9.6 g.) is extracted at room temperature with 50 cc. of chloroform overnight, and the insoluble material is washed thrice with chloroform. By evaporation of the extract to dryness, 2.6 g. of a brown solid is obtained which when recrystallized from absolute methyl alcohol yields 1.75 g. of unreduced nitro-dimethyl ester.

The material insoluble in chloroform is extracted by boiling with 100 cc. of absolute ethyl alcohol, and the material insoluble in alcohol is washed with 50, 50, 30 and 20cc. portions of hot absolute ethyl alcohol. The insoluble residue (2.2 g.) is sodium chloride.

---

[2] Pratesi [*Gazz. chim. ital.*, [1] **22**, 242 (1892)] reports the melting point as 73°.

[3] Pratesi, Ref. 2, reports needles melting at 182–184°.

The alcoholic extract is evaporated to dryness, and the fawn-colored solid (3.3 g.) is extracted by stirring it at room temperature for 30 minutes with 25 cc. of water. The suspension is centrifuged, and the extraction process is repeated; the solid then remaining is washed with 10 cc. of water and dried at 80°. The white powder (1.2 g.) is slightly crude 6-carbomethoxy-3-keto-3,4-dihydro-1,4-benzoxazine; when recrystallized from absolute methyl alcohol, this compound (0.9 g.) is obtained as white needles; m. p., 188–190.5°. It is soluble in acetone, hot methyl alcohol and hot chloroform but insoluble in water, dil. hydrochloric acid, ether, cold methyl alcohol, cold chloroform and cold, dil. sodium hydroxide solution; it dissolves gradually when heated in aqueous sodium hydroxide.

Anal. Calcd. for $C_{10}H_9O_4N$: C, 57.9; H, 4.38; N, 6.77. Found: C, 57.1; H, 4.21; N, 6.95.

When the aqueous extract referred to above is evaporated to dryness, 2.18 g. of orange-brown solid is obtained which yields white, feathery needles (1.45 g.) when recrystallized from absolute methyl alcohol. This is the sodium salt of the monomethyl ester of 2-nitro-4-carboxy-phenoxyacetic acid, that is, the sodium salt of VIII or IX. It melts at 149–152° and effervesces at 153–154°; it is soluble in water, glacial acetic acid and hot methyl and ethyl alcohols but insoluble in chloroform, ether, benzene and acetone. Acidification of an aqueous solution of this salt causes the separation of colorless needles.

Anal. Loss at 105°, 10.8, 11.0. Calcd. for $C_{10}H_8O_7NNa$: N, 5.06; Na, 8.30. Found: N, 4.89, 5.27, 5.13; Na, 8.11.

By hydrolyzing 0.18 g. of this sodium salt with sodium hydroxide in the manner previously described, 0.07 g. (58%) of slightly impure 3-nitro-4-hydroxybenzoic acid (m. p., 176–180°) is obtained. When this material is mixed with a known specimen (m. p., 180–181°) the mixture melts at 179–181°.

When an aqueous solution of 0.8 g. of this sodium salt is acidified with hydrochloric acid, 0.45 g. of a monomethyl ester of 2-nitro-4-carboxy-phenoxyacetic acid VIII or IX is obtained as white needles; m. p., 151–154°. It is soluble in methyl and ethyl alcohols, acetone, ether and aqueous sodium bicarbonate but insoluble in water and chloroform.

Anal. Calcd. for $C_{10}H_9O_7N$: C, 47.0; H, 3.56; N, 5.49. Found: C, 46.6, 46.7; H, 3.48, 3.34; N, 5.71.

B. Two g. of 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine X is esterified by means of absolute methyl alcohol and dry hydrogen chloride. As the starting material is insoluble in cold methyl alcohol, the procedure used in methylating *p*-carboxyphenoxyacetic acid is followed. As the crude material which is obtained by evaporation of the reaction mixture is insoluble in ether, it is powdered and stirred at room temperature for 30 minutes with 35 cc. of water and 2 cc. of 10.75 *N* sodium hydroxide solution. The insoluble material is collected by centrifuging, washed twice with water and dried at 83°. This solid (0.6 g.) yields 0.45 g. of 6-carbomethoxy-3-keto-3,4-dihydro-1,4-benzoxazine as long, colorless needles, m. p. 192.5–193°, when recrystallized from absolute methyl alcohol. A mixture of this specimen with one obtained by Method **A** (m. p., 188–190.5°) melts at 189.5–192°.

Anal. Calcd. for $C_{10}H_9O_4N$: C, 57.9; H, 4.38; N, 6.77. Found: C, 57.6; H, 4.36; N, 6.59.

When the sodium hydroxide extract of the crude reaction product is acidified with hydrochloric acid, 1.46 g. of the unmethylated carboxy-benzoxazine is recovered.

6-Carbomethoxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine. XVI.—A solution of 2.2 g. of 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine (X) in 32 cc. of water and 2.6

cc. of 10.75 *N* sodium hydroxide solution is stirred mechanically at room temperature and treated with four 0.62cc. portions of dimethyl sulfate at 10, 12 and 23 minute intervals. Another 0.5 cc. of the sodium hydroxide solution is added after both the third and fourth portions of dimethyl sulfate in order to keep the reaction mixture alkaline to phenolphthalein. The mixture is centrifuged for 2.5 hours after the last addition of dimethyl sulfate and the white residue is washed thrice with water and dried at 85°. When the slightly impure reaction product (0.3 g.) is recrystallized from 20 cc. of absolute methyl alcohol, it yields 0.24 g. of 6-carbomethoxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine as white plates, m. p. 165–166°, which are insoluble in water, hydrochloric acid and sodium hydroxide solution.

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.7; H, 5.02; N, 6.34. Found: C, 59.7; H, 4.79; N, 6.08.

6-Carboxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine. XV.—When the alkaline mother liquor from the crude methylation product obtained as described above is acidified and cooled, a slightly pink solid (2.18 g.) is obtained which, when recrystallized twice from 50% alcohol, yields 1.35 g. of 6-carboxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine as faintly salmon-colored, transparent needles; m. p., 287–290°. It is soluble in aqueous sodium bicarbonate and hot glacial acetic acid, slightly soluble in acetone, chloroform and cold glacial acetic acid, and insoluble in water, ether, cold alcohol and hydrochloric acid.

Anal. Calcd. for $C_{10}H_9O_4N$: C, 57.9; H, 4.38; N, 6.77. Found: C, 57.5; H, 4.41; N, 6.46.

Summary

1. The preparation and properties of the following compounds are described: methyl 4-carbomethoxy-phenoxyacetate, 4-carbomethoxy-phenoxyacetamide, 4-carboxy-phenoxyacetamide, *O*-*p*-hydroxybenzoyl-glycolamide, 4-carbamido-phenoxyacetamide, methyl 2-nitro-4-carbomethoxy-phenoxyacetate, methyl 2,6-dinitro-4-carbomethoxy-phenoxyacetate, 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine, 6-carbomethoxy-3-keto-3,-4-dihydro-1,4-benzoxazine, 6-carbomethoxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine, 6-carboxy-3-keto-4-methyl-3,4-dihydro-1,4-benzoxazine.

2. The two isomeric monomethyl esters of 2-nitro-4-carboxy-phenoxyacetic acid are reported.

BOSTON 17, MASSACHUSETTS