in 0.1*N* sodium hydroxide solution and made up to 50 ml. with each of the following solutions: 0.1*N* hydrochloric acid, *p*H 7.2 phosphate buffer, and 0.1*N* sodium hydroxide. The ultraviolet spectra and *p*H values of these solutions are shown in Table I.

TABLE I

ULTRAVIOLET SPECTRA OF SYNTHETIC SPONGOSINE

*p*H	1.35	7.2	12.2
Max. (mμ)	251, 275 (252, 275)[10]	268 (268)	268 (268)
Min. (mμ)	257, 228 (258, 229)	232 (233)	233 (232)

Spongosine from Crotonoside. A 50-mg. sample of crystalline crotonoside prepared from croton seed[11] was suspended in 1 ml. of water and 1.8 ml. of 0.1*N* sodium hydroxide solution. The mixture was warmed until the crotonoside had dissolved, and an excess of silver nitrate solution was added with stirring. The precipitate was collected by centrifugation, washed three times with water and twice with methanol, and finally dried *in vacuo* over anhydrous potassium hydroxide. It was then ground to a fine powder and suspended in 5 ml. of absolute methanol; 2 ml. of methyl iodide was added and the mixture stirred at room temperature for 2 hr. The precipitate of silver iodide was separated by centrifugation, and the liquid taken to dryness at reduced pressure. The residue was dissolved in a few drops of hot water and chromatographed on paper in three solvent systems; see Table II.

TABLE II

PAPER CHROMATOGRAPHY OF METHYLATED CROTONOSIDE

Solvent System	BuOH-NH_3-H_2O[12]		BuOH-EtOH-H_2O[13]		BuOH-H_2O[14]	
Solvent front	36.0 cm.	R_F	37.9 cm.	R_F	39.6 cm.	R_F
Spongosine	13.0 cm.	0.36	12.5 cm.	0.33	12.9 cm.	0.33
Crotonoside	0.9 cm.	0.025				
Reaction mixture	0.7 cm.	0.019			0.4 cm.	0.010
	2.4 cm.	0.067	2.2 cm.	0.057	2.3 cm.	0.058
	4.4 cm.	0.122	4.2 cm.	0.111	4.4 cm.	0.111
	13.3 cm.	0.37	12.7 cm.	0.34	13.9 cm.	0.35

TABLE III

ULTRAVIOLET SPECTRA OF METHYLATED CROTONOSIDE (SPONGOSINE)

0.1*N* NaOH	0.1*N* HCl
Max. 267 mμ (268)[10]	Max. 274, 248 mμ (275, 251)[10]
Min. 232 mμ (233)	Min. 257, 228 mμ (257, 228)
280/260 0.645 (0.65)	280/260 1.45 (1.41)
250/260 0.77 (0.85)	250/260 1.02 (1.0)

Two chromatograms were run in the BuOH-NH_3-H_2O solvent system and the spots with R_F values corresponding to spongosine were eluted with 0.1*N* hydrochloric acid and 0.1*N* sodium hydroxide solution. The principal features of the ultraviolet absorption spectra of these solutions are shown in Table III.

NEW HAVEN, CONN.

(10) The bracketed figures are those reported for natural spongosine.[2]

(11) E. Cherbuliez and K. Bernhard, *Helv. Chim. Acta*, 15, 464 (1932).

(12) W. S. Macnutt, *Biochem. J.*, 50, 384 (1952).

(13) E. Chargaff, E. Vischer, R. Doniger, R. Green, and F. Misani, *J. Biol. Chem.*, 177, 405 (1949).

(14) 1-Butanol saturated with water at 23°.

[CONTRIBUTION FROM THE WARNER-CHILCOTT LABORATORIES]

Thyroxine Analogs

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Received December 26, 1956

3,5-Diiodo-4-(4′-hydroxyphenoxy)benzoic, 3,5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic, and β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acids were prepared by improved procedures.

Reports on the activity of 3,5-diiodo-4-(4′-hydroxy-3′-iodophenoxy)phenyl acetic acid as a thyroxine-like material in rats[1] *in vitro*[2] and clinically[3] resulted in these laboratories in a renewed and enlarged interest in this type of compound. For the preparation of such compounds we required 3,5-diiodo-4-(4′-hydroxyphenoxy)benzoic acid (Va), 3,5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic acid (Vb), and β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl] propionic acid (Vc).

Of these compounds, the benzoic[4] (Va) and phenylacetic[5] (Vb) acid analogs had been previously prepared *via* a comparatively cumbersome proce-

(1) R. Pitt-Rivers, *Lancet*, II, 234 (1953).

(2) O. Thibault and R. Pitt-Rivers, *Lancet*, I, 285 (1955).

(3) J. Lerman and R. Pitt-Rivers, *J. Clin. Endocrinol.*, 15, 653 (1955).

(4) C. R. Harington and G. Barger, *Biochem. J.*, 21, 169 (1927).

(5) C. R. Harington and R. Pitt-Rivers, *Biochem. J.*, 50, 438 (1952).

dure. The β-[3,5-diiodo-4-(4′-hydroxyphenoxy)-phenyl]propionic acid (Vc) had been prepared by Clayton *et al.*[6] by an elegant sequence of reactions which we planned to adopt for the preparation of all three of the required compounds. After we had finished our own laboratory work, a report appeared by Wilkinson[7] recording the preparation of the acetic analog by a series of reactions also based on the work of Clayton. Recent publication of the details[8] indicated, however, that our differences in procedure are worth noting.

Demethylation of the commercially[9] available *p*-methoxyphenylacetic acid, gave *p*-hydroxyphenylacetic acid which was esterified and nitrated. The resulting ethyl 3,5-dinitro-4-hydroxyphenylacetate (Ib) was allowed in turn to react in pyridine with methanesulfonyl chloride and then with *p*-methoxyphenol to yield ethyl 3,5-dinitro-4-(4′-methoxyphenylacetate (IIb). Clayton *et al.*[6] and Wilkinson[8] used p-toluenesulfonyl chloride in place of methanesulfonyl chloride. Their reactions required an elevated temperature for a period of at least an hour. In our hands, the yields were not consistent. We considered that part of the difficulty might result from the reaction of the pyridine with the product under the very conditions used in the preparation. The reaction of pyridine with dinitrophenyl ethers of this type had been reported.[10] We had further noticed the instability of this compound even when left wet with pyridine at room temperature for two days. We therefore changed reagents with the thought that the methanesulfonyl chloride might permit a faster reaction under milder conditions which would spare the resultant ether. The result was an improved yield of a cleaner product in a shorter period of time.

Like Wilkinson[8] we found that the ethyl 3,5-dinitro-4-(4′-methoxyphenoxy)phenylacetate (IIb) required considerable purification to induce crystallization. Instead of resorting to chromatographic procedures, however, we hydrolyzed our crude reaction mixture to yield the corresponding acid, IIc, which crystallized readily. When this product was catalytically reduced to the diamine, IIIb, and then tetrazotized and treated with sodium iodide according to procedures similar to those reported by Clayton for related compounds, there was obtained 3,5-diiodo-4-(4′-methoxyphenoxy)phenylacetic acid (IVb). Demethylation gave the required 3,5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic acid (Vb).

For the preparation of 3,5-diiodo-4-(4′-hydroxyphenoxy)benzoic acid (Va), methyl 3,5-dinitro-4-hydroxybenzoate was etherified to form methyl 3,5-dinitro-4-(4′-methoxyphenoxy)benzoate (IIa). Catalytic reduction to IIIa, followed by tetrazotization and treatment with sodium iodide gave methyl 3,5-diiodo-4-(4′-methoxyphenoxy)benzoate (IVa). Reaction with hydriodic acid cleaved both methyl ether and methyl ester to give the required compound, Va.

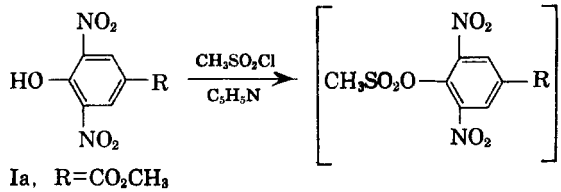
Reduction of methyl 3,5-diiodo-4-(4′-methoxyphenoxy)benzoate (IVa) by excess lithium aluminum hydride in ether was attempted in the expectation of attaining the corresponding benzyl alcohol. The product obtained, however, was iodine-free and analyzed satisfactorily for 4-(4′-methoxyphenoxy)benzyl alcohol. Even at −30°, considerable amounts of iodine were liberated.

The greater ease of etherification of the methyl 4-hydroxy-3,5-dinitrobenzoate over the ethyl 4-hydroxy-3,5-dinitrophenylacetate, be it with *p*-toluenesulfonyl chloride or with methanesulfonyl chloride, suggested that the carbomethoxy group exerted an activating effect. Further, Barnes *et al.*[10] found that although they could replace the chloro group of methyl 4-chloro-3,5-dinitrobenzoate by *p*-methoxyphenoxyl they could not so replace the chloro group of 4-chloro-3,5-dinitrotoluene. For the preparation of our phenylpropionic acid series we therefore did not use as starting material β-(4-hydroxyphenyl)propionic acid as had previously been used (Clayton *et al.*[6] and subsequently Tomita *et al.*[11]). Rather we chose the more easily attainable diethyl 4-hydroxybenzalmalonate in which the activating effects of the carbethoxy groups might be transmitted to the ring through the ethylene linkage. Etherification of the nitrated product, Ic, occurred almost as rapidly as the reagents were added to one another in the proper sequence. Reduction of the resulting diethyl 3,5-dinitro-4-(4′-methoxyphenoxy)benzalmalonate (IId) gave the diamine, IIIc. Tetrazotization was used to introduce two iodine atoms. Hydrolysis of the methyl ether and the ethyl esters was accompanied by decarboxylation to give the previously described β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid[6] (Vc).

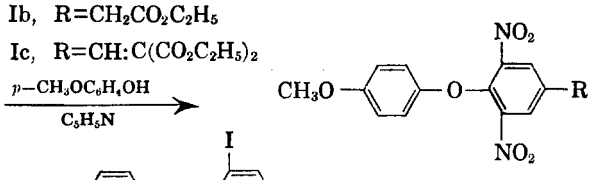
Iodination of the diiodo compounds (V) according to procedures in the literature,[5,6] gave the corresponding triiodo (VI) and tetraiodo (VII) compounds. Because all the triiodo compounds showed some contamination with the tetraiodo compounds, it was thought to prepare the pure materials using 4-methoxy-3-nitrophenol in place of *p*-methoxyphenol. Hexazotization at that point in a series where tetrazotization had been carried out, should then give triiodo compound free of tetraiodo compound. Accordingly, the reactions were carried out in both the benzoic and phenylacetic acid series. In the phenylacetic acid series, pure ethyl 3,5-dinitro-4-(4′-methoxy-3′-nitrophenoxy)phenylacetate (VIIIb) was obtained, but it could not be con-

(6) J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, 2467 (1951).
(7) J. H. Wilkinson, *Chemistry & Industry*, 1352 (1955).
(8) J. H. Wilkinson, *Biochem. J.*, 63, 601 (1956).
(9) Kay-Fries Chemicals, Inc., New York, N. Y.
(10) J. H. Barnes, E. T. Borrows, J. Elks, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, 2824 (1950).
(11) K. Tomita and H. A. Lardy, *J. Biol. Chem.*, 219, 595 (1956).

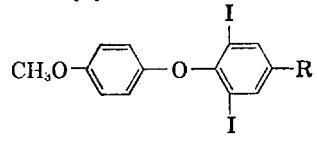
verted to pure ethyl 3,5-diiodo-4-(3′-iodo-4′-methoxyphenoxy)phenylacetate (Xb). We did not have this difficulty in the benzoic acid series and obtained both methyl 3,5-dinitro-4-(4′-methoxy-3′-nitrophenoxy)benzoate (VIIIa) and methyl 3,5-diiodo-4-(3′-iodo-4′-methoxyphenoxy)benzoate (Xa) in a pure state. Demethylation of the latter material without simultaneously removing some or all of the 3′-iodo group was not feasible. This was true whether we used hydrobromic or hydriodic acids with or without red phosphorus. Gemmill *et al.*[12] subsequently reported a similar experience in attempts to demethylate α-benzamido-3-iodo-4-(3′-iodo-4′-methoxyphenoxy)cinnamic acid.



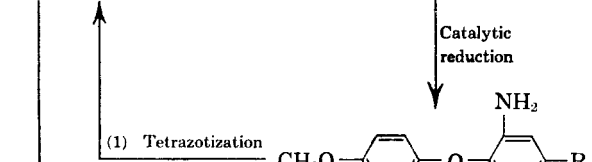
Ia, R=CO_2CH_3
Ib, R=$CH_2CO_2C_2H_5$
Ic, R=$CH{:}C(CO_2C_2H_5)_2$



IIa, R=CO_2CH_3
IIb, R=$CH_2CO_2C_2H_5$
IIc, R=CH_2CO_2H
IId, R=$CH{:}C(CO_2C_2H_5)_2$

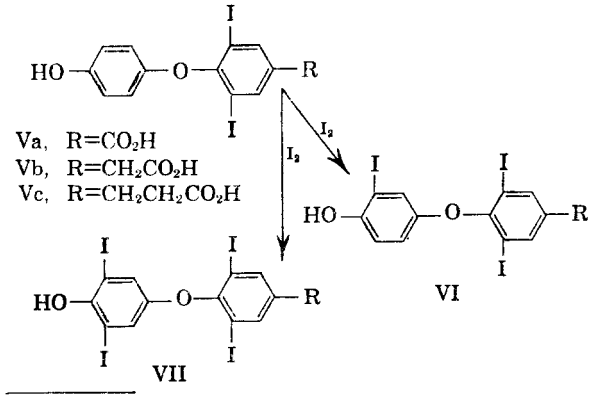


IVa, R=CO_2CH_3
IVb, R=CH_2CO_2H
IVc, R=$CH_2CH(CO_2C_2H_5)_2$



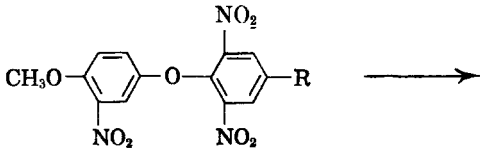
Hydrolysis HI

IIIa, R=CO_2CH_3
IIIb, R=CH_2CO_2H
IIIc, R=$CH_2CH_2(CO_2C_2H_5)_2$

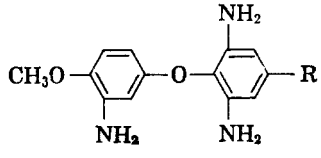


Va, R=CO_2H
Vb, R=CH_2CO_2H
Vc, R=$CH_2CH_2CO_2H$

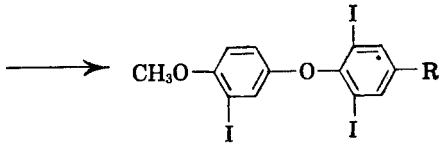
(12) C. L. Gemmill, J. J. Anderson, and A. Burger, *J. Am. Chem. Soc.*, **78**, 2434 (1956).



VIIIa, R=CO_2CH_3
VIIIb, R=$CH_2CO_2C_2H_5$



IX



Xa, R=CO_2CH_3
Xb, R=$CH_2CO_2C_2H_5$

EXPERIMENTAL[13]

Diethyl p-hydroxybenzalmalonate. A mixture of 160 g. (1 mole) of diethyl malonate, 122 g. (1 mole) of *p*-hydroxybenzaldehyde, 20 ml. of acetic acid, 6 ml. of piperidine, and 250 ml. of dry benzene was stirred at reflux under a water separator until no further collection of water occurred. The reaction mixture was cooled and filtered. The precipitate was washed with cold benzene. The product, which was suitable for nitration, weighed 170 g. (65%) and melted at 89–91°. After recrystallization from benzene the product melted at 91–93° (reported[14] 93°).

Ethyl p-hydroxyphenylacetate. A mixture of 200 g. (1.2 moles) of 4-methoxyphenylacetic acid, 10 g. of red phosphorus, 1 l. of acetic acid and 500 ml. of 57% (d 1.7) hydriodic acid was maintained at reflux for 1.5 hr. The filtered reaction mixture was concentrated to dryness and the residue was esterified with ethanol in the presence of hydrogen chloride.[15] The product, 136 g., (63%) distilled at 155–157° (1.5 mm.) and had n_D^{25} 1.5213.

Diethyl 3,5-dinitro-4-hydroxybenzalmalonate (Ic). To 2 l. of concentrated sulfuric acid at −10° to −5°, there was added portionwise with stirring 100 g. (0.38 mole) of powdered diethyl *p*-hydroxybenzalmalonate. After 10 min. the stirred mixture was cooled to −15° and 125 ml. of concentrated nitric acid was added dropwise. Stirring was continued while the temperature of the mixture was allowed to rise to 2–5° at which point the mixture was poured onto ice and filtered. The precipitate was washed with water and with petroleum ether (b.p. 60–71°). Recrystallization from acetonitrile gave 98 g. (73%) of product, m.p. 142–144°.

Anal. Calcd. for $C_{14}H_{14}N_2O_9$: C, 47.46; H, 3.98. Found: C, 47.06; H, 4.11.

Ethyl 3,5-dinitro-4-hydroxyphenylacetate (Ib). The nitration was carried out in a manner similar to that used for the preparation of Ic. The crude product was purified by solution in cold benzene, by filtration, and by precipitation by the addition of petroleum ether (b.p. 60–71°). When this was done the product in 82% yield melted at 72° (reported 71°).

Anal. Calcd. for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73. Found: C, 44.23; H, 3.84.

(13) Temperatures are not corrected. Melting points were taken on a Fisher-Johns melting point block.

(14) A. Chrzaszcewska, *Roczniki Chem.*, **5**, 72; *Chem. Zentr.*, **II**, 2905 (1926).

(15) H. Salkowski, *Ber.*, **22**, 2137 (1889).

Diethyl [3,5-dinitro-4-(4'-methoxyphenoxy)benzalmalonate (IId). To a solution of 35.4 g. (100 mmoles) of diethyl 3,5-dinitro-4-hydroxybenzalmalonate in 90 ml. of dry pyridine at about 80° was added dropwise with stirring 15.2 ml. (22.8 g.; 200 mmoles) of methanesulfonyl chloride. Gentle cooling was required during the addition. There was then added 43.5 g. (350 mmoles) of *p*-methoxyphenol. Stirring was continued for 10 min. before the reaction was poured into 1.5 l. of cold water. The resulting solid was taken up in benzene and washed well with 4*N* hydrochloric acid and then with water. The benzene solution was concentrated to dryness and the residue was recrystallized from 95% ethanol to give 42 g. (90%) of product, m.p. 115.5–116.5°.

Anal. Calcd. for $C_{21}H_{20}N_2O_{10}$: C, 54.78; H, 4.38; N, 6.09. Found: C, 55.03; H, 4.15; N, 6.10.

3,5-Dinitro-4-(4'-methoxyphenoxy)phenylacetic acid (IIc). To 2.3 g. (8.5 mmoles) of ethyl 3,5-dinitro-4-hydroxyphenylacetate dissolved in 12 ml. of dry pyridine, was added 0.75 ml. (1.1 g., 9.6 mmoles) of methanesulfonyl chloride. The mixture was heated to reflux and maintained at reflux for 2 min. There was then added 3.1 g. (25 mmoles) of 4-methoxyphenol and the reaction mixture was maintained at reflux for an additional 5 min. At the end of this time the reaction mixture was poured into water. This aqueous mixture was extracted with benzene. The benzene was washed with 4*N* hydrochloric acid and then with water. The benzene solution was dried over magnesium sulfate and the solvent was removed by evaporation. The residue was dissolved in 75 ml. of glacial acetic acid and 35 ml. of 6*N* hydrochloric acid and heated at reflux for 40 min. The reaction mixture was then evaporated to dryness. The residue from this hydrolysis was taken up in 20 ml. of cold 5% sodium hydroxide solution. The solution was filtered and the filtrate was acidified to precipitate the product. This product after recrystallization from aqueous acetic acid, melted at 187–189° and weighed 2.1 g. (73%).

Anal. Calcd. for $C_{15}H_{12}N_2O_8$: C, 51.72; H, 3.47; N, 8.05. Found: C, 51.55; H, 3.75; N, 7.81.

Ethyl 3,5-dinitro-4-(4'-methoxy-3'-nitrophenoxy)phenylacetate (VIIIb). This was prepared similarly to the manner in which the analogous dinitro compound was prepared. 3-Nitro-4-methoxyphenol was used in place of *p*-methoxyphenol and the period of reflux after the addition of the phenol was increased to 10 min. Extraction of the decomposed reaction mixture with chloroform gave, after washing, a chloroform residue which crystallized on heating with 50% methanol. Recrystallization from *n*-propanol gave 60% yield of product m.p. 149.5–150.5°. The free acid melted at 172.5–173°.

Anal. Calcd. for $C_{17}H_{15}O_{10}N_3$: C, 48.46; H, 3.59; N, 9.97. Found: C, 48.73; H, 3.52; N, 9.93.

Methyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzoate (IIa). Etherification of methyl 3,5-dinitro-4-hydroxybenzoate[16] (Ia) in a manner similar to that used in the preparation of diethyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzalmalonate, gave similar or higher yields of product, IIa. Recrystallization from alcohol resulted in a product m.p. 131–132° (reported[17] 129°).

Methyl 3,5-dinitro-4-(4'-methoxy-3'-nitrophenoxy)benzoate (VIIIa). This preparation was similar to the preparation of methyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzoate except that 3-nitro-4-methoxyphenol was used in place of *p*-methoxyphenol. The product, obtained in 82% yield, melted at 175–178° after recrystallization from aqueous acetic acid.

Anal. Calcd. for $C_{15}H_{11}O_{10}N_3$: C, 45.81: H, 2.82. Found: C, 45.23; H, 2.79.

Diethyl 3,5-diamino-4-(4'-methoxyphenoxy)benzylmalonate (IIIc). Reduction of 18.4 g. (40 mmoles) of diethyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzalmalonate in 150 ml. of acetic acid in the presence of 1 g. of 10% palladium-on-charcoal in a Parr shaker required about 1 hr. for reduction of both nitro groups and the double bond. Concentration of the filtered acetic acid solution left an oily residue which crystallized from absolute ethanol solution to give 12 g. (75%) of product which melted at 71.5–72.5°.

Anal. Calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51. Found: C, 62.75; H, 6.43.

It is not essential that this product be isolated. The over-all yield may be substantially increased by carrying out the tetrazotization on the filtered reaction mixture.

3,5-Diamino-4-(4'-methoxyphenoxy)phenylacetic acid (IIIb). The reduction was similar to that used for the preparation of the analogous benzylmalonate, IIIc. The product, obtained in 63% yield on recrystallization from acetic acid, melted at 177.5–178°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.22; H, 5.53; N, 9.46.

Methyl 3,5-diamino-4-(4'-methoxyphenoxy)benzoate (IIIa). The reduction was similar to that used for the preparation of the analogous benzylmalonate, IIIc. The product, recrystallized from aqueous acetone, melted at 171–173° (reported[17] 166°).

Methyl 3,5-diamino-4-(3'-amino-4'-methoxyphenoxy)benzoate (IX, R = CO_2CH_3). The preparation was similar to that of the analogous diamino compound, IIIa. Recrystallization from acetonitrile gave 57% yield of product m.p. 185–6°.

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65. Found: C, 59.03; H, 5.01.

Diethyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzylmalonate (IVc). To a solution of 11.2 g. (28 mmoles) of diethyl 3,5-diamino-4-(4'-methoxyphenoxy)benzylmalonate in 23 ml. of acetic acid, was added with cooling 17.5 ml. of sulfuric acid. The resulting solution was immediately added at −10° to a solution of 5.1 g. (74 mmoles) of powdered sodium nitrite in 38 ml. of cold sulfuric acid and 75 ml. of acetic acid while being kept cold. The reaction mixture was stirred in an ice bath for 1 hr. and then rapidly added to a stirred mixture of 30 g. (200 mmoles) of sodium iodide, 21 g. (83 mmoles) of iodine, 3.2 g. (53 mmoles) of urea, 400 ml. of water, and 230 ml. of chloroform at room temperature. The resultant mixture was stirred at room temperature for 1 hr. and then warmed to 40°. The layers were separated and the aqueous layer was further extracted with chloroform. The combined chloroform layers were washed twice with water, with aqueous sodium metabisulfite, and finally again with water. The chloroform solution was dried over magnesium sulfate; the solvent was evaporated; and the residue was recrystallized from absolute ethanol to give 11 g. (63%) of product which melted at 88.5–89.5°.

Anal. Calcd. for $C_{21}H_{22}I_2O_6$: C, 40.40; H, 3.55. Found: C, 40.18; H, 3.69.

3,5-Diiodo-4-(4'-methoxyphenoxy)phenylacetic acid (IVb). The preparation was similar to that of diethyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzylmalonate (IVc). The yield, starting with isolated amine, was 70% of product melting at 163–165°. Wilkinson[8] found 161–162°.

Methyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzoate (IVa), was similarly prepared from pure amine in 45% yield, m.p. 152.5–154° (reported[17] 153–154°).

β-[3,5-Diiodo-4-(4'-hydroxyphenoxy)phenyl]propionic acid (Vc). A solution of 11.2 g. (18 mmoles) of diethyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzylmalonate in 100 ml. of 57% hydriodic acid and 200 ml. of acetic acid was maintained at reflux for 2 hr., during which time there was a vigorous evolution of methyl iodide and carbon dioxide. The reaction mixture was concentrated to about 125 ml. and then cooled. The product which crystallized weighed 6.9 g. (75% yield) and melted at 247–249° on a block or at 238–238.5° in a capillary (reported[6] melting point, 250°).

3,5-Diiodo-4-(4'-hydroxyphenoxy)phenylacetic acid (Vb). The procedure for the preparation from IVb was similar

(16) F. Reverdin, *Bull. soc. chim. France*, [4] **3**, 592 (1908).

(17) E. T. Borrows, J. C. Clayton, and B. A. Hems, *J. Chem. Soc.*, S185 (1949).

to that for the preparation of the analogous propionic acid from IVc. Recrystallization from aqueous acetic acid gave 90% of product m.p. 218–219.5°. Further recrystallization could raise the melting point to 223.5–225° (reported[5] 219°).

3,5-Diiodo-4-(4'-hydroxyphenoxy)benzoic acid (Va). The procedure for the preparation from IVa was similar to that for the preparation of the analogous propionic acid from IVc. The product, in 80% yield, melted at 264.5–265.5° (reported[6] 260°).

Methyl 3,5-diiodo-4-(3'-iodo-4'-methoxyphenoxy)benzoate (Xa). To nitrosyl sulfate prepared from 7.8 g. (113 mmoles) sodium nitrate and 120 ml. of sulfuric acid, was added at −10° to 0° a solution of 2.7 g. (9 mmoles) of methyl 3,5-diamino-4-(3'-amino-4'-methoxyphenoxy)benzoate in 60 ml. of acetic acid. After stirring the reaction mixture in an ice bath for 0.5 hr., 45 ml. of phosphoric acid was added and stirring was continued for an additional 0.5 hr. in an ice bath. Replacement of the diazonium groups by iodine was carried out as in the preparation of IVc. The product weighed 1.9 g. (10%) and melted at 180–181°. Repeated recrystallization from acetonitrile raised the melting point to 192–193°.

Anal. Calcd. for $C_{15}H_{11}O_4I_3$: C, 28.33; H, 1.74; I, 59.87. Found: C, 28.99, 28.73; H, 1.79, 1.69; I, 59.84, 59.61.

4-(4'-Methoxyphenoxy)benzyl alcohol. In a Soxhlet Thimble was placed 5 g. of methyl 3,5-diiodo-4-(4'-methoxyphenoxy)-benzoate. This material was extracted by refluxing ether into a solution of 1.5 g. of lithium aluminum hydride in 200 ml. of dry ether. When practically all of the ester had been extracted into the reaction mixture, 120 ml. of 10% sulfuric acid was added. The separated aqueous layer was washed with ether and the combined ether solutions were washed with water and dried over magnesium sulfate. Evaporation of the ether gave a solid melting at about 93°. Recrystallization of the ether from aqueous ethanol raised the melting point to 100–100.5°. Analysis was in agreement for 4-(4'-methoxyphenoxy)benzyl alcohol.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.55; H, 6.02.

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[CONTRIBUTION FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LIMITED]

Nitration of 1-Substituted-2-iminoimidazolidines

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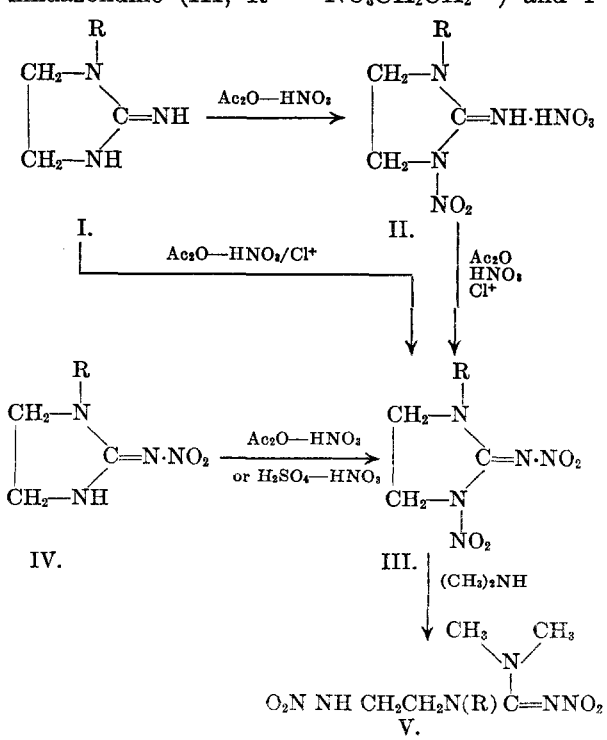
Received May 27, 1957

Nitration of 1-substituted-2-iminoimidazolidines in acetic anhydride–nitric acid medium in the absence of chlorine gives 1-substituted-2-imino-3-nitroimidazolidine nitrates. The same nitration medium containing chloride ion converts both 1-substituted-2-iminoimidazolidines and 1-substituted-2-imino-3-nitroimidazolidine nitrates into the corresponding 1-substituted-2-nitrimino-3-nitroimidazolidines. Thus electropositive chlorine catalyzes the nitration of an imino group to a nitrimino group in this series of compounds. 1-Methyl-2-nitrimino-3-nitroimidazolidine adds dimethylamine to give *N*-(β-nitraminoethyl)-*N*-methyl-*N'*,*N'*-dimethyl-*N''*-nitroguanidine, which is a tetrasubstituted nitroguanidine derivative.

Recently[1] it was found that 1-(β-hydroxyethyl)-2-iminoimidazolidine hydrochloride (I, HCl, R = $HOCH_2CH_2$) could be nitrated in acetic anhydride–nitric acid medium to 1-(β-nitroxyethyl)-2-nitrimino-3-nitroimidazolidine (III, R = $NO_3CH_2CH_2$). A further study of this reaction showed that nitration of the imino group in 1-substituted-2-iminoimidazolidines (I) is catalyzed by chlorine. The catalysis of amine nitration by electropositive chlorine and the mechanism of this reaction have been described fully by Wright.[2] The same mechanism will explain the results obtained in the nitration of the 1-substituted-2-iminoimidazolidines.

1-(β-Hydroxyethyl)- and 1-methyl-2-iminoimidazolidines (I, R = CH_3) as their free bases or their nitrate salts are converted respectively into 1-(β-nitroxyethyl)-2-imino-3-nitroimidazolidine nitrate (II, R = $NO_3CH_2CH_2$—) and 1-methyl-2-imino-3-nitroimidazolidine nitrate (II, R = CH_3) on nitration in acetic anhydride-nitric acid medium in the absence of chloride ion. If these nitrate salts are nitrated further in acetic anhydride-nitric acid solution containing ammonium chloride, they are converted into 1-(β-nitroxyethyl)-2-nitrimino-3-nitroimidazolidine (III, R = $NO_3CH_2CH_2$—) and 1-



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(2) H. Gilman, *Organic Chemistry*, John Wiley and Sons Inc., New York, 1953, Vol. IV, p. 988.