had, at *p*H 10.1, λ_{max} 279 mμ (log ε 4.22); at *p*H 7.0, λ_{max} 270 mμ (log ε 4.24); at *p*H 2.95, λ_{max} 278 mμ (log ε 4.16). $[\alpha]^{24}_{D}$ −123.3°, 3*N* hydrochloric acid; $[\alpha]^{24}_{D}$ −88.3°, *p*H 6.4; *c* = 1.

Anal. Calcd. for $C_{14}H_{11}O_2N_5$: C, 51.49; H, 4.75; N, 30.03. Found: C, 51.10; H, 5.00; N, 29.43.

*N-(6-Purinyl)-*DL*-serine.* DL-Serine, 3.42 g. (0.032 mole) with 2.1 g. (0.018 mole) of sodium carbonate in 25 ml. of water gave *p*H 9.2; 6-chloropurine (2.5 g., 0.016 mole) was added and the solution refluxed for 3 hr. After cooling the final *p*H was 8.8. The solution was adjusted to *p*H 3 with formic acid and cooled overnight; 2.88 g. (79.6%) of the crude product was obtained. This was recrystallized from hot water (650 ml.), yield, 2.3 g. (80%). A second recrystallization from 250 ml. of boiling water gave 1.82 g. of product (79%); m.p. 219–221° dec. with effervescence. The ultraviolet absorption spectra had, at *p*H 10.1, λ_{max} 270 mμ (log ε 4.19); at *p*H 7.0, λ_{max} 267 mμ (log ε 4.21); at *p*H 2.95, λ_{max} 274 mμ (log ε 4.19).

Anal. Calcd. for $C_8H_9O_3N_5$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.12; H, 4.07; N, 31.32.

*N-(6-Purinyl)-*DL*-threonine.* DL-Threonine, 3.88 g. (0.032 mole), and sodium carbonate, 2.01 g. (0.016 mole), were dissolved in 25 ml. of water and 6-chloropurine was added, 2.5 g. (0.016 mole). The solution was refluxed for 3 hr. No precipitate was obtained after adjusting to *p*H 3 with formic acid. The solution was readjusted to *p*H 6.8 with sodium hydroxide, the solution diluted 200 ml. and applied to a Dowex-2 formate column. The column was washed with 0.1*M* formic acid until all ninhydrin positive material was removed (650 ml.). The product was gradually eluted with 0.3*M* formic acid (650 ml.) and finally 0.6*M* formic acid (300 ml.) to elute remaining product. The 0.3 and 0.6*M* eluates were combined and taken to dryness in a rotary evaporator. An additional 50 ml. of water was added and the sample taken to dryness; this was repeated three more times to remove most of the formic acid. The product was washed to a lyophilizing flask. After freeze-drying, 3.0 g. (89%) of pure product was obtained; m.p. 130° dec. with effervescence. After drying at 100° for 48 hr., the m.p. was 161° dec. with effervescence. The material with the lower melting point had an analysis corresponding to the monohydrate after drying over phosphorus pentoxide *in vacuo* for 48 hr. at room temperature; it was dried at 100° for 48 hr. and the analysis shown below was obtained. The ultraviolet absorption spectra had, at *p*H 10.1, λ_{max} 271 mμ (log ε 4.19); at *p*H 7.0, λ_{max} 267 mμ (log ε 4.23); at *p*H 2.95, λ_{max} 275 mμ (log ε 4.19).

Anal. Calcd. for $C_9H_{11}O_3N_5$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.63; H, 4.79; N, 29.47.

*N-(6-Purinyl)-*DL*-valine.* DL-Valine, 3.8 g. (0.032 mole) was suspended in 50 ml. of water and the *p*H adjusted to 9 with sodium hydroxide. Sodium carbonate, 2.1 g. (0.018 mole), giving *p*H 9.7, and 6-chloropurine, 2.5 g. (0.016 mole), were added. The mixture was refluxed for 3 hr. and cooled; final *p*H, 8.35. The *p*H was adjusted to 3 with formic acid; a precipitate formed at once. After standing overnight in the cold, 2.74 g. of crude product was collected (73% yield); 2.3 g. was recrystallized from hot water, giving 1.07 g. (46%) of the desired product; m.p. 225–226° dec. with effervescence. The ultraviolet absorption spectra had, at *p*H 10.1, λ_{max} 273 mμ (log ε 4.20); at *p*H 7.0, λ_{max} 269 mμ (log ε 4.26); at *p*H 2.95, λ_{max} 275 mμ (log ε 4.18).

Anal. Calcd. for $C_{10}H_{13}O_2N_5$: C, 51.05; H, 5.57; N, 29.77. Found: C, 50.83; H, 5.80; N, 29.51.

HOUSTON 25, TEX.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Thyroformic Acids. II

EARLE VAN HEYNINGEN

Received May 9, 1961

The syntheses of methoxylated analogs of 3,5,3′,5′-tetraiodothyroformic acid are reported, as well as some novel side reactions encountered in several of the syntheses.

The first paper of this series[1] dealt with the chemistry of thyroformic acids in which at least some of the iodines of the parent substance, tetraiodothyroformic acid, were replaced with methyl groups. The present report is a continuation of this study in which the replacing group is an alkoxyl function. In general the iodine substitution is in the benzoic acid ring and the alkoxyl substitution is in the phenoxy ring.

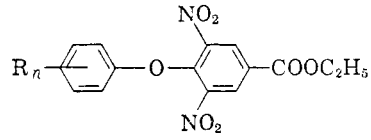
The method of synthesis employed parallels that of the literature.[2] This involved, as a general rule, the condensation of a sulfonate ester of ethyl 3,5-dinitro-4-hydroxybenzoate (II) with a phenol (I) in pyridine solution and subsequent conversion of the nitro groups into amino and then into iodo substituents as indicated in Fig. 1. In the condensations to make III in which tosyl chloride was employed and the reaction mixture was heated to boiling, brown fumes were eliminated, and the product was difficult to purify. Although the actual nature of this side reaction was not investigated, the generation of nitrous acid fumes suggested that the phenol I was also replacing one of the nitro groups. This is analogous to the experience of Loudon and McCapra[3] with 2,4-dinitro-6-benzoyl-2′-hydroxydiphenyl ether, which at high temperature in pyridine forms a dibenzodioxadiene. The condensations with either tosyl or mesyl chloride were therefore heated only to steam-bath temperature. The products obtained in the couplings are listed in Table I in the Experimental section. All the products were purified easily except the one from 2,6-dimethoxyhydroquinone. Initially,

(1) E. Van Heyningen, *J. Org. Chem.*, **26**, 3850 (1961).

(2)(a) E. T. Borrows, J. C. Clayton, and B. A. Hems, *J. Chem. Soc.*, S185, S199 (1949); E. T. Borrows, J. C. Clayton, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, S190 (1949). (b) R. I. Meltzer, D. M. Lustgarten, and A. Fischmann, *J. Org. Chem.*, **22**, 1577 (1957).

(3) J. D. Loudon and F. McCapra, *J. Chem. Soc.*, 1899 (1959).

TABLE I



R_n	M.P.[b]	Yield, %	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4′-Methoxy	98–101.5	68.5	$C_{16}H_{14}N_2O_8$	53.04	53.38	3.90	4.01		
3′-Methoxy[a]	99–101	67.5	$C_{15}H_{12}N_2O_8$	51.73	51.58	3.47	3.49	8.04	8.13
3′-Ethoxy[a]	93–95	40.0	$C_{16}H_{14}N_2O_8$	53.04	53.05	3.90	3.88	7.73	7.62
3′-Benzoyloxy	121.5–124	78.2	$C_{22}H_{16}N_2O_9$	58.41	59.09	3.57	3.69	6.19	6.16
3′,4′-Dimethoxy	130–131.5	44.2	$C_{17}H_{16}N_2O_9$	52.04	52.26	4.11	4.33	7.14	7.00
3′,5′-Dimethoxy-4′-hydroxy	139 dec.	20.6	$C_{17}H_{16}N_2O_{10}$	50.00	49.96	3.95	4.02	6.86	6.70

[a] Methyl ester. [b] All the products were recrystallized from ethanol.

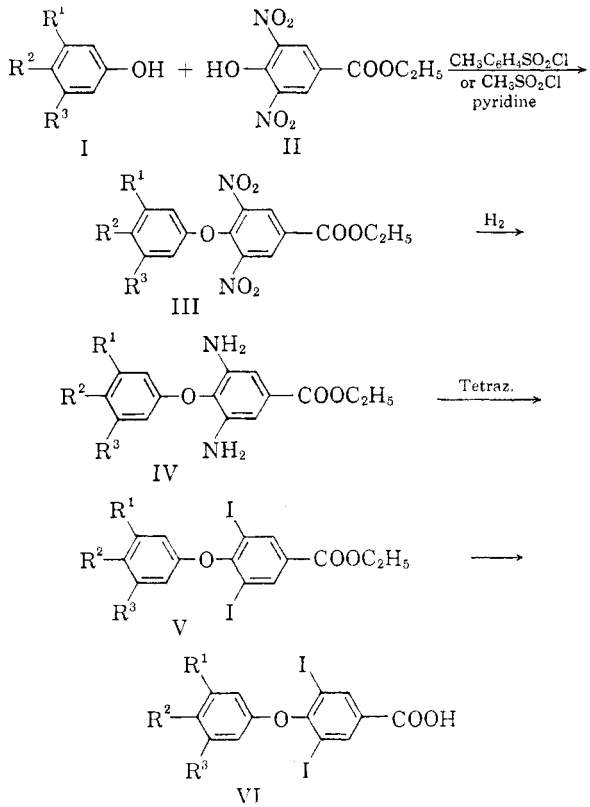


Figure 1

the assumption made was that in this coupling di-*ortho* substitution of the one hydroxyl would prohibit condensation there, and that condensation would occur at the unhindered hydroxyl. Two compounds, however, resulted from the condensation, only one of which could be purified. The pure product was obtained in larger amount, nearly double that of the other material. The spectra of the pure compound are consistent with it being the di-*ortho* substituted phenol V, (R^2 = OH; R^1, R^3 = OCH_3). The ultraviolet spectrum gives particular support for di-*ortho* substitution as there is only a small shift of the absorption maximum in alkali.

A condensation that differed from the above in the nature of the reactants was that between 5-nitrovanillin and *p*-methoxyphenol. This coupling was studied in an attempt to improve the yield as at best the product was formed in only 13% of the theoretical amount. Both mesyl chloride and tosyl chloride were used, but mesyl chloride gave poorer yields under identical conditions. Slight modifications of the usual reaction conditions were found to give the best yield. These were to form the *p*-toluenesulfonate ester of 5-nitrovanillin at room temperature and then to heat this ester with the phenol for a moderate length of time on the steam bath; short reaction times gave incomplete reaction, and extended periods of heating caused decomposition.

The permanganate oxidation of the aldehyde resulting from the condensation yielded the acid, 4-(4′-methoxyphenoxy)-3-methoxy-5-nitrobenzoic acid. A thyroformic acid with a methoxy group in the benzoic acid ring was formed from this acid by the following sequence of reactions. The carboxyl group was esterified, the nitro group replaced by an iodine through reduction and a Sandmeyer reaction, and the ester converted by saponification to the acid, 4-(4′-methoxyphenoxy)-3-methoxy-5-iodobenzoic acid.

The attempted preparation of a 3,5-dimethoxylated thyroformic acid yielded some interesting results. The best method for converting 3,5-diaminothyronine derivatives and analogs into diiodo compounds is to bisdiazotize in a concentrated sulfuric–glacial acetic acid mixture.[4] Hodgson[5] has shown that a diazonium salt in sulfuric–acetic acids can be reduced with ethanol. It is well known that while ethanol treatment of diazonium salts results in reduction, similar treatment with methanol often gives methoxyl replacement of the diazonium group rather than reduction.[6] With this in view,

(4) E. Duintjer and A. Jönsson, *Acta Chem. Scand.*, **9**, 203 (1955).

(5) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).

(6) F. K. Cameron, *Am. Chem. J.*, **20**, 229 (1898).

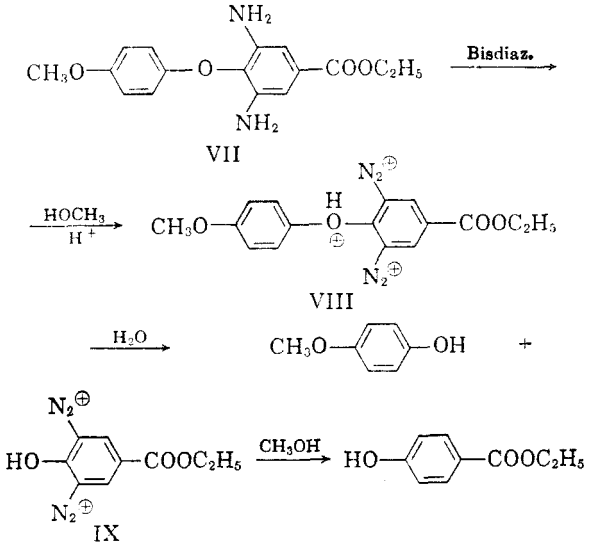


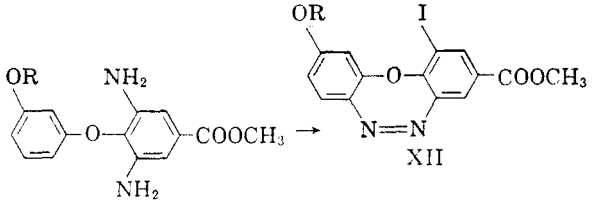
Figure 2

ethyl 4-(4′-methoxyphenoxy)-3,5-diaminobenzoate (VII, Fig. 2) was bisdiazotized in sulfuric acid-acetic acid and this solution was treated with methanol. None of the anticipated ethyl 4-(4′-methoxyphenoxy)-3,5-dimethoxybenzoate was isolated from the tarry product. The only material obtained pure, although in minute amount, was ethyl 4-hydroxybenzoate. Evidently, some of the bisdiazonium salt by reaction with water, generated from the interaction of acetic acid and methanol, was cleaved in the strong acid solution to the bisdiazonium salt IX which was reduced by the methanol to the observed product. The synthesis of the dimethoxy compound was not pursued further.

The reduction of the nitro esters III in acetic acid with a 5% palladium on charcoal catalyst was without complication. In some instances the diamines were isolated and characterized, but they proved to be quite easily air oxidized. Several syntheses in which the reduction mixtures freed of catalyst were used in the bisdiazotization reaction indicated that the small amount of water formed in the reduction did not cause any complication or noticeably lower yields.

The bisdiazotization of the diamines gave varied results. The nitro ester III (R^1, R^3 = OCH_3; R^2 = OH) was benzoylated prior to its reduction as an attempt to perform the bisdiazotization on hydroxy diamine gave an intractable, tarry product. The benzoylated nitro ester did furnish a somewhat cleaner product, but purification was difficult and the analysis indicated that there was some reduction of the bisdiazonium salt, because not all the iodine theoretically possible was present. As saponification proved to give a more readily purifiable product, complete purification of this intermediate was not attempted. A thyroformic acid dimethoxylated in the phenoxy ring resulted from this synthesis.

The bisdiazotization of the diamino esters (IVa, the methyl ester corresponding to IV), in which R^2 and R^3 were hydrogen and R^1 either methoxyl or ethoxyl, proceeded to give abnormal products. The products contained nitrogen and were brightly colored, yellow-orange solids. Analytical data and infrared and ultraviolet spectra established these products as oxadiazepines (XII). Evidently, a diazo group had coupled with the phenoxy ring at



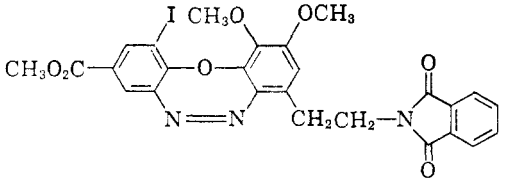
the activated position *para* to the alkoxyl group (undoubtedly favored over the more sterically hindered position *ortho* to the alkoxy group), either during the bisdiazotization in the acetic acid–sulfuric acid solution or more likely in the very strongly acid solution resulting when the Sandmeyer replacement with iodide-iodine was performed. In contrast with this result, a very similar compound, differing only in having a propionic acid instead of a formic acid side chain, is reported to give a diiodo derivative in good yield in a Sandmeyer reaction.[7] It does correspond, however, to the report by Crowder and co-workers[8] of the bisdiazotization of a thyroformic acid derivative.

As the diazo coupling to give XII is undoubtedly due to activation of the *para* position by the alkoxyl group, it was thought reasonable to replace the alkoxyl group with a benzoyloxy group. The benzoyloxy group would provide a lower electron density in the *para* position and the desired Sandmeyer reaction might take precedence over coupling. This was found to be the case to at least some extent for the desired diiodo compound V (R^1 = C_6H_5COO; R^2, R^3 = H) was obtained, although in very small yield (10%). None of the oxadiazepine was isolated from the tarry product. The diester was easily saponified to the hydroxy acid VI (R^1 = OH; R^2, R^3 = H).

An attempt to hydrolyze the oxadiazepine esters XII with acid gave red intractable tars, but saponi-

(7) T. C. Bruice, *J. Org. Chem.*, 19, 333 (1954).

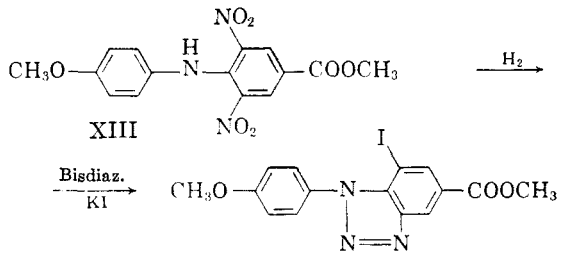
(8) J. R Crowder, M. F. Grundon, and J. R. Lewis, *J. Chem. Soc.*, 2142 (1958). Their product was



They did successfully isolate some diiodo compound in small amount.

fication of one of the esters in alcoholic potassium hydroxide furnished the corresponding acid.

A somewhat related coupling reaction occurred when methyl 4-(4′-methoxyphenylamino)-3,5-dinitrobenzoate (XIII) was reduced to the diamine,



XIII

the diamine bisdiazotized, and the Sandmeyer replacement with iodine attempted. Instead of the expected diiodo compound, a benzotriazole was formed. Cookson[9] reported a similar benzotriazole formation in a study of the synthesis of the "diphenylamine analog" of thyroxine.

Most of these compounds were tested by Dr. Roy Herrmann of our laboratory for their cholesterol-lowering effects. In rats on a high carbohydrate, 1% cholesterol, vitamin-D diet, none of the above compounds showed any improvement in cholesterol-lowering activity over their iodine substituted counterparts or isomeric 4-alkoxyl or hydroxyl analogs.

EXPERIMENTAL[10]

Formation of diphenyl ethers (III). The method of coupling ethyl 3,5-dinitro-4-hydroxybenzoate (II) with phenols followed in general that of Borrows, Clayton, and Hems[2a] as modified by Meltzer, Lustgarten, and Fischmann[2b] in which mesyl chloride substitutes for the tosyl chloride which the former workers employed.

The general method was as follows: A solution of 0.1 mole of ethyl 3,5-dinitro-4-hydroxybenzoate[2a] in 150 ml. of dry pyridine was treated with 0.12 mole of methanesulfonyl chloride, added in one portion at room temperature. There was a sharp temperature rise and the mixture was heated further on the steam bath for 15 min. Without cooling, 0.14 mole of a phenol (0.2 mole if readily available) was added and the mixture heated and stirred for 2 hr. at steam bath temperature. The hot reaction mixture was inverted into 2 l. of cold water. The product was extracted with benzene and the benzene solution washed with 800 ml. of 3*N* hydrochloric acid in three portions, treated with decolorizing carbon, and evaporated in vacuum. The solid, orange-yellow products were easily purified by recrystallization from ethanol (see Table I).

The phenols were commercially available except for 3,4-dimethoxyphenol, which was prepared[11] by the action of performic acid on veratraldehyde (55.6% yield), and 2,6-dimethoxyhydroquinone, which was made by the method of Chapman *et al.*[12]

The isolation of ethyl 4-(4′-hydroxy-3′,5′-dimethoxyphenoxy)-3,5-dinitrobenzoate was difficult because of an uncharacterized red by-product. Separation of the red contaminant was possible by extraction of reaction product with hot benzene in which it was soluble. The yellow ester was purified by recrystallization from acetone-water (charcoal treatment) as stout yellow prisms (see Table I). An attempt was made to purify the red by-product by recrystallization from alcohol-water (red needles with indefinite melting point starting at 109°). It was obtained in about half the amount of the yellow product and no formula could be fitted to its analysis: C, 52.14; H, 4.19; N, 5.62. The methoxyls were assigned to the 3′,5′-positions in the yellow product on the basis of lack of steric hindrance in this isomer to the original coupling and the small shift in the ultraviolet absorption maximum of this compound on addition of alkali, indicating probably little salt formation of the phenol because of steric hindrance by the methoxyls. The infrared spectrum (mineral oil mull) had the following absorption bands: 2.92, 5.84, 6.44, and 7.61, and 8.46 μ which are assigned to the hydroxyl, carbonyl, nitro groups, and diphenyl ether link, respectively. The ultraviolet spectrum had a λ_{max} 224 (log ϵ 4.46) which shifted hardly perceptibly with added alkali. This lack of shift in the ultraviolet spectrum with alkali is also seen in 2,6-dimethoxyphenol[13] and is probably typical of this vicinal arrangement.

Preparation of 4-(4′-methoxyphenoxy)-3-nitro-5-methoxybenzaldehyde. Many variations of the reaction conditions failed to give the product in good yield. The preparation was best performed as follows: A solution of 88.6 g. (0.5 mole) of 5-nitrovanillin[14] in 680 ml. of dry pyridine was treated at 20° with 107 g. (0.56 mole) of *p*-toluenesulfonyl chloride and stirred at room temperature for 2 hr. Then 93.5 g. (0.774 mole) of 4-methoxyphenol was added and the mixture refluxed for 2 hr. The pyridine was distilled in vacuum, and the residue was dissolved in chloroform and washed with 2*N* hydrochloric acid followed by 2*N* sodium hydroxide and then water. The liquid residue from the evaporation of the chloroform was dissolved in 350 ml. of hot ethanol, decolorized with activated carbon and chilled to give the product (20 g., 13%), m.p. 96–98°. Recrystallized for analysis, it melted at 99–101°.

Anal. Calcd. for $C_{15}H_{13}NO_6$: C, 59.40; H, 4.32; N, 4.62. Found: C, 59.45; H, 4.31; N, 4.50.

Preparation of 4-(4′-methoxyphenoxy)-3-nitro-5-methoxybenzoic acid. In a 1-l. flask 22.5 g. (0.0743 mole) of the corresponding aldehyde was dissolved in 180 ml. of pure acetone and 120 ml. of water. A solution of 16.5 g. (0.104 mole) of potassium permanganate in 335 ml. of water was added over 1.5 hr. with stirring to the solution of the aldehyde at 60° on a steam bath. After being heated for an additional 1.5 hr., the solution was made strongly alkaline with 10% potassium hydroxide and filtered from the manganese dioxide. Acetone was removed by evaporation in vacuum and the resulting water solution acidified with 5% hydrochloric acid and chilled. The product was filtered and recrystallized from ethanol-water, m.p. 177.5–179.5°, in a yield of 22 g. (0.069 mole, 92.7%).

Anal. Calcd. for $C_{15}H_{13}NO_7$: C, 56.43; H, 4.10; N, 4.39. Found: C, 56.36; H, 4.38; N, 4.25.

Preparation of ethyl 4-(4′-methoxyphenoxy)-3-nitro-5-methoxybenzoate. The acid, 22 g. (0.069 mole), was dissolved in 500 ml. of absolute ethanol and the solution saturated with dry hydrogen chloride. After standing for 48 hr., the solution was chilled and the product crystallized as fine needles. It was filtered and recrystallized from ethanol, m.p. 102.5–103°, 20.6 g. (0.0595 mole), 86%.

Anal. Calcd. for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 59.56; H, 5.02; N, 3.91.

Reduction of nitro esters. The reduction of the nitro esters (III) was readily accomplished by low-pressure hydrogenation. From 20 to 25 g. of an ester was dissolved and sus-

(9) R. C. Cookson, *J. Chem. Soc.*, 643 (1953).

(10) All melting points and boiling points are uncorrected.

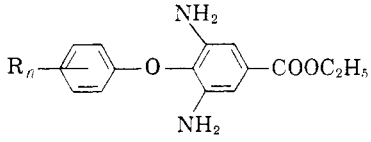
(11) J. Böeseken and J. Greup, *Rec. trav. chim.*, **58**, 530 (1939).

(12) E. Chapman, A. G. Perkins, and R. Robinson, *J. Chem. Soc.*, 3015 (1927).

(13) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **73**, 2708 (1951).

(14) W. Vogl, *Monats.*, **20**, 384 (1899).

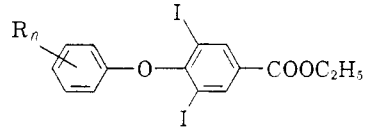
TABLE II



R_n	M.P.	Yield, %	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4′-Methoxy	116–117.5[b]	75	$C_{16}H_{18}N_2O_4$	63.56	62.89	6.00	5.99	9.27	9.19
3′-Methoxy[a]	172–174[c]	61	$C_{15}H_{16}N_2O_4$	62.49	62.25	5.59	5.30	9.72	9.85
3′-Ethoxy[a]	117–119[d]	97.5	$C_{16}H_{18}N_2O_4$	63.56	63.37	6.00	5.77	9.27	9.18
3′-Benzoyloxy	122–123[d]	87	$C_{22}H_{20}N_2O_5$	67.33	67.43	5.14	5.20	7.14	6.92

[a] Methyl ester. [b] Recrystallized from acetone-water. [c] Ethanol. [d] Ethanol-water.

TABLE III



R_n	M.P.[a]	Yield, %	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Iodine, % Calcd.	Iodine, % Found
3′-Benzoyloxy	177.5–179.5	10	$C_{22}H_{16}I_2O_5$	43.02	43.61	2.63	2.87	41.33	40.71
3′,4′-Dimethoxy	110–111	46.5	$C_{17}H_{16}I_2O_5$	37.84	36.88	2.91	3.04	45.80	45.20
3′,5′-Dimethoxy-4′-benzoyloxy	181.5	31	$C_{24}H_{20}I_2O_7$	42.75	45.32[b]	2.99	3.38[b]		
4′-Methoxy(5-methoxy)[c]	88.5–90.5	27.6	$C_{17}H_{17}IO_5$	47.68	47.87	4.00	4.36	29.64	29.20

[a] From ethanol. [b] This material had a poor analysis but saponification gave an analytically pure product. (See Experimental). [c] This compound has a methoxy group replacing one of the iodines in the benzoic acid ring.

pended in 150 ml. of glacial acetic acid and reduced in the presence of 1 g. of 5% palladium-on-carbon catalyst at an initial pressure of hydrogen of 40 p.s.i.g. The hydrogenation was rapid and there was a sharp temperature rise but no deleterious effect was noticed because of it. Usually the amino esters were soluble in the acetic acid. Those that were not, were at the end of the hydrogenation redissolved by heating before filtering off the catalyst. The reductions were usually finished in 1 or 2 hr. In several instances the amino esters were isolated and characterized (see Table II). It was found, however, that the acetic acid solution from the hydrogenation could be used in the subsequent tetrazotization reaction. Furthermore, the isolated diamines seemed to be oxidized and darkened on standing. In those instances that the diamines were isolated, the acetic acid was removed by evaporation in vacuum on the steam bath and the white to grey products were washed with water and recrystallized from alcohol or alcohol-water.

Bisdiazotization of amino esters. The method of Duintjer and Jönsson[4] was used with a few changes. The amine was dissolved in glacial acetic acid (300 ml./0.1 mole), chilled in salt ice and diluted with an equal volume of concentrated sulfuric acid at temperatures below 30°. A solution of nitrosyl sulfuric acid was prepared by cooling concentrated sulfuric acid (200 ml./0.1 mole) in a salt ice-bath and adding to it 0.28 mole of finely powdered sodium nitrite evenly over 1 min. while stirring. There was a sharp temperature rise. When the temperature had again fallen, glacial acetic (200 ml./0.1 mole) was added so the temperature did not exceed 25°. When the solution had again cooled to −2° or less, the amine solution was added dropwise with stirring at below 0°. After complete addition the solution was maintained at 0° for 0.5 hr. and then added to a mixture of 0.45 mole of iodine, 0.75 mole of potassium iodide, and 0.085 mole of urea in 1800 ml. of water so that the temperature did not rise above 40°. This addition took about 1 hr. After stirring at room temperature overnight, the reaction mixture was allowed to settle and the supernatant decanted. The black, often tarry, residue was layered with 400 ml. of ice and water and, with stirring, a stream of sulfur dioxide was led in until the color of the iodine was discharged. The product was dissolved in chloroform, washed with sodium bicarbonate solution and then water, treated with decolorizing carbon, and evaporated in vacuum on the steam bath. The orange-red or yellow residue was then recrystallized from the appropriate solvent, with decolorizing carbon treatment. The normal aryloxydiiodobenzoate esters are listed in Table III.

In the experiments in which the methyl 4-(3′-alkoxyphenoxy)-3,5-diaminobenzoates IVa (R = CH_3 or C_2H_5) were used, the products were isolated as usual but were highly colored. The infrared absorption bands at 5.8 μ and 8.25 μ indicated the presence of an ester function but the fingerprint region was more varied than that of the usual diiodo derivative. The ultraviolet maxima were at 258 and 349 mμ, the latter had a log ϵ 3.76. This corresponds well with the ultraviolet spectrum of Crowder's compound described in Footnote 8, λ_{max} 360 mμ (log ϵ 3.7). The analytical data likewise support the oxadiazepine structure XII for these compounds.

The methoxy compound XII (R = CH_3) was isolated as yellow needles, m.p. 183–185°, in 6% yield.

Anal. Calcd. for $C_{15}H_{11}IN_2O_4$: C, 43.92; H, 2.70; N, 6.83. Found: C, 43.71; H, 2.89; N, 7.08.

The ethoxy compound XII (R = C_2H_5) was obtained pure by recrystallization from methanol, m.p. 158–160°, in a 31% yield.

Anal. Calcd. for $C_{16}H_{13}IN_2O_4$: C, 45.30; H, 3.09; N, 6.60. Found: C, 45.52; H, 3.05; N, 6.80.

Preparation of 1-iodo-3-carboxy-9-ethoxydibenz-1,4,5-oxadiazepine. The methyl ester (1 g.) was dissolved in 200 ml. of methanol and mixed with a solution of 0.19 g. of sodium hydroxide in 20 ml. of methanol and refluxed for several hours. The methanol was removed by evaporation in vacuum

on the steam bath. The residue was dissolved in water and filtered to remove some insoluble material. The red filtrate on acidification with dilute hydrochloric acid gave a red precipitate that recrystallized as red needles from ethanol-water, m.p. 240–243°, in a yield of 0.66 g. (65%).

Anal. Calcd. for $C_{15}H_{11}IN_2O_4.H_2O$: C, 42.07; H, 3.06; N, 6.54. Found: C, 42.07; H, 3.60; N, 6.46.

An attempt to cleave the ethoxyl group in refluxing hydriodic acid-acetic acid gave carbonaceous products from which no pure material could be isolated.

Preparation of ethyl 4-(4′-benzoyloxy-3′,5′-dimethoxyphenoxy)-3,5-dinitrobenzoate. A solution of 12 g. (0.0294 mole) of ethyl 4-(4′-hydroxy-3′,5′-dimethoxyphenoxy)-3,5-dinitrobenzoate in 60 ml. of dry pyridine was treated with shaking with 4.5 g. (0.032 mole) of benzoyl chloride. After standing at room temperature for 3 days, the pyridine was removed by evaporation in vacuum on the steam-bath. The residue in benzene was washed successively with water, dilute hydrochloric acid, and water. Removal of benzene yielded a solid which was recrystallized from an acetone-ethanol-water mixture, m.p. 191.5° with prior softening at 165°. The yield was 13 g. (0.0254 mole, 86.4%).

Anal. Calcd. for $C_{24}H_{20}N_2O_{11}$: C, 56.25; H, 3.93; N, 5.47. Found: C, 56.21; H, 3.84; N, 5.23.

Preparation of 4-(4′-hydroxy-3′,5′-dimethoxyphenoxy)-3,5-diiodobenzoic acid. A solution of 5.3 g. (0.0078 mole) of the benzoate ethyl ester in 50 ml. of methanol containing 1.7 g. of potassium hydroxide was refluxed for 2 hr. and evaporated to dryness. The residue was dissolved in water and hydrochloric acid was added. The precipitate was collected and recrystallized three times from water-ethanol with one treatment with activated charcoal. The light yellow platelets weighed 1.8 g. (42.5%) and melted at 228–230.5° with prior softening at 208°.

Anal. Calcd. for $C_{15}H_{12}I_2O_6$: C, 33.23; H, 2.23. Found: C, 33.10; H, 2.43.

Methanolic acid cleavage and reduction of ethyl 4-(4′-methoxyphenoxy) - 3,5 - bis(diazonium)benzoate bisbisulfate (VIII). A tetrazotization as described in the general procedure above was performed with 0.0719 mole of ethyl 4-(4′-methoxyphenoxy)-3,5-diaminobenzoate. The acetic acid–sulfuric acid solution of the bisdiazonium salt was added dropwise to 1400 ml. of methanol at less than 35°. There was a slow evolution of nitrogen, the methanol solution changing from light yellow to deep red-brown at the end of the addition. After stirring for 1 hr. at room temperature, the solution was heated on the steam bath for 2 hr., and evaporated to a small volume in vacuum. Some carbonized material was filtered from the solution obtained by the addition of benzene and ether and the solution treated with activated carbon. Evaporation to dryness gave a dark red tar. Its benzene solution was passed through a Florasil column and a red material was washed off with benzene. The benzene eluate was extracted with dilute potassium hydroxide solution and the basic solution was acidified with dilute hydrochloric acid. The precipitate that separated was extracted into ether. The ether solution was treated with activiated carbon and the ether removed to give an oil that crystallized. The solid was recrystallized from acetic acid-water (activated carbon treatment) to give pink-tinged needles, 0.42 g., m.p. 112–113.5°. Analysis and ultraviolet and infrared spectra proved this compound to be ethyl *p*-hydroxybenzoate. A mixture melting point with an authentic sample was not depressed. The molecular weight by titration (pK_a 10.4, 66% dimethylformamide) was 166 (theory 168).

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07; C_2H_5O, 27.12. Found: C, 64.93; H, 6.26; C_2H_5O, 27.01.

Preparation of ethyl 4-(4′-methoxyphenylamino)-3,5-dinitrobenzoate (XIII). A mixture of 50 g. (0.182 mole) of ethyl 4-chloro-3,5-dinitrobenzoate, (m.p. 98–100.5°) prepared as was the methyl ester,[2a] 23.4 g. (0.19 mole) of *p*-anisidine and 27.6 g. (0.20 mole) of potassium carbonate in 50 ml. of water were heated in an oil bath at 150° for 1 hr., although it seemed that the reaction was complete after a few minutes. Water was added to the cooled reaction mixture and the solid collected by filtration. It was recrystallized from 2 l. of boiling acetone as garnet colored crystals, m.p. 200.5–201°, in 88.5% yield (58.4 g.).

Anal. Calcd. for $C_{16}H_{15}N_3O_7$: C, 53.19; H, 4.18; N, 11.63. Found: C, 53.35; H, 4.28; N, 11.57.

Preparation of 1-p-anisyl-5-carbethoxy-7-iodo-1,2,3-benzotriazole (XIV). The ester XIII above (58.4 g., 0.162 mole) was reduced as were its oxygen analogs previously described. The acetic acid solution (600 ml.) was likewise bisdiazotized as outlined for the oxygen analogs of the diamine and similarly added to an iodine–potassium iodide mixture in water. After sulfur dioxide reduction of the excess iodine, a black, tarry oil remained as the product. It was extracted with ether, the ether extract was treated with decolorizing carbon, washed with sodium bisulfite solution and evaporated. The residue was dissolved in boiling alcohol and chilled to give a black solid. After four recrystallizations from acetone-water the slightly pink product melted at 149.5–150.5°. The yield was 21.5 g. (0.051 mole, 31.2%). The analysis and ultraviolet spectrum indicated that this was not a diiodo derivative but a monoiodobenztriazole; λ_{max} 237, log ϵ 4.57.

Anal. Calcd. for $C_{16}H_{14}IN_3O_3$: C, 45.41; H, 3.33; N, 9.93. Found: C, 45.49; H, 3.33; N, 9.52.

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