Thyromimetics. VII. Isopropyl Analogs of Thyroid Hormones

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Received December 19, 1966

Attempts were made to prepare thyroidal hormones with isopropyl groups in place of the iodine atoms. 3,3′-Diisopropyl- and 3,3′,5′-triisopropyl-DL-thyronines (I and III) were prepared successfully. The more desirable isopropyl analogs of 3,3′,5-triiodothyronine (L-T_3) and thyroxine (II and IV) were not obtained. A number of possible routes to II and IV were studied and are described. III was tested and found inactive as a hypocholesteremic or antigoitrogenic agent and as an inhibitor of L-T_3.

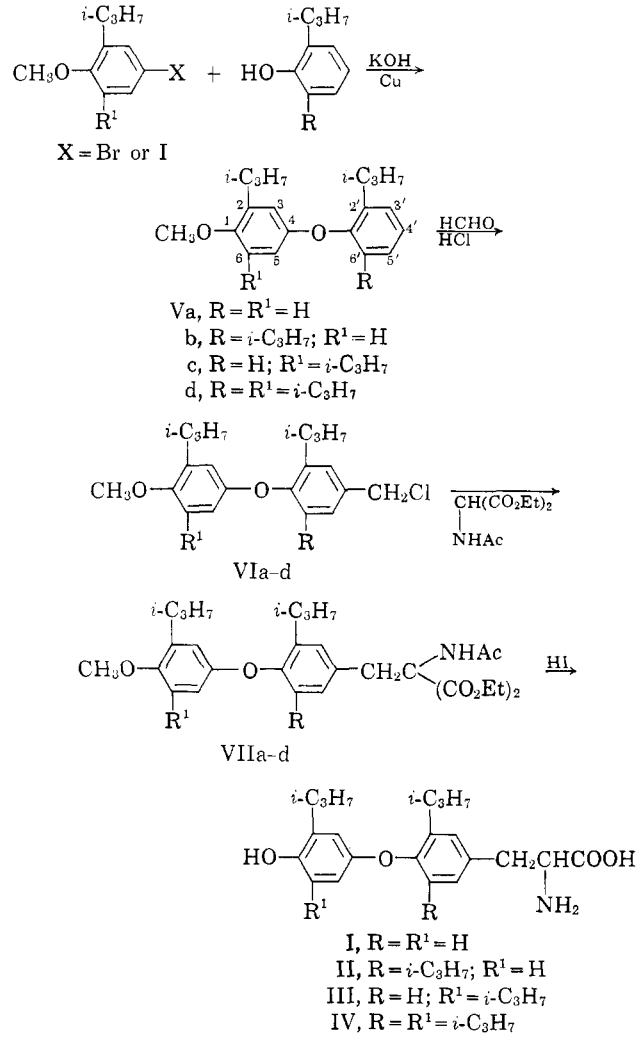
In recent years it has been shown that the biological activity of the thyroid hormones can be retained after replacement of the iodine atoms with alkyl groups.[1-6] Of particular interest has been the replacement of the 3′-iodine of 3,3′,5-triiodo-L-thyronine (L-T_3) and its thyroalkanoic acid analogs with an isopropyl group. This modification has produced compounds which are as active or more active biologically than L-T_3.[5,6]

3,5-Diiodo-3′,5′-diisopropyl-DL-thyronine, however, is essentially inactive in calorigenic assays[5d] and as a hypocholesteremic agent.[5a,d] Thus it was desirable to assess the extent to which the isopropyl group could replace the iodine atoms in the thyroid hormones. Therefore, attempts were made to prepare 3,3′-diisopropyl-DL-thyronine (I), 3,3′,5-triisopropyl-DL-thyronine (II), 3,3′,5′-triisopropyl-DL-thyronine (III), and 3,3′,5,5′-tetraisopropyl-DL-thyronine (IV).

The synthesis of I and III was accomplished following the synthetic approach developed by Bielig and Lützel[7] for the preparation of 3,3′,5,5′-tetramethyl-DL-thyronine (see Scheme I). Using these conditions only unreacted phenol and halo compound were recovered in the attempted preparation of Vb and d. This was true whether the halogen was bromine or iodine or whether the phenolic salt was prepared first or *in situ*.

In the syntheses described above it was possible for chloromethylation to yield products isomeric with VI. This is supported by the findings of Hamilton and Blanchard[8] who have reported recently that electrophilic substitution of 4-(2,6-xylyloxy)-2,6-dimethylanisole yields products substituted in the 3 position rather than in the 4′ position. This is contrary to the reports of Bielig and Lützel[7] and Van Heyningen.[9] Therefore, the infrared and nmr spectra of I and VIIc were examined to determine the site of chloromethylation in Va and c. The spectra of I are such that the position of the side chain cannot be fixed. The infrared spectrum of VIIc in Nujol shows two major bands in the 11–14-μ region. One peak is at 11.4 μ and corresponds to one free hydrogen on a benzene ring. The second, slightly more intense peak, is at 11.95 μ and corresponds to two adjacent hydrogen atoms on a benzene ring.[10] If the isomer with the side chain in the 3 position of Vc were produced, no peak should appear in the 11.6–12.5-μ region of the spectrum. The nmr spectrum of VIIc displays a fairly complex pattern for the aromatic protons (δ 6.55–7.00). The area integrates for five protons and has a sharp singlet at

SCHEME I



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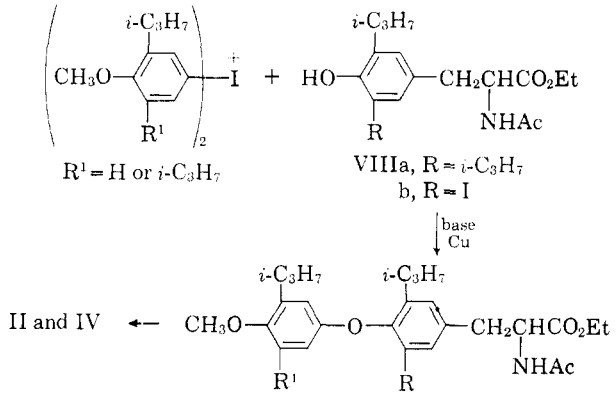
δ 6.62 which integrates for two protons. This peak can be attributed to the two equivalent protons *ortho* to the diphenyl ether bond in VIIc. Although these studies exclude chloromethylation at the 3 position of Vc, they do not eliminate the possibility of chloromethylation at the 5′ position. However, this seems unlikely on the basis of what is known about chloromethylation of substituted benzenes.[11] Thus, it is felt that the structures of VIc, VIIc, and III are correct as shown.

Since the route leading to I and III was not applicable to the preparation of II and IV, emphasis was shifted to a route using iodonium salts (Scheme II). This

SCHEME II



approach has been employed with some success by Jorgensen and Wiley[4] and by Dibbo and co-workers[12] to prepare methyl analogs of thyronine. N-Acetyl-3,5-diisopropyl-DL-tyrosine ethyl ester (VIIIa) was prepared using procedures developed by the preceding workers[4,12] and was allowed to react with iodonium salts of 3-isopropyl- and 3,5-diisopropylanisole[5a] under a variety of conditions. In no instance was a diphenyl ether detected. Only unreacted VIIIa, the iodonium salts, or their decomposition products were isolated. These results forced us to consider routes to II and IV in which the 3- and 5-isopropyl groups were produced subsequent to diphenyl ether formation.

The most suitable precursors seemed to be compounds with carboxyl groups or with substituents which could be converted easily to carboxyl groups. Therefore, the synthesis of several model compounds was studied. The first of these was *p*-(2,6-dicyano-4-nitrophenoxy)anisole (IX). Cyanation of *p*-(2,6-diiodo-4-nitrophenoxy)anisole in pyridine gave 21% of IX. Hydrolysis of IX in acid led to a mixture which infrared data showed to contain moieties with cyano, carboxylic acid, and amide groups. We next examined *p*-(2,6-diiodophenoxy)anisole (X) as a substrate in place of IX in an effort to improve the yield of cyano compound and also because subsequent Grignard reactions would be complicated by the presence of the nitro group of IX. X was obtained from IX by reduction, diazotization, and decomposition of the diazonium salt with ethanol or hypophosphorous acid or by total synthesis from 2,6-dinitrophenol. When heated with cuprous cyanide in pyridine, X produced only tars. Metalation and carbonation of X yielded an acidic product in very poor yield which was isolated as a lead salt. The lead salt did not analyze as the desired 2-(*p*-methoxyphenoxy)isophthalic acid (XI). A competitive reaction during metalation was diphenyl ether cleavage evidenced by the isolation of *p*-methoxyphenol.

Another possible intermediate in the preparation of XI was *p*-(2,6-xylyloxy)anisole (XII). Although described by Barnes, *et al.*,[13] and Bruice and co-workers,[14] XII could be prepared by us only in poor yield. Oxidation of XII with permanganate was tried in aqueous acetone at 60 and at 100° in a large volume of water. At the lower temperature XII was recovered unchanged and at 100° only a small amount of acidic product was isolated.

The direct synthesis of XI was attempted using the pyridinium tosylate of dimethyl 2-hydroxyisophthalate and *p*-methoxyphenol. This reaction yielded only unchanged starting materials and the tosylate of the 2-hydroxyisophthalate. Similar results were obtained when 3-isopropyl-4-methoxyphenol (XIII) was used for *p*-methoxyphenol. The coupling was tried under a variety of conditions with the following solvents: pyridine, quinoline, dimethyl sulfoxide, and toluene. In pyridine starting materials were recovered; in the other solvents extensive decomposition occurred. One useful outcome of this attempted synthesis was the development of an improved synthesis of XIII. XIII can be prepared expeditiously by hydrolyzing the product from the Baeyer–Villiger oxidation of 3-isopropyl-4-methoxyacetophenone. Jorgensen and Wiley had used this sequence earlier for the preparation of 4-methoxy-3-methylphenol.[15]

Since the reaction of iodonium salts with phenols to form thyroxinelike compounds is reported to proceed best when the phenolic component has two *o*-halogens and an alanine side chain,[12] N-acetyl-3-iodo-5-isopropyl-DL-tyrosine ethyl ester (VIIIb) seemed to be a compromise intermediate which could eventually lead to 3-iodo deriatives of I and III, compounds with interest comparable to II and IV. Unfortunately, we were unable to obtain the intermediate 3-isopropyl-DL-tyrosine using the procedure reported by Jorgensen and Wiley[16] for the preparation of 3-methyl-DL-tyrosine.

III was tested for hypocholesteremic activity in rats fed a diet containing 2% cholesterol and 1% cholic acid.[17] III was inactive at doses of 100, 200, 400, and 800 μg/kg. Since 3,3′,5′-triiodo-DL-thyronine is reported to inhibit the reversal of thiouracil-induced goiters by thyroxine,[18] III was given to thiouracil-treated rats alone and concomitantly with L-T_3. III at doses 100 times those of L-T_3 showed no antigoitrogenic activity and did not inhibit the antigoitrogenic action of L-T_3.

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Experimental Section[19]

2,6-Diisopropyl-4-(*o*-isopropylphenoxy)anisole (Vc).—A mixture of 45 g (0.17 mole) of 4-bromo-2,6-diisopropylanisole,[20] 19.9 g (0.15 mole) of *o*-isopropylphenol, 16.4 g (0.29 mole) of powdered KOH, and 400 mg of copper–bronze was heated in a metal bath. At a bath temperature of 180°, H_2O and a little of the bromo compound began to distil. The bromo compound was removed from the distillate and added again to the reaction flask. The metal bath was kept at 230–235° for 3.5 hr. The mass was left overnight and the residue was suspended in a mixture of $CHCl_3$ and H_2O and filtered. The aqueous phase of the filtrate was extracted with $CHCl_3$ and the combined $CHCl_3$ phases were washed with H_2O until neutral. The dried ($MgSO_4$) $CHCl_3$ was distilled and the residue weighing *ca.* 45 g was distilled *in vacuo* to give 24.6 g (53%) of an oil, bp 200–235° (14 mm). A fraction which distilled constantly at 210–211° (14 mm) was removed for analysis.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.10; H, 9.14.

Ethyl Acetamido[4-(3,5-diisopropyl-4-methoxyphenoxy)-3-isopropylbenzyl]malonate (VIIc).—Dry HCl was passed through a stirred suspension of 25.2 g (0.077 mole) of Vc, 3.2 g of paraformaldehyde, 80 ml of acetic acid, and 10 ml of concentrated HCl at 20°. When the initial exothermic reaction had subsided the cooling bath was removed and HCl was bubbled through the mixture for 7 hr at room temperature. After standing overnight the mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ was washed with water, 5% $NaHCO_3$, and again with H_2O. Evaporation of the $CHCl_3$ left 28 g of crude product. This was flash-distilled at 215–235° (16 mm) to give 12.2 g of impure product VIc.

To a solution of 0.033 mole of sodium ethoxide in 75 ml of absolute ethanol was added 7.2 g (0.033 mole) of ethyl acetamidomalonate and the solution was stirred and heated for a few minutes. A solution of 12.2 g (0.033 mole) of VIc in 75 ml of absolute ethanol was added in one portion, and stirring and refluxing were continued for 3 hr. About half of the ethanol was distilled and the residue was diluted with ice water. The solution was extracted with ether. The ethereal layers were washed with H_2O, dried (Na_2SO_4), and evaporated. The residual syrup was crystallized from petroleum ether (bp 90–100°) to give 4.5 g of crude product, mp 115–120°. Recrystallization from the same solvent gave 4 g (22%) of product, mp 133–134°.

Anal. Calcd for $C_{32}H_{45}NO_7$: C, 69.16; H, 8.16; N, 2.52. Found: C, 69.34; H, 8.11; N, 2.61.

3,3′,5′-Triisopropyl-DL-thyronine (3-[4-(4-Hydroxy-3,5-diisopropylphenoxy)-3-isopropylphenyl]-DL-alanine, III).—A mixture of 3.2 g (5.75 mmoles) of VIIc, 60 ml of 48% HBr, and 90 ml of acetic acid was refluxed for 5 hr. The solvents were removed *in vacuo* and the residue was adjusted to pH 6 with 5% $NaHCO_3$ and acetic acid. The aqueous solution was extracted with ether. The ethereal phases were washed with 10% $NaHSO_3$, H_2O, 5% $NaHCO_3$, and H_2O. The product precipitated during the final water wash. Petroleum ether was added to the ether and the resulting solid was filtered; yield 1 g, mp 210–215°. After two isoelectric precipitations at pH 6 the product (one spot on paper chromatograms) weighed 850 mg (37%), mp 225–226° dec.

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.42; H, 8.34; N, 3.54.

4-(3-Isopropyl-4-methoxyphenoxy)-3-isopropylbenzyl Chloride (VIa).—*o*-Isopropylphenol was brominated in acetic acid to give 92% of 4-bromo-2-isopropylphenol, mp 46–49° (lit.[21] mp 47–49°). Methylation with dimethyl sulfate and aqueous NaOH gave 80% of 4-bromo-2-isopropylanisole, bp 115–125° (11 mm) [lit.[22] bp 86–87° (2 mm)]. A mixture of 61.8 g (0.28 mole) of 4-bromo-2-isopropylanisole, 34 g (0.25 mole) of *o*-isopropylphenol, 38 g (0.5 mole) of powdered KOH, and 250 mg of copper–bronze was subjected to the conditions described for the preparation of Vc. The product Va was distilled to yield 50.3 g (71%) of material, bp 190–200° (10 mm).

Chloromethylation of 48.5 g (0.17 mole) of Va was effected using 7 g of paraformaldehyde in 22 ml of concentrated HCl and 170 ml of acetic acid using the conditions described for VIc. Distillation gave 48.5 g (86%) of an oil, bp 200–245° (10 mm). A fraction, bp 228–229° (10 mm), was submitted for analysis.

Anal. Calcd for $C_{20}H_{25}ClO_2$: C, 72.16; H, 7.57; Cl, 10.65. Found: C, 72.03; H, 7.51; Cl, 10.95.

3,3′-Diisopropyl-DL-thyronine (3-[4-(4-Hydroxy-3-isopropylphenoxy)-3-isopropylphenyl]-DL-alanine, I).—A hot solution of 48 g (0.14 mole) of VIa in 250 ml of absolute ethanol was added in one portion to a stirred solution of sodium ethoxide (prepared from 3.3 g of Na), 31.4 g (0.14 mole) of ethyl acetamidomalonate, and 250 ml of absolute ethanol. The product was formed and isolated as was VIIc. The resulting syrup was triturated with petroleum ether (bp 90–110°) and left at −17° for several days. The mixture of gum and solid was stirred with petroleum ether (bp 30–60°) and the resulting solid was filtered and recrystallized from cyclohexane; yield 6 g, mp 121–123°.

A mixture of 6 g of VIIa, 60 ml of HI, and 90 ml of acetic acid was refluxed for 8 hr. The solution was diluted with 250 ml of H_2O and extracted repeatedly with ether. The organic phases were washed with 10% $NaHSO_3$, H_2O, and enough 5% $NaHCO_3$ to make the ethereal layer pH 6–7. The ether was dried (Na_2SO_4) and distilled. The residual yellow solid was recrystallized from ether–petroleum ether (bp 30–60°) to give 2.2 g of solid (one spot on paper chromatograms), mp 183–185° dec with softening at 155–160°.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61. Found: C, 70.57; H, 7.60.

3,5-Diisopropyl-4-methoxybenzyl Chloride.—To a stirred mixture of 130 g (0.68 mole) of 2,6-diisopropylanisole, 640 ml of acetic acid, 85 ml of concentrated HCl, 25.6 g of 95% paraformaldehyde, and 13.7 g of fused $ZnCl_2$ was added HCl gas. The gray suspension became a clear pink solution. The HCl addition was continued for 4 hr at room temperature, the solution was left overnight, and HCl was added again for 4.5 hr the following morning. The biphasic mixture was poured into 3 l. of ice water and a solid precipitated. The solid was filtered and recrystallized from methanol; yield 45.2 g (28%), mp 91–93°. A further recrystallization from acetonitrile gave the analytical sample, mp 93–95°.

Extraction of the aqueous filtrate and the diluted recrystallization filtrates with ether gave unreacted 2,6-diisopropylanisole.

Anal. Calcd for $C_{14}H_{21}ClO$: C, 69.84; H, 8.79; Cl, 14.73. Found: C, 69.78; H, 8.53; Cl, 14.82.

Ethyl Acetamido(3,5-diisopropyl-4-methoxybenzyl)malonate.—Equimolar amounts of 2,6-diisopropyl-4-methoxybenzyl chloride, sodium ethoxide, and ethyl acetamidomalonate in absolute ethanol were refluxed for 3 hr. The reaction mixture was diluted with water and the resulting solid was filtered, washed with water, and recrytallized from aqueous ethanol; yield 80%, mp 124–125°.

Anal. Calcd for $C_{23}H_{35}NO_6$: C, 65.53; H, 8.37. Found: C, 65.59; H, 8.17.

If ethyl acetamidocyanoacetate was used in place of the malonate the corresponding product was obtained in 70% yield, mp 127–128° (THF–petroleum ether).

Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.06; N, 7.48. Found: C, 67.56; H, 8.05; N, 7.23.

If 2-propanol was used as a solvent in place of ethanol in the cyanoacetate reaction transesterification took place and the isopropyl ester was obtained, mp 169–170° (THF–petroleum ether).

Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.21; H, 8.10; N, 7.12.

3,5-Diisopropyl-DL-tyrosine.—A solution of 19 g (0.05 mole) of the isopropyl ester of N-acetyl-2-cyano-3-(3,5-diisopropyl-4-methoxylphenyl)-DL-alanine in 550 ml of 1:1 HI–AcOH was refluxed for 4 hr. The solution was evaporated to dryness *in vacuo* to give a hygroscopic solid. The solid was washed with ether and dissolved in water. The aqueous solution was adjusted to pH 8 with aqueous NH_3 and extracted once with ethyl acetate. The aqueous layer was concentrated, whereupon the product precipitated. The aqueous mixture was cooled and filtered; yield 10.8 g (80%), mp 238–240° dec. The above operation was repeated to obtain an analytical sample, mp 234–236° dec.

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.63; H, 8.64; N, 5.24.

N-Acetyl-3,5-diisopropyl-DL-tyrosine.—A solution of 7.8 g (0.029 mole) of 3,5-diisopropyltyrosine in 150 ml of 2 *N* NaOH

(19) Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by members of the Analytical and Physical Chemistry Section, Smith Kline & French Laboratories.

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was stirred and cooled as 35 ml of acetic anhydride was added slowly over 1.5 hr so that the temperature was kept below 20°. The solution was left overnight at room temperature and then was kept at 45–50° for 45 min. The solution was cooled and acidified with concentrated HCl below 15°. The resulting gum was dissolved in ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and concentrated. The residue was diluted with petroleum ether and cooled to give a mixture of solid and gum. The solvent was decanted and the residue was triturated with a mixture of ethyl acetate and petroleum ether. The solid was filtered, washed with petroleum ether, and dried to give 8.6 g (96%) of crystals, mp 105–107° with bubbling. A sample was recrystallized from ethyl acetate–petroleum ether for analysis.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.27; H, 8.42; N, 4.86.

N-Acetyl-3,5-diisopropyl-DL-tyrosine Ethyl Ester (VIIIa).—A solution of 9 g (0.03 mole) of N-acetyl-3,5-diisopropyl-DL-tyrosine, 0.3 g of *p*-toluenesulfonic acid monohydrate, 30 ml of absolute ethanol, and 300 ml of $CHCl_3$ was stirred under reflux overnight so that the H_2O formed was removed by azeotropic distillation. The solution was cooled and extracted three times with 5% Na_2CO_3 and then with H_2O until neutral. The $CHCl_3$ was dried ($MgSO_4$) and evaporated. The residual yellow oil was crystallized and recrystallized from aqueous ethanol to give a quantitative yield of ester, mp 105° to a cloudy melt which cleared at 110°.

Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.98; H, 8.67; N, 4.02.

***p*-(2,6-Dicyano-4-nitrophenoxy)anisole (IX).**—To a solution of 30.1 g (0.06 mole) of 3,5-diiodo-4-(*p*-methoxyphenoxy)-1-nitrobenzene[23] in 120 ml of pyridine was added 18.5 g of cuprous cyanide. Vigorous stirring was required to keep the viscous mass mobile. The mixture was stirred under reflux for 6 hr with solution being effected after *ca.* 30 min. The dark solution was poured into 1000 ml of ice water. A brown syrup separated which solidified when scratched. The solid was filtered and washed with H_2O. The solid was suspended in 400 ml of $CHCl_3$ and 500 ml of concentrated NH_4OH and was stirred vigorously. The mixture was filtered through a mat of Supercel to remove a brown sludge and the layers were separated. The organic layer was washed with NH_4OH, H_2O, dilute HCl, and again with H_2O. The $CHCl_3$ was dried ($MgSO_4$) and evaporated. The residue was crystallized and recrystallized from absolute ethanol; yield 3.7 g (21%) of yellow needles, mp 129–131°.

Anal. Calcd for $C_{15}H_9N_3O_4$: C, 61.02; H, 3.07; N, 14.23. Found: C, 60.89; H, 2.81; N, 14.54.

***p*-(2,6-Diiodophenoxy)anisole (X). A.**—To a suspension of 10.1 g (0.02 mole) of finely pulverized 3,5-diiodo-4-(*p*-methoxyphenoxy)aniline hydrochloride[25] in 100 ml of 90% acetic acid cooled to 5° was added 7 ml of isoamyl nitrite. The resulting reddish solution of diazonium compound was stirred an additional 30 min at 5° and was then added at a moderate rate to a mixture of 25 ml of ethanol and 1 g of $CuSO_4$ at 60–70°. When the addition had been completed, stirring at 65–70° was continued for 30 min. The ethanol was removed *in vacuo* and the residual oil was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ was washed with water, 5% $NaHCO_3$, and again with water. After drying (Na_2SO_4), the $CHCl_3$ was distilled and the residue was triturated with cyclohexane. The solid was filtered and recrystallized from aqueous ethanol; yield 1.4 g (16%) of white solid, mp 118–120°.

Anal. Calcd for $C_{13}H_{10}I_2O_2$: C, 34.54; H, 2.23; I, 56.15. Found: C, 34.51; H, 2.39; I, 55.99.

B.—A suspension of 5 g (0.01 mole) of 3,5-diiodo-4-(*p*-methoxyphenoxy)aniline hydrochloride in 25 ml of acetic acid and 10 ml of H_2SO_4 was cooled to 5° and to it was added a solution of 1.3 g of $NaNO_2$ in 10 ml of water. The suspension was stirred rapidly for 2 hr at 5° and 3.5 ml of 50% hypophosphorous acid was added gradually at 5°. Stirring was continued for 1 hr and the mixture was cooled overnight in a refrigerator. The mixture was then stirred 3 hr at room temperature. A viscous mass separated which was dissolved in ether. The ether was washed with H_2O, 5% $NaHCO_3$, and H_2O and dried (Na_2SO_4). The ether was removed and the residue was extracted with 250 ml of boiling absolute ethanol. The extract was treated with charcoal and concentrated to 50 ml. A little water was added and the concentrate was cooled to give 1.5 g (33%) of cream-colored solid, mp 105°.

C.—Equimolar amounts of 2,6-dinitrophenol[24] and *p*-methoxyphenol were allowed to react using conditions described previously.[23] The *p*-(2,6-dinitrophenoxy)anisole was isolated[25a] and recrystallized from ethanol; yield 70%, mp 93–94°.

Anal. Calcd for $C_{13}H_{10}N_2O_6$: C, 53.80; H, 3.47; N, 9.65. Found: C, 53.51; H, 3.39; N, 9.73.

Catalytic reduction, tetrazotization, and iodination were carried out using well-known procedures.[25a] The crude X was crystallized and recrystallized from aqueous ethanol to give 50% of product, mp 115–117°.

Attempted Preparation of Dimethyl 2-(*p*-Methoxyphenoxy)-isophthalate.—A solution of 10.5 g (0.05 mole) of dimethyl 2-hydroxyisophthalate[25] and 9.5 g (0.05 mole) of *p*-toluenesulfonyl chloride in 125 ml of pyridine was stirred on a steam bath for 10 min. *p*-Methoxyphenol (25.8 g, 0.2 mole) was added and stirring under reflux was continued for 1 hr. The excess pyridine was removed and the residue was dissolved in benzene. The benzene was washed three times with dilute HCl and twice with water. The benzene was diluted with $CHCl_3$ and the organic mixture was washed three times with 10% NaOH and with water until neutral. The dried ($MgSO_4$) organic phase was distilled to leave 9.5 g of almost colorless liquid. This was distilled *in vacuo* to give a distillate which boiled at 199–213° (1 mm). The distillate was dissolved in ether. Petroleum ether was added to precipitate crystals melting at 95–96°. These proved to be the tosylate of dimethyl 2-hydroxyisophthalate.

Anal. Calcd for $C_{15}H_{16}O_7S$: C, 56.03; H, 4.43. Found: C, 56.09; H, 4.48.

3-Isopropyl-4-methoxyacetophenone.—Using the method of Stadnikoff and Baryschewa[26] 150 g (1 mole) of *o*-isopropylanisole was converted to the acetophenone. The crude product distilled at 170–178° (37 mm) to give 129 g of material which was shown by vapor phase chromatography to be 96% pure. A sample was converted to its 2,4-dinitrophenylhydrazone, mp 180–182° (ethyl acetate).

Anal. Calcd for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.05. Found: C, 57.86; H, 5.47; N, 14.97.

3-Isopropyl-4-methoxyphenol (XIII).[25a]—Using the method of Jorgensen and Wiley[15], XIII was obtained as a solid, mp 42–44° (ligroin).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.29; H, 8.41.

3-Isopropyl-4-methoxybenzyl Chloride.—A solution of 120.8 g (0.81 mole) of *o*-isopropylanisole in 1 l. of acetic acid and 125 ml of concentrated HCl was cooled to 10°; 33.6 g (1.05 moles) of 95% paraformaldehyde was added and the mixture was stirred as HCl was passed through the mixture. The product was isolated as described for the 3,5-diisopropyl analog. Distillation of the crude product caused a large evolution of gas. About half of the crude product polymerized to a hard, brown, resinous solid. A fraction distilled at 131–133° (8 mm) and weighed 30.8 g (19%).

Anal. Calcd for $C_{11}H_{15}ClO$: C, 66.49; H, 7.61; Cl, 17.84. Found: C, 65.92; H, 7.52; Cl, 18.05.

N-Acetyl-2-cyano-3-(3-isopropyl-4-methoxyphenyl)-DL-alanine Ethyl Ester (XIV).—A pinch of NaI was added to a solution of sodium ethoxide [from 3.5 g (0.15 g-atom) of Na and 250 ml of absolute ethanol]. To this stirred, refluxing solution was added 26.7 g (0.15 mole) of ethyl acetamidocyanoacetate. Refluxing was continued for 20 min and a warm solution of 30 g (0.15 mole) of 3-isopropyl-4-methoxybenzyl chloride in 250 ml of absolute ethanol was added in one portion. Heating was continued for 3 hr and the reaction mixture was added to 2.5 l. of H_2O and ice. Cooling and scratching induced solidification. The gummy solid was filtered and recrystallized from benzene–petroleum ether; yield 21.6 g (43%), mp 117–119°. The analytical sample melted at 121–122°.

Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.07; H, 7.54; N, 8.40.

Acknowledgment.—We wish to thank Mr. Sterling Cooper for the preparation of XIII and Dr. C. M. Greenberg for the biological screening results.

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