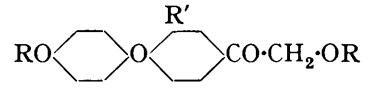
57. *Experiments on the Synthesis of Potential Cortical Hormone Substitutes. Hydroxy-carbonyl Derivatives of Diphenyl Ether and Related Compounds.*

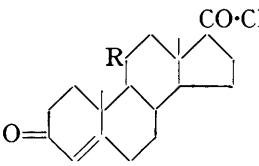
By JAMES WALKER.

Proceeding from the observation that 4 : 4′-dihydroxydiphenyl ether appeared to cause an increase in the liver glycogen of the fasting rat, a number of derivatives of diphenyl ether have been synthesised for examination for cortical hormone activity; these included *ω-hydroxy-4-(4′-hydroxyphenoxy)acetophenone* and its *diacetate*, *ω* : *3-diacetoxy-4-(4′-acetoxyphenoxy)acetophenone*, *4-(4′-hydroxyphenoxy)-acetophenone* and *3-hydroxy-4-(4′-hydroxyphenoxy)acetophenone*. The second, fourth, and fifth of these substances gave no response when tested for progesterone activity. Tests for cortical hormone activity are not yet complete.

THE extension in our knowledge of the adrenal cortex in recent years through the isolation therefrom of numerous closely related steroid hormones has stimulated interest in the therapeutic applications of these substances. Their very restricted availability, however, urgently prompts one to inquire into the possibility of elaborating substances in the laboratory, which would bear the same relationship to the cortical hormones as that of stilbœstrol and hexœstrol to the female sex hormones. The functions of the cortical hormones, however, are manifold and not coterminous, so that, while certain members of the group are predominantly of importance in carbohydrate metabolism, others are concerned in the maintenance of salt-water equilibria (compare, for example, Thorn, Engel, and Lewis, *Science*, 1941, **94**, 349). Consequently, the examination of any substance for cortical hormone activity is, of necessity, relatively complex, and the criteria which any synthetic compound must fulfil are more exacting in comparison with synthetic œstrogens, where biological differences, among compounds showing activity at all, are essentially in degree rather than in kind.

A possible clue to the type of compound which might be active was provided in this Institute by the observation that 4 : 4′-dihydroxydiphenyl ether, administered subcutaneously in nut oil, appeared to cause an increase in the liver glycogen of the fasting rat (Marks and Young, unpublished). This effect was observed in two experiments and with two specimens of dihydroxydiphenyl ether of different origins, although later experiments have failed to elicit the phenomenon, and the activity of this compound must therefore be regarded as still *sub judice*. The view was taken, however, that the diphenyl ether nucleus should be adopted as a basal unit to carry hydroxyl groups and the α-ketol side chain, characteristic of certain of the cortical hormones, as functional groups. With that object in mind, the syntheses of ω-hydroxy-4-(4′-hydroxyphenoxy)acetophenone (I; R = R′ = H) and ω : 3-dihydroxy-4-(4′-hydroxyphenoxy)acetophenone (I; R = H, R′ = OH) were undertaken as possible analogues of deoxycorticosterone (II; R = H) and corticosterone (II; R = OH) respectively.

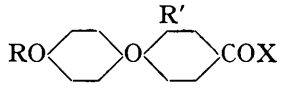
(I.) 

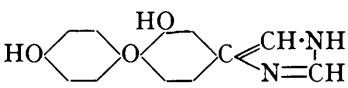


(II.)

The Ullmann condensation between *p*-bromoanisole and ethyl *p*-hydroxybenzoate in the presence of copper bronze and anhydrous potassium carbonate afforded a good yield of 4-(4′-methoxyphenoxy)-benzoic acid (III; R = Me, R′ = H, X = OH) (cf. Harington, *Biochem. J.*, 1926, **20**, 300; Harington

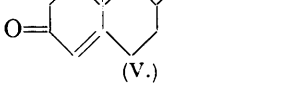
and Pitt-Rivers, J., 1940, 1101). Demethylation with hydrobromic acid in aqueous acetic acid proceeded smoothly to yield 4-(4′-*hydroxyphenoxy*)*benzoic acid* (III; R = R′ = H, X = OH), and the *ethyl* ester (III; R = R′ = H, X = OEt) was prepared by the Fischer–Speier process. Protection of the hydroxyl group in the hydroxy-acid was smoothly accomplished by using Chattaway's technique (J., 1931, 2495) and subsequent treatment of the *acetoxy-acid* (III; R = Ac, R′ = H, X = OH) with thionyl chloride and then with diazomethane afforded ω-*diazo*-4-(4′-*acetoxyphenoxy*)*acetophenone* (III; R = Ac, R′ = H, X = CHN_2). Treatment with glacial acetic acid then yielded ω-*acetoxy*-4-(4′-*acetoxyphenoxy*)*acetophenone* (I; R = Ac, R′ = H), from which, on hydrolysis, ω-*hydroxy*-4-(4′-*hydroxyphenoxy*)-*acetophenone* (I; R = R′ = H) was obtained.

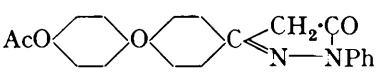
(III.) 

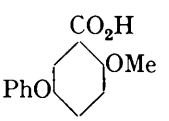
 (IV.)

The conditions used for the Ullmann condensation described above afforded a poor result when applied to the condensation between ethyl vanillate and *p*-bromoanisole. The poor yield, however, was augmented almost to theoretical by using the dry sodium derivative of the ester and applying, as catalyst, a mixture of copper bronze and anhydrous copper acetate. The subsequent methods outlined above being used, the resulting 3-*methoxy*-4-(4′-*methoxyphenoxy*)*benzoic acid* (III; R = Me, R′ = OMe, X = OH) was converted successively into 3-*hydroxy*-4-(4′-*hydroxyphenoxy*)*benzoic acid* (III; R = H, R′ = X = OH) and its *ethyl* ester (III; R = H, R′ = OH, X = OEt), 3-*acetoxy*-4-(4′-*acetoxyphenoxy*)*benzoic acid* (III; R = Ac, R′ = OAc, X = OH), ω-diazo-3-acetoxy-4-(4′-acetoxyphenoxy)acetophenone (III; R = Ac, R′ = OAc, X = CHN_2) and ω : 3-*diacetoxy*-4-(4′-*acetoxyphenoxy*)*acetophenone* (I; R = Ac, R′ = OAc). The last two stages failed to provide crystalline products, but the last-named compound was characterised by its reactions and by the *picrate* of 2 : 4′-*dihydroxy*-4-4″-*iminazolyldiphenyl ether* (IV) obtained by the action of formaldehyde and cuprammonium acetate (cf. Weidenhagen and Herrmann, *Ber.*, 1935, **68**, 1953). The keto-triol, obtained on acid hydrolysis of the triacetate, could not be obtained crystalline.

Of other known steroids, progesterone (V) bears the closest affinity to the cortical hormones and the corresponding compounds in the two series under discussion were therefore synthesised, namely, 4-(4′-hydroxyphenoxy)acetophenone (III; R = R′ = H, X = CH_3) and 3-hydroxy-4-(4′-hydroxyphenoxy)-acetophenone (III; R = H, R′ = OH, X = CH_3). 4-(4′-Acetoxyphenoxy)benzoyl chloride was condensed with ethyl sodioacetoacetate and the resulting diketo-ester was hydrolysed in two stages, first with aqueous ammonia and then with mineral acid, to give 4-(4′-*hydroxyphenoxy*)*acetophenone*

 (V.)

 (VI.)

 (VII.)

(III; R = R′ = H, X = CH_3) in good yield. The intermediate β-keto-ester was characterised as the *phenylpyrazolone* (VI). 3-*Hydroxy*-4-(4′-*hydroxyphenoxy*)*acetophenone* (III; R = H, R′ = OH, X = CH_3) was synthesised analogously by condensation of 3-acetoxy-4-(4′-acetoxyphenoxy)benzoyl chloride with ethyl sodioacetoacetate and hydrolysis of the primary product in two stages.

It was anticipated that ketones of the type (III; R = Me, R′ = H, X = alkyl) would be accessible from 4-methoxydiphenyl ether and acyl halides by the Friedel–Crafts reaction. According to von Schickh (U.S.P. 1,717,424; B.P. 286,688) and Tomita (*J. Pharm. Soc. Japan*, 1937, **57**, 689) facile diacylation of 4-methoxydiphenyl ether in the 3- and 4′-positions occurs in the Friedel–Crafts reaction with chloroacetyl chloride, accompanied by demethylation, while, with carbonyl chloride and with benzoyl chloride, 4′-monosubstitution appears to occur (Dilthey and Harenberg, *J. pr. Chem.*, 1933, **136**, 67). It is noteworthy that in the Gattermann aldehyde synthesis substitution takes place (poor yield) in the 4′-position (Harington, *loc. cit.*), and mononitration occurs at the 3-position (Lea and Robinson, J., 1926, 411). No difficulty was experienced in introducing only one acetyl group into 4-methoxydiphenyl ether, and the homogeneous product, obtained in excellent yield, was characterised as 4-(4′-*methoxyphenoxy*)*acetophenone* (III; R = X = Me, R′ = H) by oxidation with sodium hypochlorite to 4-(4′-methoxyphenoxy)benzoic acid. It was also identical with the product obtained on methylation of 4-(4′-hydroxyphenoxy)acetophenone, which has been described above. 5-*Phenoxy*-2-*methoxybenzoic acid* (VII) was synthesised, to be available if required, as a reference compound, by Ullmann condensation of ethyl 5-bromo-2-methoxybenzoate with sodium phenoxide.

Among the compounds prepared for testing purposes was ethyl 4-(4′-hydroxyphenoxy)benzoate (III; R = R′ = H, X = OEt) and it was decided to synthesise a higher homologue as well. Towards this end, 4-(4′-methoxyphenoxy)benzaldehyde (III; R = Me, R′ = X = H) was condensed with malonic acid in the presence of pyridine and piperidine. The resulting 4-(4′-methoxyphenoxy)cinnamic acid was esterified with diazomethane and the *methyl* ester was reduced catalytically to *methyl* β-4-(4′-*methoxyphenoxy*)*phenylpropionate*. The latter was saponified and demethylated in one operation with hydrobromic acid to β-4-(4′-*hydroxyphenoxy*)*phenylpropionic acid*, which was then converted into the *ethyl* ester. The methods available for the synthesis of 4-(4′-methoxyphenoxy)benzaldehyde leave much to be desired, as the early ones (Harington, *loc. cit.*; Stöhr, *Z. physiol. Chem.*, 1931, **201**, 142) afforded but poor yields and a more recent one (Harington and Pitt-Rivers, *loc. cit.*), though convenient, is lengthy. An attempt was therefore made to introduce the aldehyde group directly into 4-methoxydiphenyl ether by using formomethylanilide and phosphorus oxychloride, a modern method which may be recognised as a variation of the earlier one of Dimroth and Zoeppritz (*Ber.*, 1902, **35**, 984). Only traces of aldehyde were formed, affording a semicarbazone of the expected composition and melting point.

Through the kindness of Dr. A. S. Parkes, F.R.S., ω-acetoxy-4-(4′-acetoxyphenoxy)acetophenone, 4-(4′-hydroxyphenoxy)acetophenone and 3-hydroxy-4-(4′-hydroxyphenoxy)acetophenone were examined for progesterone activity; they produced no response. Preliminary tests with ten of the above compounds have failed to demonstrate effects on glycogen deposition in the livers of fasting rats, and tests based on potassium tolerance and survival times of adrenalectomised animals have not yet been standardised; these biological aspects are being studied by Mr. H. P. Marks and Dr. F. G. Young. Quite recently, Linnell and Roushdi (*Quart. J. Pharm. Pharmacol.*, 1941, **14**, 270; *Nature*, 1941, **148**, 595) have reported signs of cortical hormone activity in two synthetic α-ketols; one of these is the simple derivative, benzoylcarbinol, which is said to have about 1/2500th, and the other, 3′-hydroxyacetyl-4-hydroxy-αβ-diethylstilbene, is stated to have rather less than 1/200th of the activity of deoxycorticosterone in prolonging the lives of young adrenalectomised rats. The present communication is intended to intimate and record our independent approach to the same objective.

Experimental.

4-(4′-*Methoxyphenoxy*)*benzoic Acid* (III; R = Me, R′ = H, X = OH).—*p*-Bromoanisole (18·7 g.), ethyl *p*-hydroxybenzoate (16·6 g.), anhydrous potassium carbonate (14 g.), and copper bronze (0·9 g.) were refluxed at 200—215° (metal-bath) for 5 hours. After most of the unchanged *p*-bromoanisole had then been removed by steam-distillation, 50% aqueous potassium hydroxide (25 c.c.) was added to the mixture, which was steam-distilled for a further 15 minutes and then largely diluted with water to dissolve the potassium salt which had separated. The filtered solution was washed with ether and acidified to Congo-red with hydrochloric acid. The precipitated acid (17·1 g.), recrystallised from 60% aqueous acetic acid, afforded thin colourless plates of approximately rectangular outline, m. p. 176—177° (Found: C, 68·9; H, 4·9. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 4·9%). Harington (*loc. cit.*) records m. p. 177°. The potassium salt separated from dilute aqueous solution in minute crystals.

4-(4′-*Hydroxyphenoxy*)*benzoic Acid* (III; R = R′ = H, X = OH).—The foregoing methoxy-acid (56·5 g.) was refluxed for 6 hours with a mixture (800 c.c.) of equal parts of glacial acetic acid and constant-boiling hydrobromic acid. The solution was diluted with water (1000 c.c.) and cooled. The acid which crystallised was collected and dried (49·3 g.) and a further quantity (3·2 g.) was obtained by concentrating the mother-liquor to small bulk and adding water. The *compound* separated from 50% aqueous acetic acid in flat, elongated, colourless, hexagonal prisms, m. p. 192—193° (Found: C, 67·5; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%). Walter (*Festschrift Emil Barell*, Basel, 1936, p. 270), giving the formula of this compound in a table, records m. p. 190°, but no other details (mode of synthesis, etc.) appear to be on record.

The *ethyl* ester, prepared by refluxing the acid (15 g.) for 6 hours with ethyl alcohol (125 c.c.) containing 5% of dry hydrogen chloride, and isolated with the aid of ether and water (yield, 16·5 g.), separated from 65% aqueous alcohol in short stout prisms, m. p. 112—113° (Found: C, 69·9; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

4-(4′-*Acetoxyphenoxy*)*benzoic Acid* (III; R = Ac, R′ = H, X = OH).—The hydroxy-acid (23 g.; 1 mol.) was dissolved in N-sodium hydroxide (200 c.c.; 2 mols.), cooled internally with ice, and shaken with acetic anhydride (10 c.c.; 1 mol.) for 1—2 minutes. The solution was acidified, and the precipitated *acid* extracted with ether (yield, 27·2 g.) and recrystallised from benzene, affording fine, silky, colourless, thin, flat prisms, m. p. 149—150° (Found: C, 66·4; H, 4·5. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

ω-*Diazo*-4-(4′-*acetoxyphenoxy*)*acetophenone* (III; R = Ac, R′ = H, X = CHN_2).—The foregoing acetoxy-acid (26·7 g.) was refluxed in chloroform (150 c.c.) for 2½ hours with thionyl chloride (21 c.c.; *ca.* 3 mols.). Solvent and the excess of thionyl chloride were then distilled off and the last traces of the latter were entrained by distillation with two small volumes of benzene. The crude acid chloride in dry ether (120 c.c.) was added at room temperature to a dried (potassium hydroxide pellets) ethereal solution (*ca.* 500 c.c.) of diazomethane (from 60 g. of nitrosomethylurea) and the mixture was left overnight at room temperature. Filtration through a thin layer of kieselguhr to remove amorphous flocks and evaporation yielded a light orange solid (30·2 g.),

which was partly purified by recrystallisation from benzene–petrol; m. p. 111—114° (25·2 g.). The *compound* was readily soluble in warm benzene and separated on cooling in fine yellow prisms, m. p. 118—119·5° (Found : C, 64·7; H, 4·2; N, 9·7. $C_{16}H_{12}O_4N_2$ requires C, 64·8; H, 4·1; N, 9·5%).

ω-Acetoxy-4-(4′-acetoxyphenoxy)acetophenone (I; R = Ac, R′ = H).—The preceding diazo-ketone (2·05 g.; m. p. 115—117°) was warmed on the water-bath with glacial acetic acid (5 c.c.) for 1½ hours. The brown solution was mixed with ether and washed with water and sodium bicarbonate solution until free from acetic acid. The dried ethereal solution, on evaporation, yielded a light orange, crystalline solid (2·14 g.). The pure *compound* separated from methyl alcohol (norit) in colourless rectangular prisms (1·5 g.), m. p. 117·5—118° (Found : C, 65·6; H, 4·7. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9%). The substance, on very gentle warming, readily reduced Fehling's, Benedict's (qualitative) and ammoniacal silver nitrate solutions.

ω-Hydroxy-4-(4′-hydroxyphenoxy)acetophenone (I; R = R′ = H).—A solution of the diazo-ketone (1 g.) in dioxan (10 c.c.) was warmed with 2N-sulphuric acid (6 c.c.) at 50° for ½ hour and then diluted with water. The product (0·78 g.), isolated with the aid of ether, partly crystallised and was obviously a mixture. It was refluxed with ethyl alcohol (10 c.c.) and N-hydrochloric acid (10 c.c.) for 2½ hours and worked up with ether. The brown solid (0·65 g.) isolated was boiled with much water (norit), recovered in ether, and recrystallised from small volumes of methyl alcohol. The pure *keto-diol* formed clusters of thin colourless plates, m. p. 171—172·5° (Found : C, 68·7; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%). The substance readily reduced Fehling's and Benedict's (qualitative) solutions and, in the cold, ammoniacal silver solution. It was also prepared by hydrolysing the diacetate with aqueous alcoholic hydrochloric acid in the manner just described.

3-Methoxy-4-(4′-methoxyphenoxy)benzoic Acid (III; R = Me, R′ = OMe, X = OH).—Ethyl vanillate (9·8 g.; 1 mol.) was added to a solution of sodium ethoxide (from 1·2 g. of sodium; 1 atom) in absolute alcohol (40 c.c.), and the alcohol distilled away from the precipitated ethyl sodiovanillate, finally at 100°/16 mm. A mixture of the finely divided residue, copper bronze (1 g.), and anhydrous copper acetate (1 g.) (Davidson and Griswold, *J. Amer. Chem. Soc.*, 1931, **53**, 1341) was heated with *p*-bromoanisole (14 g.; 1·5 mols.) at *ca.* 240° (metal-bath) for 3 hours. The reaction mixture was cooled and distributed between water and ether. The separated ethereal solution was washed twice with cold 2N-sodium hydroxide and then with water, dried, and evaporated. The light brown oil obtained (19·5 g.) was refluxed with 6% methyl-alcoholic potassium hydroxide (100 c.c.) for 5 hours, and the reaction mixture worked up for acidic material, which was obtained as a solid (12·75 g.); this crystallised from 50% aqueous acetic acid in fine colourless prisms, m. p. 170—171° (Found : C, 65·6; H, 5·2. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%).

3-Hydroxy-4-(4′-hydroxyphenoxy)benzoic Acid (III; R = H, R′ = X = OH) *and Ethyl Ester.*—The preceding compound (9·23 g.) was refluxed for 10 hours with a mixture (240 c.c.) of equal parts of glacial acetic acid and constant-boiling hydrobromic acid, and the product (8·14 g.) isolated by concentration of the solution to small bulk under reduced pressure and dilution with water. The pure *compound* separated from 15% aqueous acetic acid (norit) in colourless hexagonal plates, m. p. 204—205° (Found : C, 63·4; H, 4·0. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%).

The *ethyl* ester, prepared by the Fischer–Speier process in nearly quantitative yield, separated from ethyl acetate–ligroin in minute colourless rhombs, m. p. 128—129° (Found : C, 65·6; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%).

3-Acetoxy-4-(4′-acetoxyphenoxy)benzoic Acid (III; R = Ac, R′ = OAc, X = OH).—When the above dihydroxy-acid (1 mol.) was treated with N-sodium hydroxide (3 mols.) and acetic anhydride (2 mols.), under the conditions outlined above in an analogous case, quantitative acetylation took place; the product was isolated with the aid of ether. The *substance* separated from benzene in colourless, microscopic, diamond-shaped plates, m. p. 173—174° (Found : C, 61·6; H, 4·4. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·2%).

ω : 3-Diacetoxy-4-(4′-acetoxyphenoxy)acetophenone (I; R = Ac, R′ = OAc).—The foregoing diacetoxy-acid (9·07 g.) was refluxed with freshly purified, colourless thionyl chloride (6·2 c.c.) in alcohol-free chloroform (50 c.c.) for 2½ hours. The solvent and the excess of thionyl chloride were distilled off and the last traces of the latter were entrained with benzene in the usual way. The crude acid chloride, a syrup, in dry ether (30 c. c.), was added slowly and with efficient agitation to a cold ethereal solution (*ca.* 270 c.c.) of diazomethane (from 20 g. of nitrosomethylurea), which had been dried over potassium hydroxide pellets and filtered. The solution was kept at room temperature for 18 hours, filtered from amorphous flocks, and evaporated under reduced pressure (bath not above 40°). The product did not crystallise and was therefore treated with glacial acetic acid (12 c.c.) on the water-bath for ¾ hour and at the b. p. for 10 minutes. The stiff, light brown gum (10·3 g.), which was isolated in the manner described above in an analogous case, was distilled in a vacuum in small batches (*ca.* 2 g.); a stiff, pale yellow gum was obtained, b. p. approx. 255°/1·6 mm., leaving a small charred residue (Found : C, 62·3; H, 4·9. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%). The distilled product readily reduced Fehling's and Benedict's (qualitative) solutions and, slowly in the cold and rapidly on gentle warming, ammoniacal silver solution.

The substance was characterised as the *picrate* of *2 : 4′-dihydroxy-4-4″-iminazolyldiphenyl ether* (IV) as follows : the gum (2·5 g.) in 60% aqueous alcohol (50 c.c.) was treated with copper acetate (1·4 g., anhydrous), 40% formalin solution (1·5 c.c.), and 25% aqueous ammonia (10 c.c.) on the water-bath (cf. Weidenhagen and Herrmann, *loc. cit.*). The copper derivative which separated (1·8 g.) was collected, dried, and freed from copper in boiling water with hydrogen sulphide. The filtered solution, after cooling, was separated from a brown amorphous precipitate, evaporated to small bulk, and treated with an excess of aqueous picric acid. The

picrate which separated gradually became crystalline; it was recrystallised several times from (approx.) 40% aqueous methyl alcohol, forming orange rhombs, which effervesced at 128—130°, resolidified in prisms, and melted finally at 183—184° (Found: loss at 140° in a high vacuum over phosphoric oxide, 5·0. Found for anhydrous material: C, 51·1; H, 3·4; N, 14·3. $C_{15}H_{12}O_3N_2,C_6H_3O_7N_3,1{\cdot}5H_2O$ requires H_2O, 5·2%. $C_{15}H_{12}O_3N_2,C_6H_3O_7N_3$ requires C, 50·7; H, 3·0; N, 14·1%).

4-(4'-Hydroxyphenoxy)acetophenone (III; R = R' = H, X = CH_3).—4-(4'-Hydroxyphenoxy)benzoic acid (23 g.; 1 mol.) was acetylated and treated with thionyl chloride as described above. The acid chloride, dissolved in benzene (50 c.c.), was added to ethyl sodioacetoacetate (2 mols., from 26 g. of ethyl acetoacetate and 4·6 g. of powdered sodium) in benzene (300 c.c.). The mixture was refluxed for 3½ hours and then left at room temperature for 48 hours. The precipitated yellow sodium derivative was collected and washed with ether (yield, 32·9 g.; theo., 36·4 g.).

The sodium derivative was dissolved in water (100 c.c.) and warmed on the water-bath with ammonium chloride (5·5 g.) and 12% aqueous ammonia (20 c.c.) for 20 minutes. The heavy oil that separated was recovered in ether and the extract, after being washed with water and dilute sulphuric acid, was evaporated, finally at 100°/22 mm., yielding a stiff, light yellow, clear syrup (22·9 g.). This product gave a port-wine colour in alcoholic solution with a drop of aqueous ferric chloride and was characterised as the *phenylpyrazolone* (VI). The syrup (0·26 g.) and freshly distilled phenylhydrazine (0·1 c.c.) were heated on the water-bath for 3 hours. The resulting light brown gum solidified on trituration with ether; after being washed with ether (yield, 0·2 g.), it separated from 60% aqueous acetic acid as a colourless micro-crystalline powder, m. p. 128·5—130° (Found: C, 71·9; H, 4·8; N, 7·2. $C_{23}H_{18}O_4N_2$ requires C, 71·5; H, 4·7; N, 7·2. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·6; N, 8·1%). The analysis showed that the acetyl group had not been lost.

The remainder of the keto-ester (22·5 g.) was refluxed with 10% sulphuric acid (100 c.c.) for 5½ hours. The product was extracted with ether, washed with sodium bicarbonate solution, dried, and recovered (yield, 16·3 g.; over-all yield, 73%). The *substance* separated from 60% aqueous methyl alcohol in colourless plates, m. p. 155—156° (Found: C, 73·4; H, 5·2. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%).

3-Hydroxy-4-(4'-hydroxyphenoxy)acetophenone (III; R = H, R' = OH, X = CH_3).—3-Acetoxy-4-(4'-acetoxyphenoxy)benzoic acid (11·5 g.) was converted into the acid chloride with thionyl chloride (10 c.c.) in the usual way. The crude chloride, freed from the excess of thionyl chloride, was added in benzene (50 c.c.) to ethyl sodioacetoacetate (from 9·2 c.c. of ethyl acetoacetate and 1·6 g. of powdered sodium) in benzene (100 c.c.). The solution became clear and it was refluxed for 4½ hours. No separation of the sodio-derivative of the product occurred in this case and the reaction mixture was worked up by treatment with excess of dilute sulphuric acid. Evaporation of the benzene solution, finally at 100°/18 mm., yielded a light brown, viscous syrup (20 g.).

Although the presence of ammonium chloride was not theoretically necessary for the first stage of the hydrolysis in this case, it was nevertheless added, since it has been established empirically that the use of ammonium chloride, together with ammonia, is beneficial in hydrolyses of this type (cf. Shriner and Schmidt, *J. Amer. Chem. Soc.*, 1929, **51**, 3636). The crude diketo-ester was shaken with water (50 c.c.), ammonium chloride (6 g.), and 12% aqueous ammonia (15 c.c.) at 45—50° for 10 minutes. The heavy oil which separated was recovered with the aid of ether and isolated as a reddish-brown syrup (15·9 g.), giving a typical blood-red colour in alcoholic solution with a drop of aqueous ferric chloride. The crude product was at once refluxed with 10% sulphuric acid (100 c.c.) for 6 hours. The product was distributed between water and ether, and the ethereal solution washed with sodium bicarbonate solution. The product was removed from the ether by three washings with 2N-sodium hydroxide, and recovered by acidification and extraction with ether. Evaporation of the ether afforded a dark brown gum (7·2 g.). Treatment in boiling 40% aqueous methyl alcohol with norit and recovery by means of ether extraction gave a light golden-yellow glass (5·9 g.). The *compound* separated from ethyl acetate–ligroin (1 : 2) as a colourless microcrystalline powder, m. p. 149—150·5° (Found: C, 68·6; H, 5·1. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%).

The 2 : 4-*dinitrophenylhydrazone* separated from alcohol in deep orange-red sheaves, m. p. 234° (Found: N, 13·4. $C_{20}H_{16}O_7N_4$ requires N, 13·2%).

Friedel–Crafts Reaction between 4-Methoxydiphenyl Ether and Acetyl Chloride. 4-(4'-*Methoxyphenoxy*)-*acetophenone* (III; R = X = CH_3, R' = H).—(A) 4-Methoxydiphenyl ether was prepared by treating dry sodium phenoxide with *p*-bromoanisole in the presence of copper bronze and copper acetate in the manner outlined above (yield, 70%; b. p. 166°/16 mm.). It (10 g.; 1 mol.) was treated in carbon disulphide (50 c.c.) containing acetyl chloride (3·7 c.c.; 1 mol.) with successive portions of finely powdered aluminium chloride (total, 13·3 g.; 2 mols.) at room temperature. The reaction was very vigorous and two liquid layers formed. After an hour at room temperature and 10 minutes at 40°, the carbon disulphide was decanted, and the deep red lower layer poured on ice. The product crystallised as a faintly pink solid. It was taken up in ether, washed twice with 2N-sodium hydroxide and once with dilute sulphuric acid, dried, and recovered as a viscous syrup (11·4 g., 94%), which rapidly crystallised on cooling, m. p. 49—53°. Distillation under diminished pressure (b. p. approx. 233°/16 mm.) raised the m. p. to 54—56°. The *compound* was finally obtained in sheaves of colourless plates, m. p. 60—61°, by recrystallisation from ligroin (Found: C, 74·3; H, 5·8; OMe, 12·8. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8; OMe, 12·8%).

The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in microscopic crimson prisms, m. p. 171° (Found: C, 59·6; H, 4·2; N, 13·4. $C_{21}H_{18}O_6N_4$ requires C, 59·7; H, 4·3; N, 13·3%).

(B) 4-(4′-Hydroxyphenoxy)acetophenone (0·5 g.) in 35% potassium hydroxide solution (40 c.c.) was treated with four portions of methyl sulphate (each of 2 c.c.), with shaking and cooling. The oil which separated crystallised at room temperature. The mixture was finally heated on the boiling water-bath for 5 minutes, cooled, and extracted with ether. The extract was washed with 2N-sodium hydroxide, dried, and evaporated, yielding a colourless viscous syrup (0·51 g.) which rapidly crystallised, m. p. 55—56°, raised to 59° by recrystallisation from ligroin. Sublimation at 16 mm. (bath, 190°) raised the m. p. to 60—61°, alone and in admixture with the product obtained in (A) (Found : C, 74·5; H, 5·8%).

Oxidation of Preceding Compound with Sodium Hypochlorite. 4-(4′-*Methoxyphenoxy*)*benzoic Acid.*—The foregoing ketone (1 g.), prepared as in (A), was refluxed with 2·5% sodium hypochlorite solution (85 c.c.) for 2 hours; the oil rapidly dissolved. The excess of oxidant was destroyed with sodium sulphite. On cooling, the characteristic, sparingly soluble sodium salt separated and was kept in solution by dilution with water. The solution was washed with a small volume of ether, and the free acid (0·91 g.; m. p. 175—177°) was recovered, *via* ether, in the normal way. Recrystallisation from 60% aqueous acetic acid afforded 4-(4′-methoxyphenoxy)-benzoic acid in its characteristic crystalline habit, m. p. 177°, alone and in admixture with an authentic sample (Found : C, 68·7; H, 5·0. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 4·9%).

Ethyl 5-*Phenoxy*-2-*methoxybenzoate.*—(i) 5-Bromosalicylic acid (40·6 g.) (Hewitt, Kenner, and Silk, J., 1904, **85**, 1228) in methyl alcohol (120 c.c.) was methylated with 50% potassium hydroxide solution and methyl sulphate (total, 57 c.c.) and the product was isolated as the methoxy-acid (40·3 g.), which crystallised from 50% aqueous acetic acid in fine needles (35·5 g.), m. p. 111—112·5° (lit., m. p. 119°). Esterification by the Fischer–Speier process (75 c.c. of 6% ethyl-alcoholic hydrogen chloride; 6 hours' refluxing) yielded the ethyl ester (35·1 g.) as a colourless limpid oil, b. p. 179°/21 mm.

(ii) A mixture of the foregoing ethyl 5-bromo-2-methoxybenzoate (35 g.) and dry sodium phenoxide (from 15 g. of phenol and 3·2 g. of sodium in absolute alcohol) was heated at 230° (metal-bath) with copper bronze (0·5 g.) and anhydrous copper acetate (0·5 g.) for 5½ hours, cooled, and distributed between ether and water. After filtration, the separated ethereal layer was washed with cold 3N-sodium hydroxide and with dilute sulphuric acid, dried, and fractionated. The limpid brown oil distilled almost entirely at 215—230°/18 mm. Further fractionation gave : (*a*) b. p. to 210°/18 mm. (5·4 g.); (*b*) a colourless limpid oil (19·8 g., 54%), b. p. 225—232°/18 mm., fairly steady at 227°/18 mm. (Found : C, 70·2; H, 5·8. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). The second fraction subsequently crystallised and the *substance* then separated from petrol in clusters of colourless, approximately rectangular plates, m. p. 63°.

5-*Phenoxy*-2-*methoxybenzoic Acid* (VII).—The preceding compound (2·53 g.) was quantitatively saponified by refluxing with absolute alcohol (5 c.c.) and 50% aqueous potassium hydroxide (5 c.c.) for several hours. The free *acid*, recovered by means of ether, separated from 65% aqueous acetic acid in small, colourless, hexagonal plates, m. p. 108·5—110° (Found : C, 68·7; H, 4·8. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%).

4-(4′-*Methoxyphenoxy*)*cinnamic Acid.*—Crude 4-(4′-methoxyphenoxy)benzaldehyde (7·6 g.) (Harington and Pitt-Rivers, *loc. cit.*), dissolved in pyridine (40 c.c.), was treated with malonic acid (3·7 g.) and piperidine (10 drops). The mixture was warmed over a free flame to initiate reaction and then left on the water-bath for an hour. To ensure complete reaction, more malonic acid (1·9 g.) was added and the mixture was boiled for 10 minutes. When it was poured into water, a microcrystalline solid separated. The product was taken up in ether and freed from pyridine by washing with water and zinc chloride solution. The crude product was a light yellow, somewhat sticky, solid (7·95 g., 88%) and separated from 60% aqueous acetic acid in thin colourless plates, m. p. 176—177° (Found : C, 71·1; H, 5·2. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%). Harington (*loc. cit.*) records m. p. 175·5°.

The sparingly soluble *methyl* ester, obtained by the action of an excess of diazomethane, separated from methyl alcohol in thin colourless plates, m. p. 129—130° (Found : C, 72·0; H, 5·6. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%).

Methyl β-4-(4′-*Methoxyphenoxy*)*phenylpropionate.*—The preceding unsaturated ester (4·7 g.) was dissolved in warm ethyl acetate (90 c.c., which barely sufficed for solution at room temperature), and hydrogenated in the presence of 2% palladised strontium carbonate (5 g.) with hydrogen under slight pressure (*ca.* 2 feet of water). After the lag period (20 minutes), rather more than the required volume of hydrogen was absorbed in about 10 minutes (corrected observed vol. 425 c.c.; theo., 371 c.c.). The solution was filtered and evaporated, the product crystallising promptly on removal of the solvent. The saturated *ester* was more soluble than its precursor, and separated from methyl alcohol in thin rhomboid plates, m. p. 55—56° (Found : C, 71·1; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

β-4-(4′-*Hydroxyphenoxy*)*phenylpropionic Acid and Ethyl Ester.*—The foregoing hydrogenation product (4·5 g.) was refluxed for 6½ hours with a mixture (60 c.c.) of equal parts of glacial acetic acid and constant-boiling hydrobromic acid. The product (3·75 g.) separated in a pure condition on dilution with water. The *acid* separated from 30% aqueous acetic acid in radiating clusters of fine colourless needles, m. p. 161° (Found : C, 69·8; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

The *ethyl* ester, obtained in practically quantitative yield by the Fischer–Speier process, was a colourless viscous syrup, b. p. 225—230°/2·2 mm. (Found : C, 71·8; H, 6·5. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%), which subsequently crystallised spontaneously; it then separated from ligroin, containing a small proportion of ethyl acetate, in colourless, well-developed prisms, m. p. 76—77°.

Attempted Preparation of 4-(4′-*Methoxyphenoxy*)*benzaldehyde from* 4-*Methoxydiphenyl Ether and Formo-*

methylanilide. 4-(4′-*Methoxyphenoxy*)*benzaldehyde Semicarbazone.*—4-Methoxydiphenyl ether (10 g.) was treated with formomethylanilide (9 g.), and phosphorus oxychloride (6·1 c.c.) on the boiling water-bath for 6 hours (cf. β-naphthyl methyl ether, *Organic Syntheses*, 1940, **20**, 11). The product, isolated by pouring into ice-water and extraction with ether, gave a positive test for carbonyl with Brady's reagent. Vacuum distillation, however, gave largely unchanged starting material (judged by the b. p.), and only a small higher-boiling fraction (*ca.* 0·9 g.), b. p. 170—190°/16 mm. The latter fraction, treated with semicarbazide hydrochloride (0·45 g.) and sodium acetate (0·55 g.) in aqueous alcohol on the water-bath for several hours, yielded a semicarbazone (0·1 g.), m. p. 211—214°, recrystallisation of which from *n*-butyl alcohol afforded colourless plates, m. p. 215° (Found: C, 62·5; H, 5·4; N, 14·4. Calc. for $C_{15}H_{15}O_3N_3$: C, 63·2; H, 5·2; N, 14·7%). Harington and Pitt-Rivers (*loc. cit.*) record m. p. 212—213°.

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