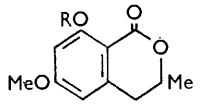
507. *A Novel Isomerization of a Homophthalic Acid Derivative.*

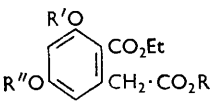
By W. R. Allison and G. T. Newbold.

3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenyl acetic acid is converted by anhydrous acidic reagents into ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate. Hot alkali caused the reverse rearrangement. A possible mechanism is discussed.

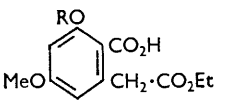
(—)-3,4-Dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (I) occurs naturally in bitter carrots.[1] The methyl ether (II) of the racemic form has been synthesized,[2] and it was planned to use a similar route to the hydroxy-compound (I). An intermediate required was the acid (VII) whose preparation and properties are now reported.



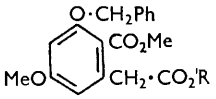
(I) R = H
(II) R = Me



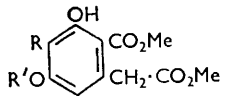
(III) R = Et, R′ = R″ = H
(IV) R = Et, R′ = H, R″ = Me
(V) R = R′ = H, R″ = Me
(VI) R = Me, R′ = H, R″ = Me
(VII) R = H, R′ = CH_2·Ph, R″ = Me
(VIII) R = Me, R′ = CH_2·Ph, R″ = Me
(IX) R = Et, R′ = CH_2·Ph, R″ = Me



(X) R = CH_2·Ph
(XI) R = H



(XV) R = Me
(XVI) R = H
(XVII) R = Et



(XII) R = CO_2H, R′ = H
(XIII) R = R′ = H
(XIV) R = H, R′ = Me

Ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate[3] (III) and diazomethane gave the 5-methyl ether (IV) which was hydrolysed to 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (V). In all the compounds having ester groups in the 2-position this ester function was stable to alkali under quite vigorous conditions because of steric hindrance. Methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (VI) was benzylated and hydrolysed to the benzyl acid (VII) which was characterized as its methyl ester (VIII) from which it was regenerated by alkaline hydrolysis.

Since the original synthetical route required the acid chloride the acid (VII) was treated with phosphorus trichloride in chloroform, but an isomeric acid, m. p. 116—117°, was formed in 75% yield; the same acid was also produced by using thionyl chloride. Neither (VII) nor the acid, m. p. 116—117°, gave a ferric colour and the latter compound was methylated to an ester isomeric with methyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate (VIII). The acid, m. p. 116—117°, although unaffected by cold dilute alkali was converted by hot aqueous alkali into 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (VII). Methylation of this acid or that of m. p. 116—117° gave the same ester (IX), each sample of which on alkaline hydrolysis gave the benzyl acid (VII). We consider that the conversion of (VII) into the acid of m. p. 116—117°, and *vice versa*, involves an interchange of carboxylic acid and ester functions and therefore that the acid, m. p. 116—117°, has structure (X).

Hydrogenolysis of the benzyl acid (VII) afforded 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (V) while the acid (X) gave ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (XI) which was isomerized to (V) by the usual alkaline treatment. The ester acid (XI) on brief treatment with diazoethane afforded ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (IV), whilst the ester acid (V) was largely unaffected by phosphorus trichloride in chloroform.

[1] Sondheimer, *J. Amer. Chem. Soc.*, 1957, **79**, 5036.
[2] Logan and Newbold, *Chem. and Ind.*, 1957, 1485.
[3] Nogami, *J. Pharm. Soc. Japan*, 1941, **61**, 56.

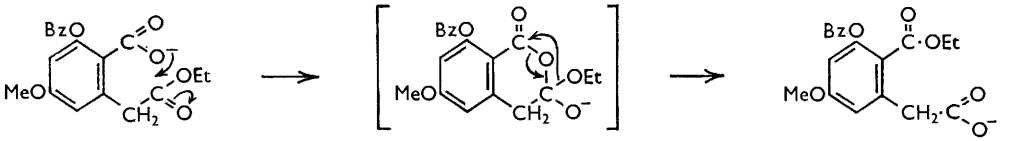
The methyl ester formed by treatment of the acid (X) with diazomethane is (XVII), synthesis of which has been achieved. Methyl acetonedicarboxylate was converted into the diester acid (XII) which was decarboxylated. After the reaction sequence (XIII) ⟶ (XIV) ⟶ (XV) ⟶ (XVI) (cf. ethyl ester series) the final product was esterified with diazoethane to give (XVII), furnishing proof of the structure of the isomerization product (X).

More vigorous treatment of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (VII) with phosphorus trichloride in chloroform gave a chlorine-free product, regarded as the anhydride of (X), since its infrared spectrum [ν 1796 and 1727 (infl.) cm.$^{-1}$ in chloroform, ν 1789 and 1730 (infl.) cm.$^{-1}$ in Nujol] is comparable with that of benzoic anhydride (1789 and 1727 cm.$^{-1}$) rather than with that phenylacetic anhydride [4] (1808 and 1745 cm.$^{-1}$). The band separations of 69 cm.$^{-1}$ in chloroform and 59 cm.$^{-1}$ in Nujol compare with the usual value of *ca.* 60 cm.$^{-1}$ for anhydrides. The anhydride also showed bands at 1750 cm.$^{-1}$ in chloroform and 1751 cm.$^{-1}$ in Nujol which we attribute to the phenylacetic ester carbonyl group. Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (X) and phosphorus trichloride in chloroform gave the same anhydride, further supporting the structure assigned to it.

We presumed that the rearrangement (VII) ⟶ (X) was catalysed by hydrogen chloride liberated by reaction of some of the original acid with phosphorus trichloride and have shown that dry hydrogen chloride in chloroform will effect the change (VII) ⟶ (X) in 20% yield. We consider that the first step is the protonation of both ethoxycarbonyl and carboxyl group. The protonated ester group forms the acylium ion,[5] the ethanol liberated entering immediately into a normal bimolecular acid-catalysed ($A_{AC}2$) esterification with the phenylacetic oxonium ion. The resulting transition state [6] then transfers the elements of water to give the protonated form of (X). The driving force in this isomerization must be primarily steric, the smaller bulk of the hydroxyl group being more acceptable than the larger ethoxyl group to the strongly hindered benzoic function; thus the reverse reaction is prevented. Such transfer of groups is facilitated by the proximity of the two carboxyl functions.

This mechanism explains why the ester acid (V) was not isomerized to (XI). In the former the steric hindrance of the benzoate group is much less than in (VII), diminishing the possibility of formation of acylium ion; also owing to the lessened steric hindrance in the ester acid (V) there will be less tendency to exchange the smaller hydroxyl group for the larger ethoxyl group.

The ester acid (X) was isomerized to (VII) in high yield by aqueous, aqueous ethanolic, and aqueous methanolic alkali. Use of the last reagent proved that the ethoxyl-ion transfer was intramolecular. We consider the reaction to follow the mechanism:



In the postulated cyclic intermediate the polarization of the carbonyl group, giving a positive charge on the carbon atom, will attract the ethoxyl group, which, examination of models suggests, could take up a favourable conformation for reaction as shown. We believe that the driving force, preventing reversal of the reaction, is electronic and depends on the effect of the electron-donating properties of the benzyloxy-group [or the anion from the phenolic hydroxy group in (XI)] on the 2-position. Steric hindrance due to the benzyloxy-group may be lessened in alkali and be greater in the acidic medium wherein the benzyloxy-group may be protonated.

[4] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1958, pp. 127—128.
[5] Newman (ed.), " Steric Effects in Organic Chemistry," Chapman and Hall, London, 1956, p. 218.
[6] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 770.

Experimental

Ultraviolet spectra were determined in ethanol, and infrared spectra in Nujol mull unless otherwise stated. All identities were confirmed by comparison of infrared spectra.

Ethyl 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate.—Ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate [3] (4·0 g.) was methylated at 0° with ethereal diazomethane [from nitrosomethylurea (5·0 g.) [7]]. *Ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate* (3·1 g.) was obtained from light petroleum (b. p. 40—60°) as felted needles, m. p. 62—64° (Found: C, 59·5; H, 6·6. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%); $\lambda_{max.}$ 220 (ε = 29,500), 262 (ε = 13,900), and 302 mμ (ε = 6600); $\nu_{max.}$ 1733 (phenylacetate C=O) and 1653 cm.$^{-1}$ (H-bonded benzoate C=O); $\nu_{max.}$ in chloroform 1736 (phenylacetate C=O) and 1661 cm.$^{-1}$ (H-bonded benzoate C=O).

2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid.—Ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (200 mg.) was refluxed for 1 hr. with aqueous sodium hydroxide (10 c.c.; 2N). The isolated product was crystallized from aqueous methanol, giving *2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid* (120 mg.) as needles, m. p. 186—188° (Found: C, 57·1; H, 5·8. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%); $\lambda_{max.}$ 216 (ε = 29,500), 260 (ε = 13,450), and 303 mμ (ε = 6300); $\nu_{max.}$ 1700 (phenylacetic acid dimer C=O) and 1667 cm.$^{-1}$ (H-bonded benzoate C=O), $\nu_{max.}$ in chloroform 1718 (phenylacetic acid monomer C=O) and 1661 cm.$^{-1}$ (H-bonded benzoate C=O). The acid in ethanol gave a red-brown colour with aqueous ferric chloride. The *methyl ester*, prepared by brief treatment with diazomethane, crystallized from light petroleum (b. p. 40—60°) as fine needles, m. p. 68—69° (Found: C, 57·9; H, 6·25. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%); $\lambda_{max.}$ 220 (ε = 16,400), 263 (ε = 14,000), and 302 mμ (ε = 6900); $\nu_{max.}$ 1739 (phenylacetate C=O) and 1653 cm.$^{-1}$ (H-bonded benzoate C=O); $\nu_{max.}$ in chloroform 1739 (phenylacetate C=O) and 1658 cm.$^{-1}$ (H-bonded benzoate C=O). The methyl ester in ethanol gave a red-brown colour with aqueous ferric chloride.

The *acetyl* derivative of the acid, prepared by the pyridine–acetic anhydride method, separated from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 148—150° (Found: C, 56·7; H, 5·2. $C_{14}H_{16}O_7$ requires C, 56·8; H, 5·4%); $\lambda_{max.}$ 213 (ε = 21,000) and 252 mμ (ε = 10,400); $\nu_{max.}$ 1757 (acetate C=O), 1718 (benzoate C=O), and 1695 cm.$^{-1}$ (phenylacetic acid C=O); $\nu_{max.}$ in chloroform 1767 (acetate C=O) and 1721 cm.$^{-1}$ (benzoate C=O).

3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid.—Methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (2·8 g.), sodium iodide (2·0 g.), anhydrous potassium carbonate (2·0 g.), benzyl chloride (2·5 c.c.), and ethyl methyl ketone (50 c.c.) were refluxed for 72 hr. The solvent was evaporated under reduced pressure, and the residue treated with water (150 c.c.) and extracted with ether (2 × 75 c.c.). The combined ethereal extracts gave the crude benzyl compound (3·5 g.) as a pale yellow gum which was refluxed for 1 hr. with potassium hydroxide (8·0 g.) in water (8 c.c.) and ethanol (72 c.c.). The solution was diluted with water (100 c.c.), the ethanol removed under reduced pressure, and the aqueous solution extracted with chloroform (50 c.c.) and acidified (Congo Red) with hydrochloric acid (*d* 1·15). The resulting emulsion was extracted with chloroform (3 × 50 c.c.) and the combined chloroform washings were extracted with saturated aqueous sodium hydrogen carbonate (3 × 50 c.c.). The combined alkaline extract was acidified (Congo Red) with hydrochloric acid (*d* 1·15), and the precipitated solid washed with water, dried, and crystallized from acetone–light petroleum (b. p. 60—80°), giving *3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid* (1·9 g.) as needles, m. p. 144—146° (Found: C, 66·5; H, 5·7%; Equiv., 340. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85%; Equiv., 344); $\lambda_{max.}$ 208 (ε = 46,700) and 284 mμ (ε = 3400); $\nu_{max.}$ 1724 (benzoate C=O) and 1681 cm.$^{-1}$ (phenylacetic acid dimer C=O); $\nu_{max.}$ in chloroform 1724 cm.$^{-1}$ (benzoate C=O). The *methyl ester*, prepared by use of diazomethane, separated from light petroleum (b. p. 40—60°) as felted needles, m. p. 39·5—41° (Found: C, 66·75; H, 5·8. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), $\lambda_{max.}$ 210 (ε = 34,800), 250 (ε = 6900), and 286 mμ (ε = 3500); $\nu_{max.}$ 1748 (phenylacetate C=O) and 1715 cm.$^{-1}$ (benzoate C=O); $\nu_{max.}$ in chloroform 1736 cm.$^{-1}$ (phenylacetate C=O). The ester was hydrolysed under reflux with 5% aqueous methanolic potassium hydroxide for 1 hr. to give 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid, m. p. and mixed m. p. 145—147°. 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (140 mg.) was refluxed with aqueous potassium hydroxide (10 c.c.; 30%) for 24 hr. Starting material (110 mg.) was obtained and separated from acetone–light petroleum (b. p. 60—80°) as needles, m. p. and mixed m. p. 145—147°.

[7] *Org. Synth.*, Coll. Vol. I, Wiley, New York, 1943, p. 165.

2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid from Hydrogenolysis of the 3-Benzyloxy-derivative.—A solution of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (190 mg.) in dry redistilled ethyl acetate (50 c.c.) was shaken for 6 hr. with hydrogen at atmospheric pressure in the presence of palladised charcoal (200 mg.; 2½% $PdCl_2$ on charcoal) and magnesium oxide (100 mg.). The solids were treated with hydrochloric acid (10 c.c.; 2N), and the mixture was extracted with chloroform (3 × 50 c.c.). The combined chloroform extract was washed with water and saturated aqueous sodium hydrogen carbonate (3 × 20 c.c.), and the combined alkaline extract acidified (Congo Red) with 2N-hydrochloric acid. Next morning the solid was washed with water, dried, and crystallized from aqueous methanol, giving 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (90 mg.) as needles, m. p. and mixed m. p. 186—188°.

Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate.—(*a*) 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (1·2 g.) and a mixture of phosphorus trichloride (850 mg.) and dry chloroform (230 c.c.) were shaken until the acid dissolved (30 min.), and then the solution was kept at room temperature for 24 hr. ($CaCl_2$ tube). The chloroform was removed at room temperature. Benzene (100 c.c.) was added to the residue, and the solution evaporated to yield a pale yellow gum which gave, from benzene–light petroleum (b. p. 60—80°), *ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate* (920 mg.) as needles, m. p. 116—117·5° (Found: C, 66·4; H, 6·05%; Equiv., 341. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85%; Equiv., 344); $\lambda_{max.}$ 210 (ε = 33,900), 258 (ε = 6000), and 286 mμ (ε = 3300); $\nu_{max.}$ 1736 (phenylacetate C=O) and 1684 cm.$^{-1}$ (benzoic acid dimer C=O); $\nu_{max.}$ in chloroform 1736 cm.$^{-1}$ (phenylacetate C=O).

(*b*) A solution of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (200 mg.) in thionyl chloride (2 c.c.) was refluxed for 10 min. Excess of thionyl chloride was removed under reduced pressure at 40°. Benzene (10 c.c.) was added to the residue and similarly evaporated, and the residual gum was crystallized from benzene–light petroleum (b. p. 60—80°), giving ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (110 mg.) as needles, m. p. and mixed m. p. 116—117° (Found: C, 66·4; H, 6·0%).

(*c*) 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (500 mg.) in a saturated solution of dry hydrogen chloride in dry chloroform (150 c.c.) was kept for 4 hr. at 40°. The chloroform was evaporated under reduced pressure at room temperature. Evaporation with benzene (50 c.c.) gave a gum which was separated by fractional crystallization from benzene–light petroleum (b. p. 60—80°) into 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (220 mg.), needles, m. p. and mixed m. p. 144—146°, and ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (110 mg.), needles, m. p. and mixed m. p. 116—117°.

Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (20 mg.) was shaken at 20° with aqueous sodium hydroxide (20 c.c.; 0·01N), and the resulting solution was kept at 20° for 1 hr., and then acidified (Congo Red) with dilute hydrochloric acid. Crystallization of the precipitate from benzene–light petroleum (b. p. 60—80°) gave the starting material as needles, m. p. and mixed m. p. 115—117°.

Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate Anhydride.—A solution of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (400 mg.) in dry chloroform (12 c.c.) containing phosphorus trichloride (300 mg.) was refluxed for 20 min. The solution was decanted from phosphorous acid, and the chloroform evaporated under reduced pressure at 25° to give a yellow gum which crystallized from benzene–light petroleum (b. p. 60—80°) giving the *anhydride* (220 mg.) as yellow plates, m. p. 170—173° [Found: C, 67·4; H, 5·6%; *M* (Rast), 610. $C_{33}H_{38}O_{11}$ requires C, 68·1; H, 5·7%; *M*, 610]. After two days the m. p. had fallen to 155—162°. Light absorption: $\lambda_{max.}$ 210 (ε = 48,000), 267 (ε = 18,700), and 304 mμ (ε = 5100). The anhydride was insoluble in cold aqueous sodium hydrogen carbonate and cold dilute aqueous sodium hydroxide; when it was heated under reflux with 5% aqueous methanolic potassium hydroxide for 1 hr., there was formed in good yield, 3-benzoyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid, needles, m. p. and mixed m. p. 146—148°, from acetone–light petroleum (b. p. 60—80°).

Action of Alkali on Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate: Formation of 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid.—(*a*) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (200 mg.) was refluxed for 1 hr. with aqueous sodium hydroxide (20 c.c.; 5%). Isolation and crystallization from acetone–light petroleum (b. p. 60—80°) gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (140 mg.) as needles, m. p. and mixed m. p. 147—149°.

(*b*) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (250 mg.) was refluxed for 1 hr. with potassium hydroxide (1 g.), water (1 c.c.), and methanol (19 c.c.). Isolation with ether followed by crystallization from acetone–light petroleum (b. p. 60—80°) gave 3-benzoyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (145 mg.) as needles, m. p. and mixed m. p. 145—147°.

Ethyl 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate.—Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (100 mg.) with ethereal diazomethane afforded *ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate* (75 mg.) as felted needles, m. p. 74—75° from light petroleum (b. p. 40—60°) (Found: C, 66·8; H, 6·3. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%); $\lambda_{max.}$ 210 (ε = 35,500), 250 (ε = 6500), and 286 mμ (ε = 3400); $\nu_{max.}$ 1736 (phenylacetate C=O) and 1712 (benzoate C=O); $\nu_{max.}$ in chloroform 1733 cm.$^{-1}$ (phenylacetate C=O).

3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic Acid.—A solution of ethyl 3-benzyloxy-2-methoxycarbonyl-5-methoxyphenylacetate (50 mg.) was refluxed with 5% aqueous methanolic potassium hydroxide (20 c.c.) for 1 hr. Isolation and crystallization from acetone–light petroleum (b. p. 60—80°) gave *3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic acid* (280 mg.) as clusters of needles, m. p. 147—149° (Found: C, 65·2; H, 5·3. $C_{18}H_{18}O_6$ requires C, 65·45; H, 5·5%); $\lambda_{max.}$ 212 (ε = 35,700), 248 (ε = 6400), and 285 mμ (ε = 3400); $\nu_{max.}$ 1727 cm.$^{-1}$ (benzoate C=O); $\nu_{max.}$ in chloroform 1724 cm.$^{-1}$ (benzoate C=O).

Action of Diazoethane on Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate and its Isomer.—(*a*) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate on treatment with diazoethane gave a gum, which did not solidify; $\nu_{max.}$ for the liquid 1733 cm.$^{-1}$ (C=O).

(*b*) Similar treatment of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid gave a gum whose infrared spectrum was identical with that of preparation (*a*). Hydrolysis of either sample by the 5% aqueous methanolic potash method gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid as needles, m. p. and mixed m. p. 145—147°.

Ethyl 2-Carboxy-3-hydroxy-5-methoxyphenylacetate.—Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (250 mg.) was hydrogenolysed, the same conditions being used as given for its isomer above. Crystallization from benzene–light petroleum (b. p. 60—80°) gave *ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate* (140 mg.) as needles, m. p. 119—120° (Found: C, 57·1; H, 5·8. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%); $\lambda_{max.}$ 214 (ε = 25,400), 260 (ε = 11,300), and 302 mμ (ε = 5700); $\nu_{max.}$ 1736 (phenylacetate C=O); $\nu_{max.}$ in chloroform 1736 (phenylacetate C=O) and 1656 cm.$^{-1}$ (H-bonded benzoate C=O). A solution of the compound in ethanol gave a red-brown colour with aqueous ferric chloride.

Conversion of Ethyl 2-Carboxy-3-hydroxy-5-methoxyphenylacetate into Ethyl 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate.—Brief treatment of ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (50 mg.) with diazoethane and crystallization from light petroleum (b. p. 40—60°) gave ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (30 mg.) as felted needles, m. p. 62—64° undepressed on admixture with a sample prepared by the action of diazomethane on ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate. Hydrolysis of the diester by the 5% aqueous methanolic potash method gave 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid, m. p. and mixed m. p. 185—187°. 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid was unchanged by treatment with phosphorus trichloride in chloroform, which converted its benzyl ether into ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate.

Isomerization of Ethyl 2-Carboxy-3-hydroxy-5-methoxyphenylacetate.—The ester (50 mg.) was refluxed with 5% aqueous methanolic potassium hydroxide (5 c.c.) for 2 hr. Isolation and crystallization from aqueous methanol gave 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid as needles, m. p. 185—187° alone or mixed with an authentic specimen.

Methyl 4-Carboxy-3,5-dihydroxy-2-methoxycarbonylphenylacetate.—By use of the method given for the ethyl ester [3] methyl acetonedicarboxylate (50 g.) afforded *methyl 4-carboxy-3,5-dihydroxy-2-methoxycarbonylphenylacetate* (12·75 g.) which separated from benzene (charcoal) as plates, m. p. 152—154° (Found: C, 51·0; H, 4·5. $C_{12}H_{12}O_8$ requires C, 50·7; H, 4·3%); $\lambda_{max.}$ 224 (ε = 21,800), 238 (ε = 17,100), and 320 mμ (ε = 5500); $\nu_{max.}$ 1742 (phenylacetate C=O) and 1692 cm.$^{-1}$ (H-bonded benzoate C=O); $\nu_{max.}$ in chloroform 1742 (phenylacetate C=O), 1697 (H-bonded benzoate C=O), and 1656 cm.$^{-1}$ (H-bonded benzoic acid C=O). An ethanolic solution of the compound gave a red-brown colour with aqueous ferric chloride.

Decarboxylation.—Methyl 4-carboxy-3,5-dihydroxy-2-methoxycarbonylphenylacetate (4 g.) was decarboxylated by the method [3] described for the diethyl ester analogue. The product, *methyl 3,5-dihydroxy-2-methoxycarbonylphenylacetate* (900 mg.), separated from benzene–light petroleum

(b. p. 60—80°) as needles, m. p. 148—150° (Found: C, 54·95; H, 5·3. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%); $\lambda_{max.}$ 216 (ε = 20,300), 265 (ε = 10,900), and 304 mμ (ε = 6100); $\nu_{max.}$ 1706 (phenylacetate C=O, lowered by intermolecular H-bonding) and 1653 cm.$^{-1}$ (H-bonded benzoate C=O); $\nu_{max.}$ in chloroform 1736 (phenylacetate C=O) and 1667 cm.$^{-1}$ (H-bonded benzoate C=O). An ethanolic solution of the compound gave a red-brown colour with aqueous ferric chloride.

Methyl 3-Hydroxy-5-methoxy-2-methoxycarbonylphenylacetate.—Brief treatment of methyl 3,5-dihydroxy-2-methoxycarbonylphenylacetate with diazomethane as described for the corresponding diethyl ester gave *methyl 3-hydroxy-5-methoxy-2-methoxycarbonylphenylacetate* in good yield which separated from light petroleum (b. p. 40—60°) as felted needles, m. p. 75—77° (Found: C, 57·05; H, 5·9. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%); $\lambda_{max.}$ 220 (ε = 14,600), 263 (ε = 12,700), and 301 mμ (ε = 6000); $\nu_{max.}$ 1739 (phenylacetate C=O) and 1661 cm.$^{-1}$ (H-bonded benzoate C=O); $\nu_{max.}$ in chloroform 1739 (phenylacetate C=O) and 1667 cm.$^{-1}$ (H-bonded benzoate C=O). An ethanolic solution of the compound gave a red-brown colour with aqueous ferric chloride.

Ethyl 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate.—When the method given above for the diethyl ester was used, methyl 3-hydroxy-5-methoxycarbonylphenylacetate was benzylated, and the product was hydrolysed to 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic acid in 55% yield, forming needles, m. p. 147—149°, from acetone–light petroleum (b. p. 60—80°), undepressed on admixture with the preparation derived from the 2-ethoxycarbonyl series. 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic acid (100 mg.) on treatment in methanol (2 c.c.) for 1 hr. with excess of ethereal diazoethane yielded ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate (70 mg.) as felted needles, m. p. 71—73°, from light petroleum (b. p. 40—60°). A mixture of this preparation with that, m. p. 74—75°, obtained by brief action of diazomethane on ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate, had m. p. 71—74°.

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