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DIHYDROISOCOUMARINS—X

THE PREPARATION AND REDUCTION OF SOME *O*-CARBOXYPHENYLACETATES

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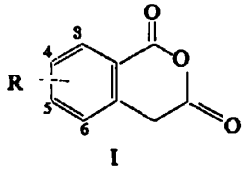
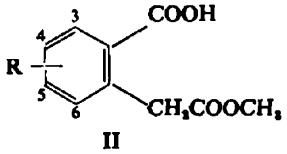
Abstract—Methanolysis of homophthalic anhydrides (Ia–c), obtained by the action of acetyl chloride on appropriate homophthalic acids, furnished the half esters, methyl *o*-carboxyphenylacetates (IIa–c) which were reduced by lithium borohydride to the corresponding dihydroisocoumarins (IIIa–c).

Two alternative routes for the synthesis of dihydroisocoumarins have been presented in earlier communications. In one,[1–3] *o*-nitrophenylacetates were reduced successively with lithium aluminum hydride and sodium dithionite to *o*-aminophenethyl alcohols, the amino group transformed into carboxyl which lactonized with the *o*-hydroxyethyl group to form dihydroisocoumarins. The scope of this synthesis is limited because very few methoxy substituted *o*-nitrophenylacetates are readily accessible. In the other method,[4–7] the formation of the hetero ring was accomplished by a four-step synthesis from homophthalic acids. Esterification followed by lithium aluminum hydride reduction and cyclodehydration of the resulting homophthalyl alcohols gave isochromans which were oxidized to dihydroisocoumarins.

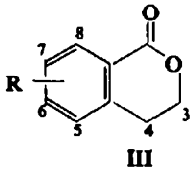
The present communication provides a third and more convenient and superior route and consequently, the preparation of isocoumarins[4–6] by the interaction of dihydroisocoumarines with N-bromosuccinimide can be accomplished without difficulty.



I



II



III

Ia, IIa. R = 4, 5—di—OCH_3
Ib, IIb. R = 4, 6—di—OCH_3
Ic, IIc. R = 5, 6—di—OCH_3

IIIa. R = 6, 7—di—OCH_3
IIIb. R = 5, 7—di—OCH_3
IIIc. R = 5, 6—di—OCH_3

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[4] J. N. Srivastava and D. N. Chaudhury, *J. Org. Chem.* **27**, 4337 (1962).
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4,5-Dimethoxy-,[8] 4,6-dimethoxy-[8] and 5,6-dimethoxy-homophthalic acid,[9] on treatment with acetyl chloride, yields the corresponding homophthalic anhydrides, (Ia,[10] Ib and Ic) which in refluxing methanol furnish almost quantitatively the pure half esters, (IIa, IIb and IIc) respectively. Fieser and Pechert[11] have shown that the carboxyl group in the side chain of homophthalic acid is more easily esterified than that joined to the nucleus, and partial esterification with methanol and hydrogen chloride in the cold yields methyl *o*-carboxyphenylacetate. But when this procedure was adopted for the preparation of the half esters (II), a mixture of neutral and half esters was obtained and this method, therefore, did not prove satisfactory.

Since lithium borohydride normally has no action on aromatic acids,[12] selective reduction of the ester group in half esters IIa and IIb by this reagent yields the dihydroisocoumarins IIIa and IIIb owing to lactonization of the resulting *o*-carboxyphenethyl alcohols. Under the same conditions, IIc yields 2-carboxy-5,6-dimethoxyphenethyl alcohol. It is readily soluble in aqueous sodium bicarbonate, is reprecipitated on acidification and crystallizes from ethyl acetate–petroleum ether as needles, m.p. 115–116°. The isolation of this stable hydroxy acid, in contrast to the other cases, lends support to our previous observation[13] that the ease with which 2-carboxyphenethyl alcohols form δ-lactones is dependent on the nature and position of the substituents in the benzene ring. However, lactonization by sublimation *in vacuo* readily affords the dihydroisocoumarin (IIIc).

EXPERIMENTAL[14]

4,5-Dimethoxyhomophthalic anhydride (Ia). The reported procedure[10] was adopted with the following modification. After refluxing a mixture of 4,5-dimethoxyhomophthalic acid[8] (5 g) and acetyl chloride (35 ml) for 90 min, the acetyl chloride was distilled off and the crystalline residue, was treated with ice-cold anhydrous ether, filtered and washed thoroughly with dry ether to yield felted cream coloured needles (4·6 g; 99·5%), m.p. 175° (lit,[10] m.p. 175°).

Methyl 2-carboxy-4,5-dimethoxyphenylacetate (IIa). A mixture of Ia (1·8 g) and pure dry methanol (25 g) was refluxed until after 25 min all the solid dissolved and after 45 min, long colourless needles separated from the boiling solution. After a total 2 hr reflux period, the reaction mixture was cooled and, the crystalline product after washing with methanol afforded pure IIa as colourless felted needles (1·6 g; 77·6%), m.p. 196°, unchanged after recrystallization from glacial acetic acid. (Found: C, 56·5; H, 5·3. $C_{12}H_{14}O_6$ requires: C, 56·4; H, 5·5%).

3,4-Dihydro-6,7-dimethoxyisocoumarin (IIIa). A solution of IIa (0·5 g) in anhydrous THF (50 ml) was made by gentle reflux and cooled to room temperature. Lithium borohydride (0·085 g) was added and the clear solution after refluxing 4 hr deposited the complex. Next day, the solvent was distilled off, the residue cooled and water was added dropwise followed by dil. H_2SO_4. The solution was then extracted with chloroform (15 ml × 3) and the extract washed ($NaHCO_3$ and water) and dried (Na_2SO_4). Evaporation of the solvent left a gum which solidified on standing to yellow needles. Sublimation under vacuum (bath temp. 120–125°/0·1 mm) afforded colourless needles, m.p. 138–140°, which crystallized from ethyl acetate–pet. ether to yield pure IIIa (0·35 g; 87·5%), m.p. 140–141°, undepressed on admixture with an authentic specimen (m.p. 140–141°) prepared earlier[4] by a different route.

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[13] S. K. P. Sinha, D. N. Chaudhury and D. Prasad, *J. Indian. Chem. Soc.* **40**, 437 (1963).
[14] All m.ps. are uncorrected. The pet. ether used had b.p. 60–80°. Microanalysis by Drs. Weiler and Strauss, Oxford.

4,6-Dimethoxyphthalic anhydride (Ib). 4,6-Dimethoxyhomophthalic acid[8] (3 g) in acetyl chloride (21 ml) was refluxed for 90 min and worked up as described for the preparation of Ia. The slightly coloured product, m.p. 190°, was sublimed under vacuum (bath temp. 135–140°/0·3 mm) to afford pure Ib as colourless needles (2·68 g; 96·7%), m.p. 192°. (Found: C, 59·7; H, 4·4. $C_{11}H_{10}O_5$ requires: C, 59·5; H, 4·5%).

Methyl 2-carboxy-4,6-dimethoxyphenylacetate (IIb). A mixture of Ib (2 g) and pure dry methanol (20 ml) was refluxed for 2 hr (clear solution). Evaporation of methanol left a gummy residue which when triturated with pet. ether furnished a colourless crystalline solid. This was recrystallized twice from dil. methanol to afford pure IIb as colourless needles (1·57 g; 70%), m.p. 135°. (Found: C, 56·7; H, 5·8. $C_{12}H_{14}O_6$ requires: C, 56·4; H, 5·5%).

3,4-Dihydro-5,7-dimethoxyisocoumarin (IIIb). A solution of IIb (1·0 g) in dry THF (80 ml) was refluxed with $LiBH_4$ (0·17 g) for 4 hr and worked up as described for the preparation of IIIa except that ethyl acetate was used for extraction. The product was purified by sublimation under vacuum (bath temp. 90–100°/0·5 mm) followed by recrystallization from ethyl acetate–pet. ether to furnish pure IIIb as colourless needles (0·71 g; 87·6%), m.p. 101°, undepressed on admixture with an authentic specimen (m.p. 100–101°) prepared earlier[9] by a different route.

5,6-Dimethoxyhomophthalic anhydride (Ic). This was prepared by the interaction of 5,6-dimethoxyhomophthalic acid (0·9 g) with acetyl chloride (7 ml) according to the procedure described for the preparation of Ia. The product was recrystallized from anhydrous benzene to furnish pure Ic as colourless plates (0·8 g; 96·3%), m.p. 151–152°. (Found: C, 59·8; H, 4·7. $C_{11}H_{10}O_5$ requires: C, 59·5; H, 4·5%).

Methyl 2-carboxy-5,6-dimethoxyphenylacetate (IIc). Ic (0·8 g) and pure dry methanol (10 ml) were refluxed for 2 hr. The solid residue, after distillation of the methanol on recrystallization from ethyl acetate–pet. ether gave pure IIc as colourless needles (0·65 g; 80·2%), m.p. 147–148°. (Found: C, 56·2; H, 5·2. $C_{12}H_{14}O_6$ requires: C, 56·4; H, 5·5%).

2-Carboxy-5,6-dimethoxyphenethyl alcohol. A solution of IIc (0·5 g) in dry THF (50 ml) and $LiBH_4$ (0·085 g) was refluxed for 5 hr, the solvent distilled off and the residue decomposed with dil. H_2SO_4. The solution was extracted with ethyl acetate (20 ml × 3), the extract washed repeatedly with water until no longer acidic, and dried (Na_2SO_4). Evaporation of the solvent left a solid residue which was crystallized from ethyl acetate–pet. ether to furnish *2-carboxy-5,6-dimethoxyphenethyl alcohol* as prismatic needles (0·43 g; 97·7%), m.p. 115–116°. (Found: C, 57·6; H, 6·4. $C_{11}H_{14}O_5$ requires: C, 57·3; H, 6·1%). It dissolves in $NaHCO_3$aq. and is reprecipitated unchanged on acidification.

3,4-Dihydro-5,6-dimethoxyisocoumarin (IIIc). Vacuum sublimation of the foregoing phenethyl alcohol (0·4 g) at 115–120°/1 mm afforded a colourless oil which gradually solidified. It was purified by recrystallization from ethyl acetate–pet. ether to afford IIIc as colourless rectangular prisms (0·3 g; 81%), m.p. 72°, undepressed on admixture with an authentic specimen (m.p. 72–73°) prepared earlier[4] by a different route.

2-Carboxy-5,6-dimethoxyphenethyl alcohol also lactonized slowly when its solution in ethyl acetate was kept at the room temperature for a week.