

## Isocoumarins: Part V—Synthesis of 3-Methyl and 4-Carboxy-3-Methylisocoumarins

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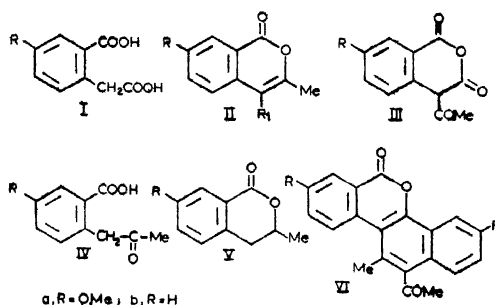
Action of acetic anhydride on 4-methoxyhomophthalic acid in the presence of pyridine at about 100° furnished 4-carboxy- and 4-acetyl-7-methoxy-3-methylisocoumarins and a small amount of a substance (VIa), but at room temperature it mainly gave 4-acetyl-7-methoxyisochroman-1,3-dione. This isochromandione was converted quantitatively on treatment with 80%  $\text{H}_2\text{SO}_4$  into 4-carboxy-7-methoxy-3-methylisocoumarin getting partly decarboxylated during the reaction to 7-methoxy-3-methylisocoumarin depending on the temperature of the reaction. Various reactions on these isocoumarins and isochroman-dione have been studied with interesting results. 2-Carboxy-4-methoxybenzyl methyl ketone was obtained in excellent yield by the action of aq. NaOH on them. The ketone cyclodehydrated to 7-methoxy-3-methylisocoumarin and on reduction with sodium borohydride furnished 7-methoxy-3-methyl-3,4-dihydroisocoumarin in very good yield. Similar results have been obtained by the action of acetic anhydride on homophthalic acid with pyridine, giving a new synthesis for 3-methylisocoumarin and 3-methyl-3,4-dihydroisocoumarin in good yields.

In a preliminary communication<sup>1</sup> we had reported the formation of 4-carboxy-7-methoxy-3-methylisocoumarin (IIa,  $\text{R}_1 = \text{COOH}$ ) by the action of acetic anhydride and pyridine on 4-methoxyhomophthalic acid (Ia) at boiling waterbath temperature. Two other substances *viz.*, 4-acetyl-7-methoxy-3-methylisocoumarin (IIa,  $\text{R}_1 = \text{COMe}$ ) and a small amount of a substance (VIa) have also been isolated from the same reaction. Further investigation led to the interesting observation that the same reaction at room temperature (25–30°) furnished, 4-acetyl-7-methoxyisochroman-1,3-dione (IIIa) in nearly 70% yield. Similar results have also been obtained in the case of homophthalic acid (Ib). With acetic anhydride and pyridine at boiling waterbath temperature it gave a mixture of 4-carboxy- and 4-acetyl-3-methylisocoumarins (IIb,  $\text{R}_1 = \text{COOH}$  and IIb,  $\text{R}_1 = \text{COMe}$ ) and a small amount of a substance (VIb). While this work was being finalised action of acetic anhydride on homophthalic acid in presence of pyridine was reported by Smith *et al.*<sup>2</sup> to give the same substances and in addition a substantial amount of the ketone (IVb). Their conditions of the reaction are however much different. They have carried the reaction at reflux temperature for 8 hrs. using large excess of pyridine. Under our conditions of the reaction no ketone derivative is isolated and the yield of (VIb) is negligible and the yield of 4-carboxy-3-methylisocoumarin is good compared to that obtained by them. The constitution to (VIb) is assigned by Smith *et al.*<sup>2</sup> on the basis of I.R., NMR and X-ray data and in analogy to that we have assigned the structure of VIa to the similar product obtained in the case

1. R. B. Tirodkar and R. N. Usgaonkar, *Curr. Sci.*, 1968, **37**, 164.
2. G. G. Smith, C. W. Delong, W. H. Wetzel and V. P. Murlidharan, *J. Heterocycl. Chem.*, 1967, **4**, 501.

of 4-methoxyhomophthalic acid (Ia). With acetic anhydride and pyridine at room temperature, homophthalic acid (Ib) furnished 4-acetyliso chroman-1,3-dione (IIIb) in excellent yield. The same substance was obtained by Schnekenburger<sup>3b</sup> by the action of acetyl chloride on homophthalic anhydride in the presence of pyridine.

The isochromandione IIIa got quantitatively converted on treatment with aq.  $H_2SO_4$  (80%) into 4-carboxy-7-methoxy-3-methylisocoumarin (IIa,  $R_1 = COOH$ ) getting partly decarboxylated to the isocoumarin (IIa,  $R_1 = H$ ), depending on the temperature of the reaction. When the reaction was carried out at 0–10°, the major product isolated was the carboxy derivative (IIa,  $R_1 = COOH$ ) but when the reaction was carried out by warming



on a waterbath for 45 mins., the major product was the decarboxylated *i.e.*, 7-methoxy-3-methylisocoumarin (IIa,  $R_1 = H$ ). It, thus, provided an excellent method for synthesis of both these isocoumarins which can be obtained in an overall yield of 50 and 70% respectively from 4-methoxyhomophthalic acid in two stages. Similar results are also obtained in the case of the isochromandione (IIIb) on treatment with sulphuric acid, thus providing an excellent new method for synthesis of 3-methylisocoumarin (IIb,  $R_1 = H$ ) and also for its 4-carboxy derivative (IIb,  $R_1 = COOH$ ). The synthesis known in the literature<sup>4</sup> for (IIb,  $R_1 = H$ ) is a lengthy one and the overall yield is poor. The development of this synthesis for 3-methylisocoumarin derivatives from homophthalic acids in two stages is important in view of the fact that some simple 3-methylisocoumarin derivatives have been isolated from fungus *e.g.*, 8-hydroxy-3-methylisocoumarin<sup>5</sup> and Reticulol<sup>6</sup>. It is to be noted here that Schnekenburger<sup>3d</sup> had tried and failed to convert the isochromandione IIIb by using EtOH/HCl and  $Me_2CO/HCl$ , though he was successful in rearranging 4-benzoyliso chroman-1,3-dione into the corresponding isocoumarin derivative by the same reagents.

Conversion of the isochromandiones (III) can also be effected by heating them with acetic anhydride and pyridine at waterbath temperature, but together with the 4-carboxy-isocoumarin derivative (II,  $R_1 = COOH$ ), the 4-acetyl derivative (II,  $R_1 = COMe$ ) and small

3. J. Schnekenburger, a) *Arch. Pharm.*, 1964, **297**, 734 (*C.A.*, 1965, **62**, 13081); b) *ibid.*, 1965, **298**, 4 (*C.A.*, 1965, **62**, 7672); c) *ibid.*, 411 (*C.A.*, 1965, **63**, 18010); d) *ibid.*, 715 (*C.A.*, 1966, **64**, 3468).
4. a) S. Gabriel and A. Neumann, *Ber.*, 1892, **25**, 3563; b) H. Nogami, *J. Pharm. Soc. Japan*, 1941, **61**, 46., *C.A.*, 1941, **35**, 4764.
5. G. Bendz, *Arkiv. Kemi.*, 1959, **14**, 511; *C.A.*, 1960, **54**, 10056.
6. L. A. Mitscher, W. W. Andres and W. McCrae, *Experientia*, 1964, **20**, 258.

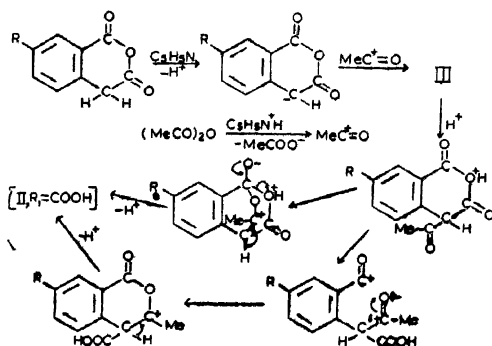
amount of (VI) were also isolated. The 4-acetylisocoumarin-derivative is probably formed *via* acetylation of the isochromandione (III) to give the diacetyl derivative which gets rearranged and then decarboxylated to form the 4-acetyl derivative (II,  $R_1 = \text{COMe}$ ). It may be recalled here that the same products were also obtained when the homophthalic acids (I) were heated directly with acetic anhydride and pyridine, thus suggesting that this reaction probably proceeds *via* the isochromandione formation. On heating with acetic anhydride alone, the isochromandiones (IIIa and IIIb) gave the acetoxy derivatives formed probably by acetylation of their enolic forms to which the constitutions of 3-acetoxy-4-acetyl-7-methoxy-isocoumarin and 3-acetoxy-4-acetylisocoumarin respectively have been assigned. It may be interesting to note that the homophthalic anhydrides do not give colouration with aq.  $\text{FeCl}_3$  but the 4-acetylisochromandiones (III) give intense colouration with alc. and aq.  $\text{FeCl}_3$ , suggesting the existence of their enolic forms. I.R. spectrum of the isochromandione (IIIa) showed a strong band at  $1734\text{ cm}^{-1}$  (for lactonic ring) with bands at  $1614$  and  $1550\text{ cm}^{-1}$ , all characteristic of the isocoumarin structure and a band at  $1654\text{ cm}^{-1}$  for  $> \text{C} = \text{O}$  group of  $-\text{COCH}_3$ , thus confirming the existence of the enolic form (3-hydroxyisocoumarin structure). The characteristic band for free  $-\text{OH}$  is not obtained. This may be due to bonding of the  $-\text{OH}$  with the keto carbonyl group of  $-\text{COCH}_3$  which has also resulted in lowering the frequency of  $> \text{C} = \text{O}$  absorption. Nearly the same I.R. frequency values are reported by Schnekenburger<sup>3c</sup> for the isochromandione (IIIb).

The 4-carboxy-3-methylisocoumarins (II,  $R_1 = \text{COOH}$ ) readily decarboxylated to give the corresponding 3-methylisocoumarins (II,  $R_1 = \text{H}$ ) by heating their methanolic solution with conc.  $\text{H}_2\text{SO}_4$  or by heating them in a metal bath above their m.p. These, incidentally, are better methods for decarboxylation than the one used by Smith *et al.*<sup>2</sup> for decarboxylation of (IIb,  $R_1 = \text{COOH}$ ) using  $\text{Cu}$ /quinoline. The methyl esters of these 4-carboxyisocoumarins have been prepared with diazomethane.

The isochromandione (IIIa) and the isocoumarins (IIa,  $R_1 = \text{H}$ ), (IIa,  $R_1 = \text{COOH}$ ) and (IIa,  $R_1 = \text{COMe}$ ) on treatment with aq.  $\text{NaOH}$  furnished the same benzyl ketone *viz.*, 2-carboxy-4-methoxy-benzyl methyl ketone (IVa) and in the same way 2-carboxybenzyl methyl ketone (IVb) was obtained by the action of aq.  $\text{NaOH}$  on the isochromandione (IIIb), and the isocoumarins (IIb,  $R_1 = \text{H}$ ), (IIb,  $R_1 = \text{COOH}$ ) and (IIb,  $R_1 = \text{COMe}$ ). The reaction naturally takes place by opening of the anhydride or the lactonic ring as the case may be and the resulting products, which in the first three cases being derivatives of  $\beta$ -keto acid, get decarboxylated and in the last case being deriv. of acetylacetone get deacetylated and that is why the isochromandione and all the isocoumarins of the same series give the same benzyl ketone (IV). The benzyl ketones (IVa) and (IVb) readily cyclodehydrated on keeping with 90%  $\text{H}_2\text{SO}_4$  to give quantitative yield of 7-methoxy-3-methylisocoumarin (IIa,  $R_1 = \text{H}$ ) and 3-methylisocoumarin (IIb,  $R_1 = \text{H}$ ) respectively thus providing an alternative route for the synthesis of these isocoumarins in an overall yield of about 60% from homophthalic acids in three stages as shown: (I)  $\rightarrow$  (III)  $\rightarrow$  (IV)  $\rightarrow$  (II,  $R_1 = \text{H}$ ). The benzyl ketones (IVa) and (IVb) on reduction with  $\text{NaBH}_4$  in methanolic solution furnished 7-methoxy-3-methyl-3,4-dihydroisocoumarin (Va) and 3-methyl-3,4-dihydroisocoumarin (Vb) respectively in very good yields. The various reactions discussed above establish unambiguously the structures assigned to the various isocoumarin derivatives. The

structures also find the confirmation in their U.V. and I.R. Spectra. The isocoumarin (IIa,  $R_1 = H$ ) gives I.R. absorption bands at  $1724\text{ cm}^{-1}$  with shoulder at  $1740\text{ cm}^{-1}$  (lactonic ring) and bands at  $1620, 1560\text{ cm}^{-1}$ , all characteristics of isocoumarin ring.\* The isocoumarin (IIa,  $R_1 = COOH$ ) gives I.R. absorption band at  $1740\text{ cm}^{-1}$  (for lactone) with bands at  $1615, 1550\text{ cm}^{-1}$  and a strong band at  $1670\text{ cm}^{-1}$  (for  $>C=O$ ) with  $-OH$  stretching frequencies between  $2550\text{--}2750\text{ cm}^{-1}$  showing presence of  $-COOH$  group. The isocoumarin (IIa,  $R_1 = COMe$ ) gives I.R. band at  $1732\text{ cm}^{-1}$  with shoulder at  $1739\text{ cm}^{-1}$  (lactone) with bands at  $1614$  and  $1560\text{ cm}^{-1}$  and strong absorption band at  $1694\text{ cm}^{-1}$  for  $>C=O$  group of  $-COMe$ . Similar absorption bands are obtained by Smith *et al.*<sup>2</sup> for the isocoumarins (IIb,  $R_1 = COOH$ ), and (IIb,  $R_1 = COMe$ ) respectively.

Under the conditions used, no reaction of acetic anhydride on mono- and diesters of 4-methoxyhomophthalic acid took place in the presence of pyridine, thus suggesting that the reaction takes place on the anhydride of 4-methoxyhomophthalic acid. This is further confirmed by the fact that the same products as obtained from 4-methoxyhomophthalic acid (Ia) were also obtained from the anhydride of Ia by the action of acetic anhydride and pyridine. Acetylation of the  $-CH_2-$  group of the anhydride therefore seems to be the first stage in the reaction. The acetyl derivative gets rearranged at higher temperature due to pyridonium ions in the solution. The rearrangement also takes place in the presence of  $H^+$  ions (strong acid). It is important to note that base like pyridine is essential for acetylation as no reaction was found to take place by treating 4-methoxyhomophthalic acid with acetic anhydride and conc.  $H_2SO_4$ . This suggests the following mechanism for acetylation and rearrangement. The rearrangement may have taken place in one or both possible ways as shown below



The higher reactivity shown by the anhydride of Ia in comparison to that of its ester in the acetylation is due to higher acidity of the  $-CH_2-$  group of the former. The two carbonyl groups of the anhydride retain greater electron withdrawing capacity than those of the ester as the mesomeric shifts of these carbonyl groups are not well competed in the anhydride as in the ester.

\* K. Nakanishi, *Infra red absorption Spectroscopy* (Holden Day Inc and Nankodo Co Ltd.), p. 52.

## EXPERIMENTAL

*Action of acetic anhydride on 4-methoxyhomophthalic acid (Ia).*

i) *With pyridine at room temperature* : 4-Acetyl-7-methoxyisochroman-1,3-dione (IIIa) : 4-Methoxyhomophthalic acid<sup>7</sup> Ia (2 g.) was added in small portions during 15 mins. to a mixture of acetic anhydride (4 ml) and dry pyridine (1 ml) with mechanical stirring. More of acetic anhydride (1 ml) was then added and stirring continued. The acid slowly dissolved to form yellowish green solution and then an yellow solid slowly precipitated. Dry ether (8 ml) was added to the mixture to facilitate the stirring and after 1½ hrs. the solid was filtered, washed well with ether and dried in vacuum; crude yield 1.6 g., m.p. 160–64°. It crystallised from chloroform as shining plates, m.p. 165–66°; yield 1.25 g. (Found : C, 61.1, H, 4.3.  $C_{12}H_{10}O_5$  requires : C, 61.5, H, 4.3%). I.R. spectrum (in KBr) shows bands at 1734, 1654, 1614, 1550 and 1496  $cm^{-1}$ .

ii) *With pyridine at boiling waterbath temperature* : 4-Carboxy- and 4-Acetyl-7-methoxy-3-methylisocoumarins (IIa,  $R_1 = COOH$  and IIa,  $R_1 = COMe$ ) and the compound (VIa) : A mixture of the acid Ia (2 g.), acetic anhydride (4 ml) and dry pyridine (2 ml) was heated on a boiling water bath for 2 hrs. and the product poured into cold water (70 ml), acidulated with conc. HCl (7 ml). The sticky solid product was dissolved in benzene (50 ml) with few drops of ethanol and the aq. filtrate was extracted with ethyl acetate. The benzene solutions and also ethyl acetate extracts were separately shaken repeatedly with aq.  $NaHCO_3$  (in all 24 ml. in each case). The aq.  $NaHCO_3$  solution on acidification gave 4-carboxy-7-methoxy-3-methylisocoumarin (IIa,  $R_1 = COOH$ ) which slowly separated as yellow solid. It was first crystallised from water (charcoal) as tiny needles (m.p. 209–10°; yield 0.33 g.) and then from ethyl acetate as colourless needles, m.p. 210–11° (Found : C, 61.3; H, 4.7.  $C_{12}H_{10}O_5$  requires : C, 61.5; and H, 4.3%). U.V. absorption  $\lambda_{max}^{MeOH}$  230, 270, 348  $m\mu$  ( $\log \epsilon$  4.46, 4.06 and 3.71). I.R. spectrum (in nujol) shows bands at 1740, 1670, 1615, 1550, 1500  $cm^{-1}$  and at 2550–2750  $cm^{-1}$  –OH stretching frequencies.

The benzene solution (S) was concentrated to a small bulk (7–8 ml) and allowed to crystallise when 8-acetyl-5,11-dimethoxy-7-methylnaphtho (1,2-c) isocoumarin (VIa) separated as needles, m.p. 211–13°, yield 0.06 g. It crystallised from benzene as pale pink needles, m.p. 215–16° (Found : C, 73.0; H, 4.8.  $C_{22}H_{18}O_5$  requires : C, 72.9 and H, 4.9%). Benzene was then evaporated from the mother liquor (S) and the residue was extracted in boiling petrol ether (80–100°), (50 ml), charcoaled and then concentrated to a small bulk when 4-acetyl-7-methoxy-3-methylisocoumarin (IIa,  $R_1 = COMe$ ) separated as yellow needles, m.p. 128–32°, yield. 0.25 g. It crystallised from acetone-petrol mixture, m.p. 133–35° (Found : C, 67.6; H, 5.4.  $C_{13}H_{12}O_4$  requires : C, 67.2 and H, 5.2%). I.R. spectrum (in KBr) shows bands at 1739 (shoulder), 1732, 1694, 1634, 1560 and 1500  $cm^{-1}$ .

The reaction of 4-methoxyhomophthalic anhydride (2 g.) with acetic anhydride (4.0 ml) and pyridine (2.0 ml) gave the same 3 products, as above, in nearly the same yield.

iii) *With fused sodium acetate* : The isocoumarin (IIa,  $R_1 = COOH$ ) and a neutral compound (A) : The acid Ia (2 g.), fused sodium acetate (2.5 g.) and acetic anhydride (4 ml)

were heated on a boiling waterbath for 2 hrs. and then poured into water and worked up as in the case (ii) above. Acidification of aq.  $\text{NaHCO}_3$  extract gave 4-carboxy-7-methoxy-3-methylisocoumarin, m.p. and mixed m.p. with the specimen obtained above,  $210-11^\circ$  (yield 0.25 g.). The benzene solution after evaporation of solvent gave a neutral compound (A) which crystallised from benzene as needles (yield 0.070 g., m.p.  $234-35^\circ$ ; Found : C, 61.4 and H, 4.6).

*Rearrangement of the isochromandione IIIa : With  $\text{H}_2\text{SO}_4$  (80%) :* 4-Carboxy-7-methoxy-3-methylisocoumarin (*IIa*,  $R_1 = \text{COOH}$ ) and 7-methoxy-3-methylisocoumarin (*IIa*,  $R_1 = \text{H}$ ) : i) The isochromandione IIIa (0.2 g.) was added in small portions to sulphuric acid (1 ml., 80%) cooled in ice, with shaking till it dissolved. The mixture was left overnight in the refrigerator and was then poured on crushed ice. The white solid product was triturated with aq.  $\text{NaHCO}_3$ . Acidification of the  $\text{NaHCO}_3$  solution gave the 4-carboxyisocoumarin (*IIa*;  $R_1 = \text{COOH}$ ). It crystallised from water as colourless needles, m.p. and mixed m.p. with the previous specimen  $210-11^\circ$ ; yield 0.12 g. The insoluble residue was the isocoumarin (*IIa*;  $R_1 = \text{H}$ ). It crystallised from petrol ether ( $60-80^\circ$ ) as colourless needles, m.p.  $93-94^\circ$ ; yield 0.03 g. (Found : C, 69.5; H, 5.6.  $\text{C}_{11}\text{H}_{10}\text{O}_3$  requires : C, 69.4; H, 5.2%). U.V. absorption  $\lambda_{\text{max}}^{\text{MeOH}}$  230, 269, 348 m $\mu$  ( $\log \epsilon$  4.53, 4.03 and 3.60). I.R. spectrum (in KBr) shows bands at 1740 (shoulder) 1724, 1660, 1600, 1566 and 1500  $\text{cm}^{-1}$ .

ii) The above reaction was carried out by warming the reaction mixture on a waterbath at  $90-95^\circ$  for 45 mins. and then working up as described above in (i). The same two products were obtained but in different yields. The 4-carboxy isocoumarin (*IIa*;  $R_1 = \text{COOH}$ ) yield 0.02 g. and the isocoumarin (*IIa*,  $R_1 = \text{H}$ ) yield 0.10 g.

*With acetic anhydride and pyridine :* 4-Carboxy- and 4-acetyl-7-methoxy-3-methylisocoumarins (*IIa*;  $R_1 = \text{COOH}$  and *IIa*,  $R_1 = \text{COMe}$ ) and the Compound *VIa* : The isochromandione IIIa (1.0 g.), acetic anhydride (2 ml) and dry pyridine (1 ml.) were mixed and heated on a boiling waterbath for 2 hr. and then poured into acidulated water and the product worked up in the same manner as described under the action of acetic anhydride on 4-methoxyhomophthalic acid (ii). The same three substances viz., the 4-carboxyisocoumarin (*IIa*,  $R_1 = \text{COOH}$ ), (m.p.  $210-11^\circ$ ; yield 0.09 g.); the 4-acetylisocoumarin (*IIa*,  $R_1 = \text{COMe}$ ) (m.p.  $133-35^\circ$ ; yield 0.2 g.) and the substance *VIa* (m.p.  $215-16^\circ$ ; yield 0.1 g.) were isolated in the same manner and crystallised. They were identified by taking mixed m.p. with the respective specimens obtained before which showed no lowering.

4-Acetyl-3-acetoxy-7-methoxyisocoumarin : The isochromandione IIIa (0.5 g.) and acetic anhydride (1.5 ml) were heated together on a boiling water bath for 2 hr. and then poured into cold water (20 ml) and left overnight. The solid product was triturated with aq.  $\text{NaHCO}_3$  and the insoluble residue was crystallised from benzene as colourless needles, m.p.  $115-16^\circ$ ; yield 0.27 g. (Found : C, 61.0; H, 4.3.  $\text{C}_{14}\text{H}_{12}\text{O}_6$  requires : C, 60.8, H, 4.3%).

*Decarboxylation of the 4-carboxyisocoumarin (*IIa*,  $R_1 = \text{COOH}$ ) :* 7-methoxy-3-methylisocoumarin (*IIa*,  $R_1 = \text{H}$ ). i) *By heating :* The 4-carboxyisocoumarin (*IIa*,  $R_1 = \text{COOH}$ ) (0.2 g.) was heated in a metal bath at  $275^\circ$  for 30 min., cooled and the residue washed with aq.  $\text{NaHCO}_3$  by trituration and then crystallised from petrol ether ( $60-80^\circ$ ) (charcoal) as colourless needles, m.p. and mixed m.p. with the previous specimen  $93-94^\circ$ , Yield : 0.06 g.

ii) *With sulphuric acid*: The carboxyisocoumarin (0.2 g.) dissolved in methanol (5.0 ml) was mixed with conc.  $\text{H}_2\text{SO}_4$  (0.5 ml) and was refluxed on a waterbath for 16 hr. Methanol was then removed under reduced pressure and the residue diluted with water. The crystalline material obtained was washed with aq.  $\text{NaHCO}_3$  (by trituration) and then crystallised from petrol (60–80°) as needles, m.p. and mixed m.p. with the authentic specimen, 93–94°. Yield: 0.1 g.

*4-Carbomethoxy-7-methoxy-3-methylisocoumarin (IIa,  $R_1 = \text{COOMe}$ )*: Diazomethane solution in ether (20 ml, from 2.06 g. of nitrosomethyl urea) was added with shaking to the ethereal suspension of the carboxyisocoumarin (IIa,  $R_1 = \text{COOH}$ ) (0.2 g.) cooled in ice. After shaking the mixture well it was left overnight in the refrigerator. The colourless crystalline substance obtained after removing ether was washed with aq.  $\text{NaHCO}_3$  and then crystallised from petrol ether (60–80°) as needles m.p. 114–16°; yield 0.19 g. (Found: C, 62.8; H, 5.0.  $\text{C}_{13}\text{H}_{12}\text{O}_5$  requires: C, 62.9 and H, 4.8%).

*2-Carboxy-4-methoxybenzyl methyl ketone (IVa)*: The isochromandione IIIa (1 g.) with aq.  $\text{NaOH}$  (20 ml., 10%) was heated to reflux temperature for 1½ hrs. On acidification of the resulting clear solution (filtered, if necessary) with conc.  $\text{HCl}$ , a crystalline solid separated with evolution of  $\text{CO}_2$ . It crystallised from water (charcoal) as colourless needles, m.p. 133–34°; yield 0.65 g. (crude yield 0.76 g.) (Found: C, 63.2; H, 5.9.  $\text{C}_{11}\text{H}_{12}\text{O}_4$  requires: C, 63.4, H, 5.7%).

The carboxyisocoumarin (IIa,  $R_1 = \text{COOH}$ ), the 4-acetyl-isocoumarin (IIa,  $R_1 = \text{COMe}$ ) and 3-acetoxy-4-acetyl-7-methoxy-isocoumarin by treatment with aq.  $\text{NaOH}$  in the same manner as described above gave the same ketone (IVa) identified by taking mixed m.p. with each other which showed no lowering.

*Cyclodehydration of the ketone (IVa): 7-methoxy-3-methylisocoumarin (IIa,  $R_1 = \text{H}$ )*: The ketone IVa (0.5 g.) was mixed with sulphuric acid (1.5 ml, 90%) and was left overnight at room temperature. A green coloured solution resulted. It was poured on crushed ice. The solid product was washed with aq.  $\text{NaHCO}_3$  by trituration and then crystallised from petrol ether (60–80°) as colourless needles, m.p. and mixed m.p. with the previous specimen 93–94°; yield 0.36 g.

(±) *7-Methoxy-3-methyl-3,4-dihydroisocoumarin (Va)*: Sodium borohydride (0.35 g.) was added slowly to a solution of the ketone IVa (0.5 g.) in methanol (8 ml) and the reaction mixture was kept aside at room temperature for 2 hrs. It was then acidified with conc.  $\text{HCl}$  and was diluted with water (40 ml.) when slowly a colourless solid separated on scratching and cooling. It was washed with aq.  $\text{NaHCO}_3$  (by trituration) and then was crystallised from petrol (60–80°), m.p. 90–92°; yield 0.35 g.; (Found: C, 68.3; H, 5.8.  $\text{C}_{11}\text{H}_{12}\text{O}_3$  requires: C, 68.7; H, 6.2). Mixed m.p. with an authentic specimen of 7-methoxy-3-methyl-isocoumarin showed a marked depression.

*Action of acetic anhydride on homophthalic acid (Ib).*

i) *With pyridine at room temperature*: *4-Acetylisochroman-1,3-dione (IIIb)*: Homophthalic acid<sup>8</sup> Ib (2 g.) was added slowly during 15 minutes to a mixture of acetic anhydride

(4 ml) and dry pyridine (1 ml) with mechanical stirring. After adding more of acetic anhydride (1 ml) the reaction was carried out and worked up as described under similar reaction on 4-methoxyhomophthalic acid (Ia). The solid product (crude yield, 1.65 g.) crystallised from chloroform as shining plates, m.p. 160–61° (Lit.<sup>3b</sup> m.p. 162.5°), yield 1.3 g. (Found : C, 64.4; H, 4.2. Calculated for  $C_{11}H_8O_4$  C, 64.7; H, 3.9%). It decomposes slowly on keeping.

ii) *With pyridine at boiling waterbath temperature : 4-Carboxy- and 4-acetyl-3-methylisocoumarins (IIb,  $R_1 = COOH$  and IIb,  $R_1 = COMe$ ) and the compound VIb :* Homophthalic acid Ib (2 g.), acetic anhydride (4 ml) and dry pyridine (2 ml) were mixed and heated on a boiling water bath for 2 hr. and then poured into cold water (70 ml) acidulated with conc. HCl (7 ml.). The reaction product was then worked up as described under the similar reaction on 4-methoxy-homophthalic acid (Ia).

Aq.  $NaHCO_3$  solution on acidification gave 4-carboxy-3-methylisocoumarin (IIb,  $R_1 = COOH$ ) as yellow solid. It was crystallised first from water (charcoal) as tiny needles (m.p. 217–19°, yield 0.21 g.) and then from ethyl acetate as colourless needles, m.p. 220–21° (Lit.<sup>2</sup> m.p. 224°). (Found : C, 64.8; H, 3.7. Calculated for  $C_{11}H_8O_4$  : C, 64.7 and H, 3.9%). On concentration of the benzene solution (S) (6–7 ml.), 8-acetyl-7-methylnaphtho (1,2-c) isocoumarin (VIb) separated as needles, yield, 0.07 g. Crystallised from benzene as colourless needles, m.p. 185–86° (Lit.<sup>2</sup> m.p. 190°, Found : C, 79.1; H, 4.6. Calculated for  $C_{20}H_{14}O_3$  : C, 79.4 and H, 4.6%). After removing benzene from the mother liquor of original benzene solution (S), a solid product was obtained. It was extracted in petrol ether (40–60°), charcoaled and concentrated to a small bulk when 4-acetyl-3-methylisocoumarin (IIb,  $R_1 = COMe$ ) separated as needles. It crystallised from light petrol ether as colourless needles, m.p. 94–95°, yield 0.16 g. (Lit.<sup>2</sup> m.p. 99°) (Found : C, 71.6; H, 5.1. Calculated for  $C_{12}H_{10}O_3$  : C, 71.2, and H, 4.9%).

#### *Rearrangement of the isochromandione (IIIb) :*

i) *With  $H_2SO_4$  (80%) :* 4-Carboxy-3-methylisocoumarin (IIb,  $R_1 = COOH$ ) and 3-methylisocoumarin (IIb,  $R_1 = H$ ) : The isochromandione (IIIb) (0.2 g.) was added in small portions to  $H_2SO_4$  (1 ml., 80%), cooled in ice with shaking till it dissolved. The mixture was left in a refrigerator overnight and then worked up as in the case of the isochromandione IIIa. Acidification of aq.  $NaHCO_3$  solution gave 4-carboxy-3-methylisocoumarin (IIb,  $R_1 = COOH$ ). It crystallised from water as colourless needles, m.p. and mixed m.p. with the previous sample, 220–221°, yield 0.11 g. The residue, insoluble in aq.  $NaHCO_3$ , was 3-methylisocoumarin (IIb,  $R_1 = H$ ), which crystallised from petrol (40–60°) as colourless needles, m.p. 71–72° (Lit.<sup>2,4</sup> m.p. 73–74°). Yield 0.04 g. (Found : C, 74.5; H, 5.3. Calculated for  $C_{10}H_8O_2$  : C, 75.0; H, 5.0%).

ii) The above reaction was carried out by warming the reaction mixture at 90–95° for 45 min. and then worked up as described above. The same two products were obtained in different yields. The 4-carboxyisocoumarin (IIb,  $R_1 = COOH$ ), yield 0.016 g. and the isocoumarin (IIb,  $R_1 = H$ ), yield 0.10 g.

With acetic anhydride and pyridine : 4-Carboxy- and 4-acetyl-3-methylisocoumarin (*I Ib*,  $R_1 = \text{COOH}$  and *I Ib*,  $R_1 = \text{COMe}$ ) and the compound *VIb*. The isochromandione *IIIb* (1 g.), acetic anhydride (2 ml) and dry pyridine (1 ml) were heated together on a boiling water bath for 2 hrs. and then poured into acidulated water. The reaction product was worked up as described under action of acetic anhydride on homophthalic acid *Ib(ii)*. The same three substances, viz.: the 4-carboxyisocoumarin (*I Ib*,  $R_1 = \text{COOH}$ ) (m.p. 220–21°, yield 0.08 g.), the 4-acetylisocoumarin (*I Ib*,  $R_1 = \text{COMe}$ ) (m.p. 94–95°, yield 0.06 g.) and the compound *VIb* (m.p. 185–86°, yield 0.07 g.) were isolated and crystallised in the same manner. They were identified by taking mixed m.p. with the respective specimens obtained earlier with no lowering.

4-Acetyl-3-acetoxyisocoumarin : The isochromandione *IIIb* (0.5 g.) and acetic anhydride (2.0 ml) were heated together on a boiling waterbath for 3 hrs and then poured into cold water (30 ml) and left overnight. The solid product was triturated with aq.  $\text{NaHCO}_3$  and the insoluble residue was crystallised from petrol ether (60–80°) as shining plates, m.p. 104–05°, yield 0.09 g. (Found : C, 63.3; H, 4.4.  $\text{C}_{13}\text{H}_{10}\text{O}_5$  requires : C, 63.4; H, 4.1%).

Decarboxylation of the 4-carboxyisocoumarin (*I Ib*,  $R_1 = \text{COOH}$ ) : 3-methylisocoumarin (*I Ib*,  $R_1 = \text{H}$ ).

i) *By heating* : The 4-carboxyisocoumarin (*IIa*,  $R_1 = \text{COOH}$ ) (0.2 g.) was heated in a metalbath at 270° for 35 min. (evolution of  $\text{CO}_2$ ), then cooled and the residue was washed with aq.  $\text{NaHCO}_3$  by trituration and then crystallised from petrol ether (40–60°) (charcoal) as colourless needles, m.p. and mixed m.p. with the previous specimen, 71–72°, yield 0.05 g.

ii) *With sulphuric acid* : The 4-carboxyisocoumarin (0.2 g.) dissolved in methanol (6 ml) was mixed with conc.  $\text{H}_2\text{SO}_4$  (0.5 ml) and refluxed on a waterbath for 16 hr. The reaction product was worked up as described under decarboxylation of *IIa* ( $R_1 = \text{COOH}$ ) (ii) and the aq.  $\text{NaHCO}_3$ -insoluble product was crystallised from petrol (40–60°) (charcoal) as colourless needles, m.p. and mixed m.p. with the authentic specimen, 71–72°; yield 0.08 g.

4-Carbomethoxy-3-methylisocoumarin (*I Ib*,  $R_1 = \text{COOMe}$ ) : Diazomethane solution in ether (20 ml. from 2.06 g., nitrosomethylurea) was added with shaking to ethereal suspension of the carboxyisocoumarin (*I Ib*,  $R_1 = \text{COOH}$ ) (0.2 g.) cooled in ice. After shaking the mixture well, it was left overnight in refrigerator and then worked up as in the case of (*IIa*,  $R_1 = \text{COOMe}$ ). After trituration with aq.  $\text{NaHCO}_3$ , the insoluble residue was crystallised from petrol ether (60–80°) in colourless needles, m.p. 94–95°, Yield 0.18 g. (Found : C, 66.4; H, 4.5.  $\text{C}_{12}\text{H}_{10}\text{O}_4$  requires : C. 66.1; H, 4.6%).

2-Carboxybenzyl methyl ketone (*IVb*) : The mixture of the isochromandione (1 g.) and aq.  $\text{NaOH}$  (20 ml) 10%) was refluxed for 1½ hrs. The resulting solution (filtered, if necessary) was acidified with conc.  $\text{HCl}$ , (evolution of  $\text{CO}_2$ ) and then extracted with benzene. The benzene extracts were washed with water, dried and concentrated to small bulk (6–7 ml). After diluting it with petrol ether (40–60°) to crystallisation point, the ketone (*IVb*) separated as pale yellow needles, m.p. 116–18°; yield 0.74 g. Recrystallisation from benzene gave

colourless cubes, m.p. 120–21° (Lit.<sup>3a,9,2</sup> m.p., 122°, 118–19°, 120°). (Found : C, 67.9; H, 5.5; calculated for  $C_{10}H_{10}O_3$  : C, 67.4; H, 5.6%).

The carboxyisocoumarin (IIb,  $R_1 = \text{COOH}$ ), the 4-acetylisocoumarin (IIb,  $R_1 = \text{COMe}$ ) and 3-acetoxy-4-acetylisocoumarin on treatment with aq. NaOH in the same manner as described above gave the same ketone (IVb). The products were identified by taking mixed m.p. with each other which showed no lowering. N.B. Hydrolysis of the isochromandione (IIIb) and the isocoumarin (IIb,  $R_1 = \text{COMe}$ ) was reported earlier to give the ketone (IVb) by Schnekenburger<sup>3a</sup> and Smith *et al.*<sup>2</sup> respectively.

*Cyclodehydration of the ketone (IVb) : 3-methylisocoumarin (IIb,  $R_1 = \text{H}$ ) :* The ketone IVb (0.5 g.) was mixed with sulphuric acid (1.5 ml, 90%) and left overnight when a dark red-coloured solution resulted. It was poured on crushed ice. The solid product after triturating with aq.  $\text{NaHCO}_3$ , was crystallised from petrol (40–60°) as colourless needles, m.p. and mixed m.p. with the previous specimen, 71–72°. Yield 0.35 g.

*(±)3-Methyl-3,4-dihydroisocoumarin (Vb) :* Sodium borohydride (0.37 g.) was added slowly to the solution of the ketone IVb (0.5 g.) in methanol (7 ml) and the reaction mixture was kept at the room temperature for 2 hrs. It was then acidified with conc. HCl, diluted with water (50 ml.) and extracted with ether. Evaporation of solvent gave an oil which distilled at 124°/2 mm. It solidified on cooling, m.p. 30°\* (Found : C, 73.8; H, 6.2.  $C_{10}H_{10}O_2$  requires : C, 74.1; H, 6.2%).

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\* The compound (Vb), synthesised from 3-methylisochroman by oxidation is reported in Lit.<sup>10</sup> to have m.p. 53°. The present synthesis is unambiguous and this synthetic method is used successfully for synthesis of many of 3,4-dihydroisocoumarins in Lit.<sup>11,5</sup>.

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