

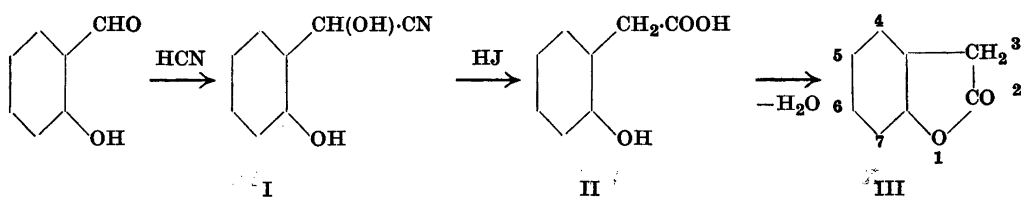
Some New Derivatives of Isocoumaranone

OTTO AUBERT, ELSE AUGDAHL and ENDRE BERNER

Universitetets Kjemiske Institutt, Blindern — Oslo, Norway

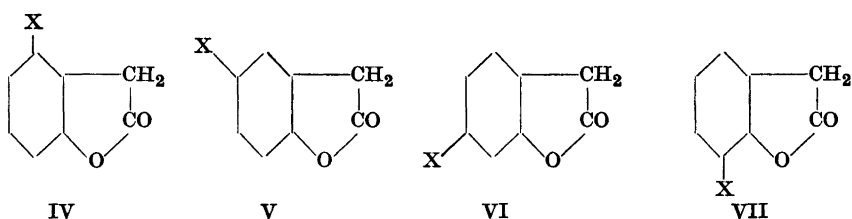
It has been found previously in this institute^{1,2} that certain derivatives of isocoumaranone will undergo some interesting reactions. In the first place they show a pronounced tendency to pass into mostly yellow-coloured enolic forms of varying stability. The enolization may take place either by the action of alkali, when the enol form will be present as the salt, or by the action of diazomethane, in which case the methyl ether of the enol form is formed. Secondly, the isocoumaranone derivatives are easily oxidized to intensely red-coloured bimolecular compounds with an indigoid structure. Up to the present relatively few simple derivatives of isocoumaranone are known, and we have therefore found it of interest to prepare some new compounds of this type. It ought to be remarked that isocoumaranone in the literature will be found under several other names, *e.g.* 2-benzofuranone and 2-keto-2.3-dihydrobenzofuran.

Isocoumaranone and its derivatives can be regarded as the lactones of *o*-hydroxyphenylacetic acid and its derivatives respectively. Isocoumaranone itself (III) was first prepared by Baeyer and Fritsch³ by distillation of *o*-hydroxyphenylacetic acid (II). A convenient method for the preparation of the latter was introduced by Czaplicki, v. Kostanecki and Lampe⁴ consisting in the addition of hydrogen cyanide to salicylic aldehyde and boiling the hydroxymandelonitrile (I) with hydriodic acid. This method has been used by us, but instead of salicylic aldehyde its homologues and carboxylic acids formed the starting materials. The latter substances were prepared from the



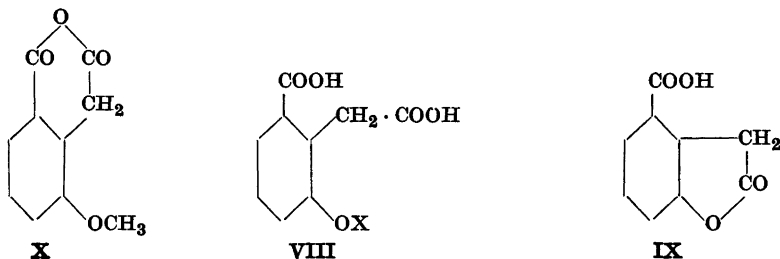
isomeric cresols and hydroxybenzoic acids respectively by introducing an aldehyde group according to the well-known method of Reimer-Tiemann. In some cases it was found advantageous to methylate the hydroxyaldehydes before the addition of hydrogen cyanide. The details are given in the experimental part.

The following 8 new derivatives of isocoumaranone have been prepared, *viz.* the monomethyl-isocoumaranones with methyl in the positions 4,5,6, and 7 (IV–VII, X = CH₃) and the corresponding carboxylic acids (IV–VII, X = COOH)



The corresponding substituted hydroxyphenylacetic acids are also as far as we know described here for the first time. The transformation of these acids into the isocoumaranones was in most cases effected very easily by sublimation either at ordinary pressure or in a vacuum. In one case, however, there was a considerable resistance against the splitting off of water, *viz.* by the 2-hydroxy-3-carboxyphenylacetic acid leading to the isocoumaranone derivative VII (X = COOH). Obviously there is a steric hindrance due to the carboxylic group in ortho position to hydroxyl. In order to obtain this isocoumaranone it was therefore necessary to treat the hydroxy-acid with acetic anhydride.

One of the isocoumaranone carboxylic acids, *viz.* that one with carboxyl in the 4-position was prepared in a different way than the others. The 2-methoxy-6-methylphenylacetic acid was oxidized to 2-methoxy-6-carboxyphenylacetic acid (VIII, X = CH₃) which was demethylated to the corresponding hydroxy-acid (VIII, X = H). This could theoretically split off water in two



ways, giving either the lactone (isocoumaranone) or, being a derivative of homophthalic acid, an acid anhydride. It could, however, be shown that on sublimation in a vacuum the isocoumaranone IX only was formed as the product gave no colour with ferric chloride. On the other hand the methoxy-acid (VIII, X = CH₃) by sublimation gave the methoxyhomophthalic anhydride (X). As in the case of homophthalic anhydride itself X gave a yellow colour with alkali due to an enolization as first described by Dieckmann⁵. The yellow colour was in this case stronger and more persistent than that occurring when alkali was added to the isocoumaranone carboxylic acids described in this paper. Obviously the enolic form of the 5-ring is less stable than that of the 6-ring. It ought, however, to be remarked that one of us¹ previously has described very stable enolic forms of isocoumaranone derivatives. Thus in one case the free enol form could be isolated in the crystalline state, as could the methyl ether of the enol form. We are of the opinion that the stability of these enolic forms is dependent upon how many substituents the isocoumaranone carries in the benzene nucleus and of the character of the substituents. We shall return to this question on a later occasion.

EXPERIMENTAL

(Melting points not corrected)

The methylisocoumaranones

The four isomeric methylsalicylic aldehydes were prepared from the isomeric cresols according to Tiemann and Schotten⁶. They were separated from the *p*-hydroxyaldehydes by distillation with steam. The two isomers obtained from *m*-cresol had to be separated by the method given by Anselmino⁷. All four methylsalicylic aldehydes were methylated with methyl sulphate according to Simonsen⁸.

Preparation of the nitriles. The sodium bisulphite compound of a methylsalicylic aldehyde was shaken with a concentrated solution of potassium cyanide, when the nitrile separated as an oil. An ethereal solution of this was shaken with a solution of sodium bisulphite in order to remove excess of aldehyde. After drying the ethereal solution the ether was distilled off in a vacuum.

2-Methoxy-3-methylmandelonitrile could only be obtained as a viscous yellow oil and had to be used as such.

2-Methoxy-4-methylmandelonitrile crystallized but could not be purified sufficiently for analysis.

The two other nitriles were obtained pure by repeated crystallization from ether-ligroin.

2-Methoxy-5-methylmandelonitrile, m.p. 37.5°. Yield 80 % (from methylated aldehyde).

Found C 67.63, 67.72 H 6.26, 6.24 N 7.79, 7.75

C₁₀H₁₁O₂N

Calc. » 67.78 » 6.26 » 7.91

2-Methoxy-6-methylmandelonitrile, m.p. 68°, yield 60 %.

Found C 67.87, 67.79 H 6.38, 6.37 N 7.80, 7.78

The *hydroxy-methylphenylacetic acids* were prepared by boiling the corresponding nitriles four hours with ten times their weight of hydriodic acid ($d = 1.7$) in the presence of a little red phosphorus. After diluting with water the acids were extracted with ether and free iodine removed by shaking with a solution of sodium thiosulphate. From the dried solutions the acids were obtained as crystalline masses. In one case (2-hydroxy-6-methylphenylacetic acid) the crude product was a mixture with the corresponding isocoumaranone. It was therefore dissolved in alkali and the free phenylacetic acid extracted with ether after adding hydrochloric acid. All four isomeric acids were easily soluble in ether, ethanol, acetone, and ethyl acetate, but only slightly soluble in ligroin. But for the 2-hydroxy-3-methyl isomer they were very little soluble in cold benzene. The 2-hydroxy-6-methyl isomer was considerably more soluble in water than the others.

2-Hydroxy-3-methylphenylacetic acid (A) was crystallized from ligroin. M.p. 88°. Yield 45 % (from the nitrile).

	Found	C 64.95, 65.01	H 6.20, 6.18	M 165.1, 165.0
$C_9H_{10}O_3$	Calc.	» 65.05	» 6.07	» 166.2

2-Hydroxy-4-methylphenylacetic acid (B) was purified by repeatedly dissolving in ether and precipitating by adding ligroin. M.p. 124°; yield 45 %.

	Found	C 65.15, 65.18	H 6.06, 6.13	M 165.4, 166.0
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2-Hydroxy-5-methylphenylacetic acid (C). Recrystallized from benzene, m.p. 123.5°. Yield 70 %.

	Found	C 65.18, 65.03	H 6.15, 6.04	M 165.3, 165.7
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2-Hydroxy-6-methylphenylacetic acid (D) was purified by crystallization from ether-ligroin. M.p. 110.5°; yield 65 %.

	Found	C 65.10, 65.04	H 6.22, 6.17	M 165.8, 165.4
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The *methylisocoumaranones* were obtained directly from the described phenylacetic acids by splitting off water.

7-Methylisocoumaranone, by sublimation of A in a vacuum, m.p. 98°.

	Found	C 72.97, 72.73	H 5.56, 5.46
$C_9H_8O_2$	Calc.	» 72.96	» 5.44

6-Methylisocoumaranone, by sublimation of B at atmospheric pressure, had about the same solubility as B. M.p. 73°.

	Found	C 72.98, 72.85	H 5.40, 5.39
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5-Methylisocoumaranone, by sublimation of C in a vacuum, was more soluble in ligroin than C. M.p. 74°.

	Found	C 72.81, 72.90	H 5.56, 5.45
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4-Methylisocoumaranone, by sublimation of D at atmospheric pressure, was less soluble in water than D. Recrystallized from petroleum ether, m.p. 93.5°.

	Found	C 73.00, 72.86	H 5.36, 5.42
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The methylisocoumaranones gave as expected no colour reaction with ferric chloride. On boiling with water a partial hydrolysis took place, and the solution gave a blue colour with ferric chloride. The hydrolysis became complete by dissolving in sodium hydroxide. From the acidified solutions the phenylacetic acids were extracted with ether. After recrystallization they had the same m.p. as the original acids.

The isocoumaranone carboxylic acids

The carboxy-hydroxybenzaldehydes were prepared from the three isomeric hydroxy-benzoic acids by current methods⁹ (in the parenthesis m.p. from literature).

3-Carboxy-2-hydroxybenzaldehyde m.p.	179°	(179°)
4- » 2- » »	233—34°	(234°)
5- » 2- » »	244—45°	(243—44°)
3- » 4- » »	248°	(248—49°)

Addition of hydrogen cyanide. The crystalline sodium bisulphite compound of one of the aldehydes was added to a saturated solution of potassium cyanide and the solution stirred until the reaction was complete. After acidifying with mineral acid the nitrile was extracted with ether, the ethereal solution dried with sodium sulphate, and most of the ether distilled off. The rest of the ether was removed in a vacuum desiccator when the nitrile was obtained in the crystalline state. Only one of the nitriles, *viz.* 5-carboxy-2-hydroxymandelonitrile, was purified sufficiently for analysis by crystallizing several times from ether-ligroin.

	Found	C 56.02, 55.98	H 3.65, 3.60
$C_9H_7O_4N$	Calc.	» 55.96	» 3.65

Preparation of the *carboxy-hydroxyphenylacetic acids*. The nitriles were boiled for five hours with 20 times their weight of hydriodic acid (1.7) and a little red phosphorus. In two cases the phenylacetic acid separated already on diluting with water. It was filtered off together with excess of red phosphorus, the mixture washed with a cold solution of potassium iodide in order to remove iodine, and then separated from the phosphorus by means of ethanol. In two other cases the phenylacetic acid had to be extracted with ether and the ethereal solution freed from iodine by shaking with sodium thio-sulphate. The acids were soluble in ether, ethanol, and acetone, slightly soluble in cold water and very slightly soluble in benzene.

3-Carboxy-2-hydroxyphenylacetic acid. Crystallized from dilute ethanol, m.p. 251—52°. Violet colour with ferric chloride.

	Found	C 54.94, 55.08	H 4.31, 4.15	M 197.0, 197.2
$C_9H_8O_5$	Calc.	» 55.11	» 4.11	» 196.15

4-Carboxy-2-hydroxyphenylacetic acid was recrystallized from dilute hydrochloric acid and obtained as colourless needles with m.p. 215—16°. It gave red colour with ferric chloride.

	Found	C 54.93, 55.01	H 4.15, 4.26	M 194.4, 193.2
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5-Carboxy-2-hydroxyphenylacetic acid was crystallized alternately from dilute hydrochloric acid and ether-ligroin. M.p. 192—93°. Violet colour with ferric chloride.

	Found	C 54.84, 55.03	H 4.23, 4.02	M 194.2, 195.8
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3-Carboxy-4-hydroxyphenylacetic acid was obtained as small colourless needles on crystallizing alternately from water and dilute ethanol. M.p. 204—205°. Violet colour with ferric chloride.

	Found	C 55.18, 55.24	H 4.17, 4.15	M 198.8
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The 6-carboxy-2-hydroxyphenylacetic acid was prepared in the following way. To 2-hydroxy-6-methylphenylacetic acid (3 g) was added 30 % sodium hydroxide (9 ml) and dimethylsulphate (6 ml) and the mixture shaken for some time at 50°. The methoxy-ester which separated as an oil was not isolated but saponified at once by adding sodium hydroxide (10 ml) and boiling till the oil had dissolved. By adding mineral acid the *2-methoxy-6-methylphenylacetic acid* separated and was recrystallized from dilute ethanol, at the same time decolourizing with active carbon. M.p. 150—152°. Yield 80 %.

	Found	C 66.61, 66.71	H 6.78, 6.76	CH_3O 17.30, 17.20	M 181.1, 180.7
$C_{10}H_{12}O_3$	Calc.	» 66.65	» 6.71	» 17.22	» 180.2

A solution of 2-methoxy-6-phenylacetic acid (2 g) in 2N sodium hydroxide (7 ml), diluted to 100 ml, was heated to 80° and 120 ml 5 % potassium permanganate added in small portions during two hours. After reducing excess of permanganate and filtering off the manganese dioxide, the solution was concentrated to a small volume and sufficient 5N sulphuric acid added. The precipitate consisted of a mixture of the starting material and 6-carboxy-2-methoxyphenylacetic acid. The latter could be obtained in a pure state by fractional crystallization from acetone. M.p. 191°. It was also soluble in ether, ethano and glacial acetic acid, but very little soluble in benzene and ligroin.

Found C 57.15, 57.03 H 4.88, 4.86 CH₃O 14.75, 14.78 M 212.0, 211.0
 C₁₀H₁₀O₅ Calc. » 57.14 » 4.80 » 14.76 » 210.18

6-Carboxy-2-hydroxyphenylacetic acid was obtained from the preceding methoxy-acid by boiling with hydriodic acid as described above. It was crystallized from ether-ligroin. M.p. 158°.

Found C 54.98, 55.25 H 4.27, 4.23 M 195.2, 195.0
 C₉H₈O₅ Calc. » 55.11 » 4.11 » 196.15

The isocoumaranone carboxylic acids. Of the four isomeric carboxy-2-hydroxyphenylacetic acids the three very easily split off water on sublimation in a vacuum, giving the corresponding isocoumaranone carboxylic acids. When the fourth, 3-carboxy-2-hydroxyphenylacetic acid, was sublimated in a vacuum only a partial dehydration took place. Even after sublimating seven times the product still gave a violet colour with ferric chloride. The acid was therefore boiled for two hours with 15 times its weight of acetic anhydride. Having removed excess of acetic anhydride the residue was sublimated in a vacuum, giving the pure isocoumaranone-7-carboxylic acid, which gave no colour with ferric chloride. The isocoumaranone carboxylic acids were soluble in ether, ethanol, and acetone, but not in cold water. Analyses are given below. Their acidities were determined by dissolving in a sufficient amount of alkali for opening the lactone ring and titrating excess of alkali.

	M.p.	C	H	M
<i>Isocoumaranone-7-carboxylic acid</i>	266°	60.59, 60.56	3.42, 3.48	181.6,
» 6- » »	210°	60.47, 60.40	3.32, 3.47	180.8, 180.0
» 5- » »	232°	60.64, 60.66	3.48, 3.50	173.4, 177.0
» 4- » »	191°	60.71, 60.49	3.56, 3.57	176.9, 179.7
» C ₉ H ₆ O ₄ Calc.		60.68	3.40	178.14

o-Methoxyhomophthalic anhydride, by sublimation of 6-carboxy-2-methoxyphenylacetic acid in a vacuum, had m.p. 153°.

Found C 62.40, 62.30 H 4.35, 4.27
 C₁₀H₈O₄ Calc. » 62.50 » 4.19

SUMMARY

Four isomeric methylisocoumaranones and four isomeric isocoumaranone carboxylic acids, all with the substituents in the benzene nucleus, have been prepared from the corresponding substituted 2-hydroxyphenylacetic acids which are also described. In the case of the carboxy-2-hydroxyphenylacetic acid with the carboxyl group in ortho position to hydroxyl there is a marked steric hindrance against the formation of the corresponding isocoumaranone

derivative. The tendency of isocoumaranone derivatives to pass into enol forms by the action of alkali or of diazomethane in the presence of methanol as well as the stability of the enol forms seem to increase when more substituents are introduced in the benzene nucleus.

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