1137. *Oxygen Heterocycles. Part XI.*[1] *The Condensation of Phenols with Homophthalic Acids and Anhydrides*

By A. Rose, N. P. Buu-Hoï, and P. Jacquignon

The syntheseis of substituted 3-hydroxyarylisocoumarins by condensation of homophthalic acid and anhydride and their 4-substituted derivatives is investigated, and a mechanism for this reaction is proposed. These isocoumarins readily undergo alkali-catalysed hydrolysis to substituted deoxybenzoin-*o*-carboxylic acids.

The condensation of homophthalic anhydride with phenol in the presence of a dehydrating agent, thought by Kauffmann [2] to lead to phenolhomophthalein, was later shown [3] to give 3-*p*-hydroxyphenylisocoumarin (I), and the generality of this isocoumarin synthesis has since been established.[4,5] This study has now been taken up anew with a view to assessing the influence of structural factors on both the homophthalic and the phenol side, and for investigating certain biological properties of the 3-hydroxyarylisocoumarins thus obtained.

[1] Part X, N. P. Buu-Hoï, N. D. Xuong, and N. V. Bac, *J.*, 1964, 173.
[2] H. P. Kauffmann, *Z. angew. Chem.*, 1927, **40**, 831.
[3] N. P. Buu-Hoï, *Compt. rend.*, 1939, **209**, 321.
[4] N. P. Buu-Hoï, *Bull. Soc. chim. France*, 1944, **11**, [5], 338.
[5] A. J. S. Sorie and R. H. Thomson, *J.*, 1955, 2244.

In the first place, it was found that the reaction could be simplified by replacing homophthalic anhydride by the corresponding acid; this modification was applied with success to the synthesis of a number of new 3-*o*- and 3-*p*-hydroxyarylisocoumarins, listed in Table 1.

TABLE 1

3-Substituted isocoumarins (I)

		Found (%)				Required (%)		
Aryl substituent	M. p.	C	H	O	Formula	C	H	O
2-Hydroxy-5-methylphenyl	169°	76·2	4·8	—	$C_{16}H_{12}O_3$	76·2	4·8	—
4-Hydroxy-3-isopropylphenyl	198	76·6	6·1	17·1	$C_{18}H_{16}O_3$	77·1	5·8	17·1
2-Hydroxy-3,5-dimethylphenyl	172	76·4	5·6	18·2	$C_{17}H_{14}O_3$	76·7	5·3	18·0
2-Hydroxy-4,5-dimethylphenyl	178	76·6	5·6	17·9	$C_{17}H_{14}O_3$	,,	,,	,,
4-Hydroxy-2,3-dimethylphenyl	184	76·4	5·6	18·3	$C_{17}H_{14}O_3$	,,	,,	,,
4-Hydroxy-3,5-dimethylphenyl	212	76·4	5·4	—	$C_{17}H_{14}O_3$	,,	,,	—

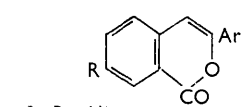
TABLE 2

3-Substituted 7-nitroisocoumarins (II) [a]

		Found (%)				Required (%)		
Aryl substituent	M. p.	C	H	N	Formula	C	H	N
4-Hydroxyphenyl [b]	255°	63·4	3·6	4·8	$C_{15}H_9NO_5$	63·6	3·2	5·0
4-Hydroxy-3-methylphenyl [c] ...	257 (decomp. >250)	64·7	3·8	4·6	$C_{16}H_{11}NO_5$	64·6	3·7	4·7
4-Hydroxy-2-methylphenyl	255	—	—	4·7	$C_{16}H_{11}NO_5$	—	—	,,
2-Hydroxy-5-methylphenyl	249 (decomp. >240)	64·4	4·0	4·9	$C_{16}H_{11}NO_5$	64·6	3·7	4·7
2-Hydroxy-4,5-dimethylphenyl	258	65·3	4·5	4·5	$C_{17}H_{13}NO_5$	65·6	4·2	4·5
4-Hydroxy-2,6-dimethylphenyl [d]	247 (decomp. >240)	65·5	4·5	4·7	$C_{17}H_{13}NO_5$	,,	,,	,,
4-Hydroxy-3,5-dimethylphenyl	316	65·2	4·3	4·6	$C_{17}H_{13}NO_5$	,,	,,	,,
4-Hydroxy-2,3-dimethylphenyl	248 (decomp. >240)	65·5	4·2	4·0	$C_{17}H_{13}NO_5$	,,	,,	,,
4-Hydroxy-2,5-dimethylphenyl	244 (decomp. >238)	65·3	4·3	4·7	$C_{17}H_{13}NO_5$	,,	,,	,,

[a] All these isocoumarins were best recrystallised from dioxan and were lemon-yellow prisms [b] Found: O, 28·0. Reqd.: O, 28·3%. [c] Found: O, 26·6. Reqd.: O, 26·9%. [d] Obtained from 1,3,5-xylenol; the structure of this compound is uncertain in view of the possibility of the xylenol to undergo condensation *ortho* to the phenol group.

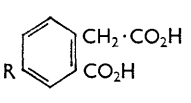
In this condensation, methyl substitution enhanced the reactivity of the phenol component (as shown by the high yields recorded with the xylenols), but chloro-substitution had a deactivating effect, as no isocoumarin was obtained from *o*-chlorophenol. On the other hand, the presence of a nitro-group in the molecule of homophthalic acid did not impede the reaction (although yields were lower), and a series of 3-aryl-7-nitroisocoumarins (II), listed in Table 2, was obtained by condensation of phenol, cresols, and xylenols with 4-nitrohomophthalic acid (IV; R = NO_2) or its anhydride.



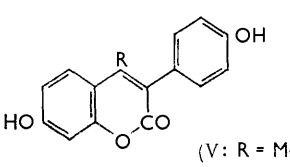
(I: R = H)

(II: R = NO_2)

(III: R = OMe)



(IV)



(V: R = Me, Pr)

In view of the œstrogenic activity of synthetic dihydroxyphenylcoumarins [6] of structural type (V) and of the natural coumestrol [7] (VI), it was interesting to prepare dihydroxylated

[6] C. Mentzer, P. Gley, D. Molho, and D. Billet, *Bull. Soc. chim. France*, 1946, **13**, [5], 211.
[7] E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, and G. O. Kohler, *J. Amer. Chem. Soc.*, 1958, **80**, 3939, 4381.

isocoumarins with a similar molecular configuration. These 7-hydroxy-3-hydroxyarylisocoumarins (VII) [listed in Table 3, along with isomeric 7-hydroxy-3-(*o*-hydroxyaryl)isocoumarins], were obtained by two methods: (*a*) direct condensation of 4-hydroxyhomophthalic acid with various *p*-unsubstituted phenols (this being possible because of the deactivating influence of the carboxyl group on the positions 3 and 5 of this acid, which prevents self-condensation); and (*b*) demethylation by pyridine hydrochloride, of the 7-methoxylated 3-hydroxyarylisocoumarins (III) (listed in Table 4) prepared by condensation of 4-methoxyhomophthalic acid with the same phenols. From among these

TABLE 3

3-Aryl-7-hydroxyisocoumarins [a]

		Found (%)			Reqd. (%)	
Aryl substituent	M. p.	C	H	Formula	C	H
4-Hydroxyphenyl	>300° (decomp. 295)	68·3	4·8	$C_{15}H_{10}O_4,0{\cdot}5H_2O$	68·4	4·2
4-Hydroxy-3-methylphenyl	297 (decomp. >268)	71·4	4·6	$C_{16}H_{12}O_4$	71·6	4·5
4-Hydroxy-2-methylphenyl	225	71·9	4·5	$C_{16}H_{12}O_4$	,,	,,
2-Hydroxy-5-methylphenyl	225 (decomp. >210)	67·4	5·1	$C_{16}H_{12}O_4,H_2O$	67·1	4·9
2,4-Dihydroxyphenyl	>300	64·0	4·2	$C_{15}H_{10}O_5,0{\cdot}5H_2O$	64·5	3·9
4-Hydroxy-2,3-dimethylphenyl...	284	72·6	5·1	$C_{17}H_{14}O_4$	72·3	5·0
4-Hydroxy-2,5-dimethylphenyl...	220	72·0	5·0	$C_{17}H_{14}O_4$	,,	,,
4-Hydroxy-3,5-dimethylphenyl...	285	71·9	5·0	$C_{17}H_{14}O_4$	,,	,,
4-Hydroxy-2,6-dimethylphenyl [b]	276 (decomp. >255)	71·9	5·0	$C_{17}H_{14}O_4$	,,	,,
2-Hydroxy-3,5-dimethylphenyl...	211	68·2	5·2	$C_{17}H_{14}O_4,H_2O$	68·0	5·4
2-Hydroxy-4,5-dimethylphenyl...	221 (decomp. >190)	67·7	5·6	$C_{17}H_{14}O_4,H_2O$	,,	,,

[a] Recrystallised from aqueous methanol or dioxan, or from ether–ethyl acetate; they were colourless or yellowish prisms, highly soluble in ethyl acetate and ethanol, poorly soluble in ether and benzene. [b] Prepared from 1,3,5-xylenol; for structure, see footnote (*b*) to Table 2.

TABLE 4

3-Aryl-7-methoxyisocoumarins (III) [a]

		Found (%)			Required (%)	
Aryl substituent	M. p.	C	H	Formula	C	H
4-Hydroxyphenyl	229°	71·6	4·5	$C_{16}H_{12}O_4$	71·6	4·5
4-Hydroxy-3-methylphenyl.....	225	72·1	5·1	$C_{17}H_{14}O_4$	72·3	5·0
4-Hydroxy-2-methylphenyl.....	219	72·1	5·0	$C_{17}H_{14}O_4$	,,	,,
4-Hydroxy-3,5-dimethylphenyl ...	209	73·1	5·5	$C_{18}H_{16}O_4$	73·0	5·4
4-Hydroxy-2,3-dimethylphenyl ...	204	72·6	5·7	$C_{18}H_{16}O_4$	,,	,,
4-Hydroxy-2,6-dimethylphenyl [b]...	193	72·9	5·7	$C_{18}H_{16}O_4$	,,	,,
4-Hydroxy-2,5-dimethylphenyl ...	168	70·5	5·5	$C_{18}H_{16}O_4,0{\cdot}5H_2O$	70·8	5·6
2-Hydroxy-4,5-dimethylphenyl ...	205	68·7	5·8	$C_{18}H_{16}O_4,H_2O$	68·8	5·8

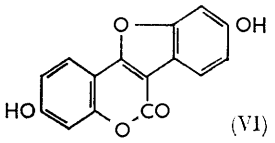
[a] Crystallised from aqueous methanol or dioxan, or from ether–ethyl acetate, as colourless or yellowish prisms. [b] Prepared from 1,3,5-xylenol; for structure, see footnote (*b*) to Table 2.

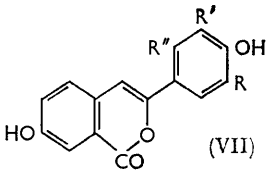
substances, 7-hydroxy-3-(2,4-dihydroxyphenyl)isocoumarin (VII; R = R′ = H, R″ = OH), prepared from resorcinol, has a structure particularly close to that of coumestrol, and the molecule of 7-hydroxy-3-*p*-hydroxyphenylisocoumarin (VII; R = R′ = R″ = H) is very similar to that of two other natural isocoumarins, hydrangeol, (3,4-dihydro-8-hydroxy-3-*p*-hydroxyphenylisocoumarin [8]) and phyllodulcin [3,4-dihydro-8-hydroxy-3-(4-hydroxy-3-methoxyphenyl)isocoumarin [9]].

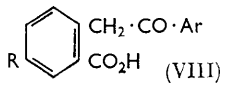
When the hydroxylated isocoumarins were treated with aqueous sodium hydroxide, an intense coloration developed (stable dark violet for the nitro-compounds, fleeting yellow for the others); after prolonged contact with the alkali, complete hydrolysis ensued in all

[8] Y. Asahina and J. Asano, *Ber.*, 1931, **64**, 1252.
[9] H. Arakawa and M. Nakazaki, *Chem. and Ind.*, 1959, 671.

cases, giving substituted deoxybenzoin-*o*-carboxylic acids (VIII), listed in Table 5. Conversely, these acids readily underwent cyclisation in the presence of dehydrating agents to give back the isocoumarins. This easy dehydration suggests, for the mechanism of the


(VI)


(VII)


(VIII)

condensation of homophthalic acids with phenols, a primary formation of the corresponding deoxybenzoin-*o*-carboxylic acid, which would then undergo dehydration under the dehydrating influence of the catalyst. This is confirmed by the inability of homophthalimide (in the molecule of which the reactive carboxyl group is blocked) to condense with phenols, in the same experimental conditions, to 3-aryl-1-isoquinolones.

TABLE 5

Deoxybenzoin-*o*-carboxylic acids (VIII)

			Found (%)			Reqd. (%)	
R	Ar	M. p.	C	H	Formula	C	H
H	4-Hydroxy-2,3-dimethylphenyl	168°	71·7	5·8	$C_{17}H_{16}O_4$	71·8	5·7
H	4-Hydroxy-3,5-dimethylphenyl	208	71·7	5·6	$C_{17}H_{16}O_4$	,,	,,
H	2-Hydroxy-3,5-dimethylphenyl	163	71·6	5·9	$C_{17}H_{16}O_4$	,,	,,
H	2-Hydroxy-4,5-dimethylphenyl	166	71·3	5·5	$C_{17}H_{16}O_4$	,,	,,
NO_2	4-Hydroxy-2-methylphenyl	218	60·5	4·6	$C_{16}H_{13}NO_6$	61·0	4·2
NO_2	4-Hydroxy-3,5-dimethylphenyl	236	61·8	4·6	$C_{17}H_{15}NO_6$	62·0	4·6
NO_2	4-Hydroxy-2,5-dimethylphenyl	219	60·4	4·6	$C_{17}H_{15}NO_6,0·5H_2O$	60·4	4·8
NO_2	4-Hydroxy-2,6-dimethylphenyl[a,b]	252	62·6	4·4	$C_{17}H_{15}NO_6$	62·0	4·6
OH	4-Hydroxyphenyl	259 (decomp. >222)	66·2	4·8	$C_{15}H_{12}O_5$	66·2	4·4
OH	4-Hydroxy-3-methylphenyl	274	66·7	5·2	$C_{16}H_{14}O_5$	67·1	4·9
OH	2-Hydroxy-5-methylphenyl	213	67·2	5·3	$C_{16}H_{14}O_5$	,,	,,
OH	4-Hydroxy-2,3-dimethylphenyl	263 (decomp. >237)	64·6	6·0	$C_{17}H_{16}O_5,H_2O$	64·2	5·7
OH	4-Hydroxy-2,5-dimethylphenyl	230	67·4	5·0	$C_{17}H_{16}O_5$	67·1	4·9
OH	4-Hydroxy-3,5-dimethylphenyl	266	64·5	5·7	$C_{17}H_{16}O_5,H_2O$	64·2	5·7
OH	4-Hydroxy-2,6-dimethylphenyl[a]	251	64·5	6·0	$C_{17}H_{16}O_5,H_2O$	,,	,,
OH	2-Hydroxy-4,5-dimethylphenyl	223	66·5	5·5	$C_{17}H_{16}O_5,0·5H_2O$	66·1	5·6
OMe	4-Hydroxyphenyl	259 (decomp. >222)	66·8	5·1	$C_{16}H_{14}O_5$	67·1	4·9
OMe	4-Hydroxy-3-methylphenyl	221	67·7	5·6	$C_{17}H_{16}O_5$	68·0	5·4
OMe	4-Hydroxy-2-methylphenyl	210	67·7	5·3	$C_{17}H_{16}O_5$	,,	,,
OMe	4-Hydroxy-2,3-dimethylphenyl	227	67·3	6·0	$C_{18}H_{18}O_5,0·5H_2O$	66·9	5·9
OMe	4-Hydroxy-2,5-dimethylphenyl	231	68·8	5·6	$C_{18}H_{18}O_5$	68·8	5·8
OMe	4-Hydroxy-3,5-dimethylphenyl	242 (decomp. >210)	68·6	5·8	$C_{18}H_{18}O_5$	,,	,,
OMe	2-Hydroxy-4,5-dimethylphenyl	204	67·1	5·7	$C_{18}H_{18}O_5,0·5H_2O$	66·9	5·9

[a] For the structure of this compound, see footnote (*b*) to Table 2. [b] Found: N, 4·7. Reqd.: N, 4·3%.

The œstrogenic activity of 7-hydroxy-3-*p*-hydroxyphenylisocoumarin was determined by two methods: Allen–Doisy test in castrated female rats, given a dose of 50 mg./kg. in aqueous suspension, by subcutaneous injection (in these animals, a positive reaction was obtained with 0·5 mcg. of œstradiol benzoate), and the nipple-growth test in male guinea pigs, given a dose of 3 mg./kg. in a suspension in olive oil, by subcutaneous injection; the compound was found inactive in both tests, and 7-hydroxy-3-(2,4-dihydroxyphenyl)-isocoumarin was inactive in the second test. Hence it is confirmed [10] that the isocoumarin nucleus is not biologically comparable to the coumarin one.

[10] N. P. Buu-Hoï, P. Jacquignon, and M. Mangane, *Rec. Trav. chim.*, 1965, **84**, 334.

Experimental

Preparation of Intermediates.—Homophthalic acid was best prepared by oxidation of indene, and was purified by repeated recrystallisation from water so as to remove substantial amounts of the accompanying phthalic acid; nitration to 4-homophthalic acid was effected by means of potassium nitrate and sulphuric acid,[11] a more satisfactory procedure than the use of fuming nitric acid. Reduction to 4-aminohomophthalic acid was achieved in over 90% yield with ammonium sulphide; conversion into 4-hydroxyhomophthalic acid (m. p. 230°; 96% yield) and methylation to 4-methoxyhomophthalic acid (m. p. 191°; theoretical yield) were effected according to the literature.[12] 4-Nitrohomophthalic anhydride was prepared by refluxing for 1 hr. a mixture of the acid (10 g.) and acetyl chloride (27 c.c.); the precipitate formed on cooling was recrystallised from acetic acid containing a few c.c. of acetic anhydride, to give shiny, yellow needles (7 g.), m. p. 156°. This compound dissolved in aqueous sodium hydroxide to give a deep-red coloration.

Condensation of Homophthalic Acids (or Anhydrides) with Phenols.—(*a*) *With stannic chloride.*[3,4] A mixture of the acid (or corresponding anhydride) (10 g.), the phenol (in 10% excess), and stannic chloride (20 c.c.) was refluxed until hydrogen chloride had ceased to evolve; after cooling and treatment with dilute hydrochloric acid, the phenol in excess was removed by steam-distillation, and the solid obtained on cooling was collected, washed with water, and recrystallised from the appropriate solvent (ethanol or dioxan in the case of isocoumarins derived from unsubstituted homophthalic acids) in the presence of charcoal. The best yield (85%) was obtained with homophthalic anhydride and 1,2,3-xylenol; least satisfactory (40%) was with 4-hydroxyhomophthalic acid and *p*-cresol.

(*b*) *With polyphosphoric acid.* This procedure was generally more convenient and gave products which were easier to purify. A mixture of the homophthalic acid (1 part) and the phenol (in 10% excess) was heated with polyphosphoric acid (8 parts; prepared by dissolving 100 g. phosphorus pentoxide in 100 c.c. orthophosphoric acid) for 1 hr. at 200—210° with stirring; after cooling, ice was added, the phenol in excess was steam-distilled, and the residue treated as above. Yields ranged from 80% (homophthalic acid) to 40—60% (4-nitrohomophthalic acid).

Demethylation of Methoxylated Isocoumarins (III).—This was achieved by refluxing for 30 min. a mixture of the methoxy-compound (1 g.) and redistilled pyridine hydrochloride (5 g.); after cooling, water was added, and the solid hydroxy-compound formed was washed with water and recrystallised from the appropriate solvent. Yields were almost theoretical.

Preparation of Deoxybenzoin-o-carboxylic Acids.—These were obtained by dissolving the corresponding isocoumarins in 10% aqueous sodium hydroxide, followed by acidification with dilute hydrochloric acid; the precipitate which formed was recrystallised from aqueous methanol or aqueous ethanol. These acids were colourless needles, except for those bearing a nitro-group, which were cream to yellow. Some nitroisocoumarins (*e.g.*, 7-nitro-3-*p*-hydroxyphenylisocoumarin) did not give the corresponding deoxybenzoin-*o*-carboxylic acid, only resinous material being obtained. Recyclisation of deoxybenzoin-*o*-carboxylic acids to the isocoumarins could be effected either thermally or in the presence of a dehydrating agent ($SnCl_4$). Yields, 50—75%, the best being obtained with isocoumarins derived from homophthalic and 4-methoxyhomophthalic acid, the least satisfactory with nitroisocoumarins.

Attempted Condensation of Homophthalimide with Phenols.—A mixture of homophthalimide (3·5 g.), phenol (5 g.), and stannic chloride (10 g.) was refluxed for 30 min., and, on cooling, treated with iced aqueous hydrochloric acid; the precipitate obtained proved to be the starting material. Several other attempts, made at higher temperatures (150° and over), gave the same negative results.

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Centre de Recherches sur les Maladies Ostéo-articulaires (I.N.S.E.R.M.),
Hôpital Cochin, Paris, France. [*Received, April 26th*, 1965.]

[11] W. Borsche, K. Diacont, and H. Hanau, *Ber.*, 1934, **67**, 675.
[12] A. Horeau and J. Jacques, *Bull. Soc. chim. France*, 1947, 53.