Oxygen Heterocycles. Part XIII.[1] From 3-Arylisocoumarins to 3-Arylisoquinolines and 4-Aryl-5*H*-2,3-benzodiazepines

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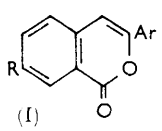
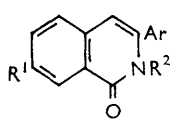
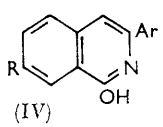
The reaction of ammonia, methylamine, or hydrazine hydrate with a large number of 3-arylisocoumarins has been investigated with a view to the preparation of derivatives of isoquinoline and 5*H*-2,3-benzodiazepine, and the determination of the structure of the parent isocoumarins, using infrared spectroscopy.

THE condensation of homophthalic anhydride with phenol in the presence of a dehydrating agent, which had been shown to give 3-*p*-hydroxyphenylisocoumarin,[2] was later extended to substituted homophthalic anhydrides and a wide variety of phenols for the preparation of new phenolic 3-arylisocoumarins [3] (I) of potential biological interest.[4] Being thus readily accessible, these isocoumarins became convenient intermediates for preparing 3-aryl-1,2-dihydro-1-oxoisoquinolines (II) by

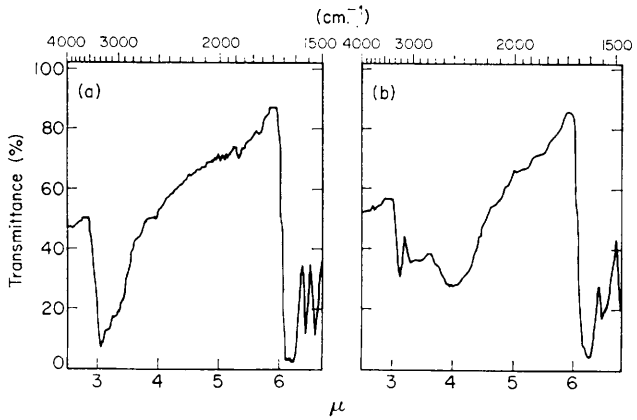

(I)


(II) R^2 = H
(III) R^2 = Me.

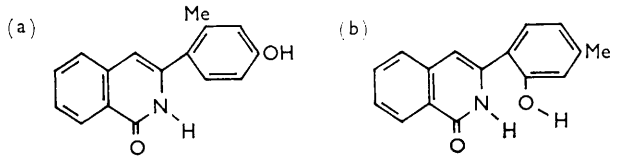

(IV)

reaction with ammonia,[5] one of the steps in the Gabriel synthesis of isoquinolines [6] which has rarely been applied to 3-arylisocoumarins.[7] The infrared absorption spectra of the new compounds thus obtained (Table 1) showed them to possess the isocarbostyril structure (II) rather than the tautomeric 1-hydroxyisoquinoline structure (IV), since, in all cases, absorption bands characteristic of the carbonyl group [maxima ranging from 1630 to 1650 cm.$^{-1}$ for compounds (II; $R^1 = R^2 = H$), and between 1645 and 1670 cm.$^{-1}$ for compounds (II; $R^1 = NO_2$, $R^2 = H$), and of the C=C group (from 1600 to 1615 cm.$^{-1}$)] were present. As expected, the spectra of the isocoumarins (I) showed corresponding absorption bands ($\nu_{C=O}$ from 1685 to 1700 and $\nu_{C=C}$ from 1615 to 1635 cm.$^{-1}$). An interesting feature of the spectra of those isocarbostyrils (II) whose aryl group carries a phenol function in a position *ortho* to the heterocyclic moiety was the presence of a broad chelation-band at 2500—3500 cm.$^{-1}$ (see Figure), which must be ascribed to an interaction of the hydrogen atom of the lactam group with the hydroxy-group, since it no longer appears in the spectra either of the *N*-methylisocarbostyrils (III) (prepared from the appropriate isocoumarins and methylamine) or of the isocarbostyrils bearing the hydroxy-group in a position *para* to the heterocycle. This observation makes it possible to identify the exact structure of the isocoumarins used as intermediates; for example, the product, m.p. 216°, of the condensation of homophthalic anhydride with

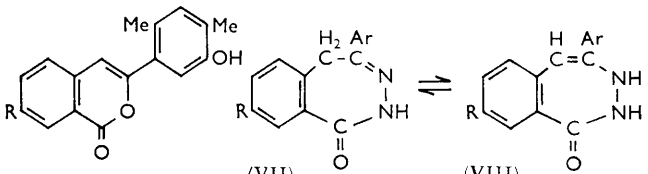
[1] Part XII, N. P. Buu-Hoï, J. P. Hoeffinger, and P. Jacquignon, *J. Chem. Soc.*, 1965, 6105.
[2] N. P. Buu-Hoï, *Compt. rend.*, 1939, **209**, 321.
[3] A. Rose, N. P. Buu-Hoï, and P. Jacquignon, *J. Chem. Soc.*, 1965, 6100.
[4] N. P. Buu-Hoï, P. Jacquignon, and A. Rose, *Med. Pharmacol. Exp.*, 1966, **14**, 401.
[5] S. Gabriel, *Ber.*, 1887, **20**, 2863; E. Heilman, *ibid.*, 1890, **23**, 3157; S. Ruhemann, *ibid.*, 1891, **24**, 3964.
[6] S. Gabriel, *Ber.*, 1886, **19**, 830; S. Gabriel and A. Neumann, *ibid.*, 1892, **25**, 3563; S. Gabriel and J. Colman, *ibid.*, 1900, **33**, 890, 995.
[7] P. Onnertz, *Ber.*, 1901, **34**, 3735; C. A. Harper, *ibid.*, 1896, **29**, 2543.



Infrared spectra of



m-cresol, tentatively formulated earlier [8] as 3-(4-hydroxy-2-methylphenyl)isocoumarin, is in fact 3-(2-hydroxy-4-methylphenyl)isocoumarin, since the corresponding isocarbostyril showed the characteristic chelation-band in the presence of stannic chloride, to give compounds (V) and (VI), and not in the normal *ortho*-position.



(V ; R = H)
(VI ; R = NO_2)

The ready availability of 3-arylisocarbostyrils from 3-arylisocoumarins prompted their use as intermediates for the synthesis of new 3-arylisoquinolines. 1,2-Dihydro-3-(4-methoxyphenyl)-1-oxoisoquinoline (m.p. 243° and not 190·3—191·5° as reported by Boyce and Levine,[9] whose product, prepared in another way, must have a different structure) was converted by phosphorus oxychloride into 1-chloro-3-(4-methoxyphenyl)isoquinoline, and by a mixture of phosphorus oxy- and pentachloride into the 1,4-dichloroisoquinoline, both of which were dehalogenated to 3-(4-methoxyphenyl)isoquinoline by Raney nickel. This same catalyst converted the 3-aryl-7-nitroisocarbostyrils (II; $R^1 = NO_2$, $R^2 = H$) into the corresponding amines (II; $R^1 = NH_2$, $R^2 = H$)

TABLE 1

3-Aryl-1,2-dihydro-1-oxoisoquinolines (II) and (III)

Aryl group	R^1	R^2	M.p.[a]	Found (%) C	H	N	Formula	Required (%) C	H	N
4-Hydroxyphenyl	H	H	242°	76·0	4·7	5·8	$C_{15}H_{11}NO_2$	75·9	4·7	5·9
4-Methoxyphenyl	H	H	243	76·5	5·3	5·5	$C_{16}H_{13}NO_2$	76·5	5·2	5·6
4-Hydroxy-3-methylphenyl	H	H	282	76·3	5·3	5·7	$C_{16}H_{13}NO_2$	76·5	5·2	5·6
2-Hydroxy-4-methylphenyl	H	H	285	76·2	5·4	5·7	$C_{16}H_{13}NO_2$	76·5	5·2	5·6
2-Hydroxy-5-methylphenyl	H	H	261	75·9	5·3	5·7	$C_{16}H_{13}NO_2$	76·5	5·2	5·6
2-Hydroxy-4,5-dimethylphenyl	H	H	293	76·6	5·7	5·6	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
4-Hydroxy-2,6-dimethylphenyl	H	H	232	76·6	6·0	5·4	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
4-Hydroxy-3,5-dimethylphenyl	H	H	267	77·1	5·8	5·3	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
4-Hydroxy-2,5-dimethylphenyl	H	H	231	76·6	5·6	5·1	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
4-Hydroxy-2,3-dimethylphenyl	H	H	273	77·0	5·9	5·2	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
3-Hydroxy-4,6-dimethylphenyl	H	H	251	77·1	5·8	5·5	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
4-Methoxyphenyl	H	Me	136	76·9	6·0	5·3	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
4-Hydroxyphenyl	H	Me	207	76·7	5·3	5·6	$C_{16}H_{13}NO_2$	76·5	5·2	5·6
2-Hydroxy-4-methylphenyl	H	Me	228	77·2	6·0	5·1	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
2-Hydroxy-5-methylphenyl	H	Me	265	76·7	6·0	5·2	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
2-Hydroxy-4,5-dimethylphenyl	H	Me	271	77·3	6·4	4·7	$C_{18}H_{17}NO_2$	77·4	6·1	5·0
2-Hydroxy-4-methylphenyl [b]	NO_2	H	337	65·2	4·1	9·1	$C_{16}H_{12}N_2O_4$	64·9	4·1	9·5
4-Hydroxy-2-methylphenyl	NO_2	H	290	65·0	4·1	9·5	$C_{16}H_{12}N_2O_4$	64·9	4·1	9·5
2-Hydroxy-5-methylphenyl	NO_2	H	346	64·7	4·2	9·6	$C_{16}H_{12}N_2O_4$	64·9	4·1	9·5
2-Hydroxy-4,5-dimethylphenyl	NO_2	H	350	65·7	4·6	9·1	$C_{17}H_{14}N_2O_4$	65·8	4·6	9·0
3-Hydroxy-4,6-dimethylphenyl	NO_2	H	330	65·7	4·5	9·1	$C_{17}H_{14}N_2O_4$	65·8	4·6	9·0
4-Hydroxy-2,5-dimethylphenyl	NO_2	H	298	65·8	4·9	9·1	$C_{17}H_{14}N_2O_4$	65·8	4·6	9·0
4-Hydroxy-2,6-dimethylphenyl	NO_2	H	302	65·8	4·9	9·2	$C_{17}H_{14}N_2O_4$	65·8	4·6	9·0

[a] Taken on a Maquenne block. [b] M.p.s for all the nitro-derivatives are instantaneous; on prolonged heating, these compounds begin to decompose 15—20° before the m.p. indicated.

(Figure); similarly, the condensation product, m.p. 257—260°, of 4-nitrohomophthalic anhydride with *m*-cresol, previously formulated as 3-(4-hydroxy-2-methylphenyl)-7-nitroisocoumarin,[3] is 3-(2-hydroxy-4-methylphenyl)-7-nitroisocoumarin. On this basis, it can also be concluded that 1,2,4-xylenol reacts abnormally in the position *meta* to the hydroxy-group on condensation with homophthalic and 4-nitrohomophthalic anhydride in the presence of hydrazine hydrate. In most instances, these amines were also obtained by direct treatment of the 3-aryl-7-nitroisocoumarins (I; R = NO_2) with hydrazine hydrate and Raney nickel, except in the case of 3-(4-hydroxy-2,5-dimethylphenyl)-7-nitroisocoumarin, where a benzodiazepine (VII; R = NH_2)

[8] N. P. Buu-Hoï, *Bull. Soc. chim. France*, 1944, **11** [5], 338.
[9] W. T. Boyce and R. Levine, *J. Org. Chem.*, 1966, **31**, 3807.

was formed. In either event, one can assume the formation of an intermediary hydrazide (IX) which in the absence of Raney nickel, cyclises to a diazepine, or, in the presence of Raney nickel, is cleaved at the N–H bond to give the amide (X) which then undergoes cyclisation to an isoquinoline (II). Accordingly, direct reduction of the nitrobenzodiazepines (VII; R = NO_2) to the corresponding amines (VII; R = NH_2) could be effected by hydrazine hydrate and Raney nickel, and complete stability twoards Raney nickel was exhibited by all the benzodiazepines of type (VII). A number of

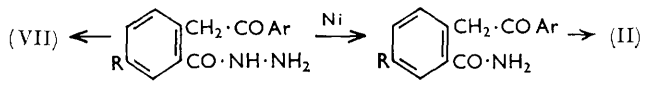
TABLE 2

4-Aryl-1,2-dihydro-1-oxo-5*H*-2,3-benzodiazepines (VII)

Aryl group	R	M.p.[a]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
4-Hydroxy-2-methylphenyl	H	211	72·0	5·5	10·3	$C_{16}H_{14}N_2O_2$	72·2	5·3	10·5
4-Hydroxy-2,3-dimethylphenyl	H	250	73·1	6·1	10·2	$C_{17}H_{16}N_2O_2$	72·8	5·8	10·0
3-Hydroxy-4,6-dimethylphenyl	H	211	72·9	5·8	10·1	$C_{17}H_{16}N_2O_2$	72·8	5·8	10·0
2-Hydroxy-4,5-dimethylphenyl[b]	H	269	73·0	5·8	9·9	$C_{17}H_{16}N_2O_2$	72·8	5·8	10·0
4-Hydroxy-2,6-dimethylphenyl	H	268	73·0	5·8	10·2	$C_{17}H_{16}N_2O_2$	72·8	5·8	10·0
4-Hydroxy-3,5-dimethylphenyl	H	256	72·7	6·0	10·0	$C_{17}H_{16}N_2O_2$	72·8	5·8	10·0
4-Hydroxy-2,5-dimethylphenyl[c]	NO_2	303	62·4	4·8	12·7	$C_{17}H_{15}N_3O_4$	62·8	4·7	12·9
4-Hydroxy-2,5-dimethylphenyl	NH_2	277	69·0	6·1	14·3	$C_{17}H_{17}N_3O_2$	69·1	5·8	14·2
4-Hydroxy-2,3-dimethylphenyl	OH	259	68·9	5·6	9·2	$C_{17}H_{16}N_2O_3$	68·9	5·4	9·5
2-Hydroxy-4,5-dimethylphenyl	OH	295	69·2	5·8	9·2	$C_{17}H_{16}N_2O_3$	68·9	5·4	9·5
4-Hydroxy-2,5-dimethylphenyl	OMe	259	69·5	6·0	9·0	$C_{18}H_{18}N_2O_3$	69·7	5·8	9·0
4-Hydroxy-3,5-dimethylphenyl	OMe	288	69·4	5·8	9·1	$C_{18}H_{18}N_2O_3$	69·7	5·8	9·0

[a] Most compounds underwent decomposition 2—5° before their instantaneous m.p. [b] 3-(2-Hydroxy-4,5-dimethylphenyl)-isocoumarin, used in this preparation, melts at 218° instead of the 176° previously recorded [3] in a typographical error. [c] As explained later, this compound exists in its tautomeric form (VIII).

these last were prepared from the corresponding isocoumarins,[10] and are listed in Table 2. In view of the possibility of the 1,2-dihydro-1-oxo-5*H*-2,3-benzodiazepines (VII) existing in the tautomeric 2,3-dihydro-1-oxo-1*H*-2,3-benzodiazepine form (VIII) [as has been



(IX) (X)

postulated [11] to account for their hydrochloric acid-catalysed rearrangement to the *N*-amines (VII)], the n.m.r. spectra of (VII) were determined; in conformity with formula (VII), these showed, in the cases where R = H (in dimethyl sulphoxide, with tetramethylsilane as internal reference), the presence of only one proton corresponding to an NH group (at 8·7 p.p.m.), and no ethylenic proton characteristic of structure (VIII) (methylene protons at 4·05 p.p.m.). In the one instance where R = NO_2, *i.e.*, the benzodiazepine derived from 3-(4-hydroxy-2,5-dimethylphenyl)-6-nitro-isocoumarin, the spectrum suggests structure (VIII), with one ethylenic proton at 6·75, an amide proton at 9·38, and the adjacent proton at 8·55 p.p.m.

EXPERIMENTAL

Condensation of Homophthalic Anhydrides with m-*Cresol and* 1,2,4-*Xylenol.*—This was effected as previously described,[3] using stannic chloride as dehydrating agent. In the case of *m*-cresol and unsubstituted homophthalic anhydride, fractional recrystallisation of the reaction product in acetic acid afforded two isomeric isocoumarins: (*a*) the less abundant (40%), less soluble compound, m.p. 216—218°, was identical with the substance considered earlier to be 3-(4-hydroxy-2-methylphenyl)isocoumarin,[8] now identified as 3-(2-*hydroxy*-4-*methylphenyl*)*isocoumarin*; (*b*) the more soluble 3-(4-*hydroxy*-2-*methylphenyl*)*isocoumarin* formed colourless prisms, m.p. 184—185° (from aqueous acetic acid) (Found: C, 76·0; H, 5·0. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%). The condensation product of 4-nitrohomophthalic anhydride with *m*-cresol was similarly separated into two isomers: (*i*) the less soluble, more abundant 3-(2-*hydroxy*-4-*methylphenyl*)-7-*nitroisocoumarin*, m.p. 257—260°; [8] (*ii*) the more soluble 3-(4-*hydroxy*-2-*methylphenyl*)-7-*nitroisocoumarin*, yellow needles, m.p. 218—219° (from acetic acid) (Found: C, 64·4; H, 3·8; N, 4·5. $C_{16}H_{11}NO_5$ requires C, 64·6; H, 3·7; N, 4·7%).

4-Nitrohomophthalic anhydride and 1,2,4-xylenol furnished, in 60% yield, 3-(3-*hydroxy*-4,6-*dimethylphenyl*)-7-*nitroisocoumarin*, yellow prisms, m.p. 255—256° (from dioxan) (Found: C, 65·3; H, 4·4; N, 4·3. $C_{17}H_{13}NO_5$ requires C, 65·6; H, 4·2; N, 4·5%).

Preparation of 3-*Aryl*-1,2-*dihydro*-1-*oxoisoquinolines* (II).—The general procedure used consisted of heating under reflux for 3—4 hr. a solution of the isocoumarin in ethanol and 29% aqueous ammonia in excess, with further addition of small portions of the last reagent every hour. (*a*) The precipitate of the *isocarbostyril* (60%), obtained after concentration and cooling, was filtered off and recrystallised from the appropriate solvent (dioxan in the case of compounds with nitro-groups; ethanol or ethanol–dioxan for the rest). The nitroisocarbostyrils were yellow, and all the others were colourless. (*b*) The *filtrate* afforded, on acidification with dilute hydrochloric acid, small amounts of the β-*deoxybenzoin*-o-*carboxylic acid* corresponding to the starting isocoumarin. The β-deoxybenzoin-*o*-carboxylic acids represent an intermediate stage in the conversion of isocoumarins into isocarbostyrils, and themselves underwent transformation into isocarbostyrils on heating with 29% aqueous ammonia in ethanol for 3—4 hr., and subsequent concentration of the reaction mixture.

[10] H. Wölbling, *Ber.*, 1905, **38**, 2845; see also ref. 1.
[11] W. F. Whitmore and R. C. Cooney, *J. Amer. Chem. Soc.*, 1944, **66**, 1237.

The *3-aryl-1,2-dihydro-2-methyl-1-oxoisoquinolines* (III) were similarly prepared by replacing ammonia by methylamine; in the preparation of 1,2-dihydro-3-(4-methoxyphenyl)-2-methyl-1-oxoisoquinoline, *4-(2-N-methylcarboxyamidophenacetyl)anisole*, prisms, m.p. 168—169° (from methanol), was isolated as the non-cyclised by-product (Found: C, 72·1; H, 6·1; N, 4·9. $C_{17}H_{17}NO_3$ requires C, 71·8; H, 6·2; N, 5·0%).

Preparation of 7-Amino-3-aryl-1,2-dihydro-1-oxoisoquinolines (II; $R^1 = NH_2$).—A solution of the corresponding 3-aryl-1,2-dihydro-7-nitro-1-oxoisoquinoline (1 part) in ethanol–dioxan was heated under reflux for 5 hr. with 95% hydrazine hydrate (10 parts) and Raney nickel (5 parts), with occasional addition of a few c.c. of hydrazine hydrate; after cooling, the catalyst was filtered off and the filtrate concentrated until a precipitate began to form. On cooling, the *7-amino-compound* was washed with water and recrystallised from methanol or ethanol. The following amines were thus obtained in 80—90% yield: *7-amino-1,2-dihydro-3-(2-hydroxy-5-methylphenyl)-1-oxoisoquinoline*, needles, m.p. 300—301° (decomp. >280°) (Found: C, 71·9; H, 5·5; N, 10·3. $C_{16}H_{14}N_2O_2$ requires C, 72·2; H, 5·3; N, 10·5%); *7-amino-1,2-dihydro-3-(2-hydroxy-4-methylphenyl)-1-oxoisoquinoline*, m.p. 321—322° (decomp. >300°) (Found: C, 71·9; H, 5·5; N, 10·3%); *7-amino-1,2-dihydro-3-(2-hydroxy-4,5-dimethylphenyl)-1-oxoisoquinoline*, m.p. 321—322° (decomp. >300°) (Found: C, 72·5; H, 5·8; N, 10·0. $C_{17}H_{16}N_2O_2$ requires C, 72·8; H, 5·8; N, 10·0%). The structure of these three compounds was verified by the presence, in their infrared spectra, of a broad chelation-band (see above). *7-Amino-1,2-dihydro-3-(4-hydroxy-2-methylphenyl)-1-oxoisoquinoline*, m.p. 263—264° (decomp. >235°) (Found: C, 72·0; H, 5·5; N, 10·6%), gave, as expected, no sign of chelation.

Reaction of 7-Nitroisocoumarins (I; $R = NO_2$) *with Hydrazine Hydrate and Raney Nickel*.—Performed under the same conditions as above, this reduction gave direct access to the four aforementioned 7-aminoisocarbostyrils. In the case of 3-(4-hydroxy-2,5-dimethylphenyl)-7-nitroisocoumarin, the reaction furnished the aminobenzodiazepine in Table 2.

Preparation of 4-Aryl-1,2-dihydro-1-oxo-5H-2,3-benzodiazepines (VIII).—A solution of the appropriate isocoumarin (0·1 mol.) and 95% hydrazine hydrate (0·2 mol.) in ethanol was heated under reflux for 3—4 hr. with occasional addition of extra hydrazine hydrate; after concentration, the mixture was cooled, or, where necessary, diluted with water, to bring about precipitation of the benzodiazepine, which was then washed with water and recrystallised from ethanol or methanol, to give colourless to pale yellow needles in yields ranging from 70 to 80%.

1-Chloro-3-(4-methoxyphenyl)isoquinoline.—A mixture of 1,2-dihydro-3-(4-methoxyphenyl)-1-oxoisoquinoline (4 g.) and phosphorus oxychloride (30 c.c.) was gently heated under reflux for 2 hr., and, after cooling, poured on ice; the precipitate formed was collected, washed thoroughly with aqueous ammonia, then with water, dried *in vacuo*, and recrystallised from hexane, to give the *isoquinoline* (3 g.) as prisms, m.p. 88° (Found: C, 70·9; H, 4·8; Cl, 13·0; N, 4·9. $C_{16}H_{12}ClNO$ requires C, 71·2; H, 4·5; Cl, 13·2; N, 5·2%).

Similar treatment of the same starting isocarbostyril (4 g.) with a mixture of phosphorus oxychloride (30 c.c.) and phosphorus pentachloride (5 g.) afforded *1,4-dichloro-3-(4-methoxyphenyl)isoquinoline* (3·6 g.), crystallising as needles, m.p. 150° (from hexane) (Found: C, 63·1; H, 3·7; Cl, 23·2; N, 4·4. $C_{16}H_{11}Cl_2NO$ requires C, 63·2; H, 3·6; Cl, 23·4; N, 4·6%).

3-(4-Methoxyphenyl)isoquinoline.—A solution of either of the foregoing compounds (2 g.) in ethanol was stirred for 36 hr. with Raney nickel (20 g.) and potassium hydroxide (2 g.), the filtrate from the catalyst was concentrated, and the precipitate recrystallised from aqueous ethanol, to give the *isoquinoline* (1·5 g.) as leaflets, m.p. 95° (Found: C, 81·3; H, 5·8; N, 6·1. $C_{16}H_{13}NO$ requires C, 81·7; H, 5·6; N, 6·0%).

1-Chloro-3-(2-hydroxy-4,5-dimethylphenyl)isoquinoline.—Prepared from 1,2-dihydro-3-(2-hydroxy-4,5-dimethylphenyl)-1-oxoisoquinoline and phosphorus oxychloride as above, this *isoquinoline* formed prisms, m.p. 159—160° (from aqueous ethanol) (Found: Cl, 13·0; N, 5·0; O, 6·0. $C_{17}H_{14}ClNO$ requires Cl, 12·5; N, 4·9; O, 5·6%).

1-Chloro-3-(2-hydroxy-4-methylphenyl)isoquinoline.—Similarly obtained from the appropriate isocarbostyril, this *isoquinoline* crystallised as prisms, m.p. 155—156° (from aqueous ethanol) (Found: C, 71·2; H, 4·6; Cl, 13·1; N, 5·3. $C_{16}H_{12}ClNO$ requires C, 71·2; H, 4·5; Cl, 13·2; N, 5·2%).

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