SECTION C
Organic Chemistry

Oxygen Heterocycles. Part XIV.[1] Hydroxylated 3-Aryl- and 3-Pyridyl-coumarins

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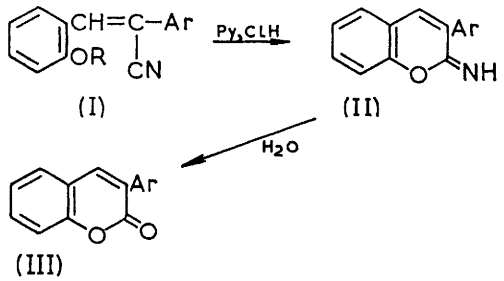
A number of new 3-aryl- and 3-pyridyl-coumarins bearing one or several phenol groups on their benzene rings have been prepared from the appropriate 2-*o*-methoxyarylated 1-aryl- and 1-pyridyl-acrylonitriles by means of the pyridine hydrochloride cyclisation method.

One of the present authors has shown [2] that 1,2-diaryl-acrylonitriles (I), the 2-aryl group of which bears an *ortho*-alkyloxy-substituent, are readily converted into



the corresponding 3-arylcoumarins (III) by boiling pyridine hydrochloride. The mechanism for the reaction was considered by Baker and Howes [3] to involve an intermediate imino-lactone (II).

This method has now been applied to the synthesis of new 3-aryl- and 3-pyridyl-coumarins bearing one or several phenolic groups which are of pharmacological interest as potential spasmolytic and uricosuric agents; [4] many of these coumarins have their phenolic function both on the heterocyclic ring and on the 3-aryl substituent (see Table 2). The acrylonitriles from which they derive (see Table 1), were all readily obtained in excellent yields, from the sodium hydroxide-catalysed condensation of the methoxybenzaldehydes (2,3-, 2,4-, and 2,5-diMeO, and 2,4,5-triMeo) and the appropriate aryl- or pyridyl-acetonitriles (Ph, 4-$MeOC_6H_4$, 3,4-di-Meo-C_6H_3, 4-$NO_2C_6H_4$, 3-pyridyl). Attempts to extend this method to the synthesis of 3-vinylcoumarins were unsuccessful, as the methylene group in allyl cyanide failed to react with the various *o*-methoxylated benzaldehydes, probably on account of the rearrangement to propenyl cyanide produced by the alkali used as catalyst.

Although only few hydroxylated 3-arylcoumarins have so far been reported in plants (coumestrol and wedelolactone can be considered as belonging to this

Table 1

New 1,2-diarylacrylonitriles

Acrylonitrile [a]	M.p.	Found (%) C	H	N	Formula	Reqd. (%) C	H	N
2-(2,5-Dimethoxyphenyl)-1-phenyl	150°	77·0	5·5	5·5	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
2-(2,4,5-Trimethoxyphenyl-1-phenyl	150	73·3	5·7	4·9	$C_{18}H_{17}NO_3$	73·2	5·8	4·7
1-*p*-Methoxyphenyl-2-(2,3-dimethoxyphenyl)	96	73·3	5·7	4·8	$C_{18}H_{17}NO_3$	73·2	5·8	4·7
1-*p*-Methoxyphenyl-2-(2,5-dimethoxyphenyl)	87	73·1	5·8	5·0	$C_{18}H_{17}NO_3$	73·2	5·8	4·7
2-(2,3-Dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)	150	70·1	6·0	4·4	$C_{19}H_{19}NO_4$	70·1	5·9	4·3
2-(2,4-Dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)	125	70·2	6·0	4·6	$C_{19}H_{19}NO_4$	70·1	5·9	4·3
2-(2,5-Dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)	160	70·4	6·0	4·4	$C_{19}H_{19}NO_4$	70·1	5·9	4·3
2-(2,3-Dimethoxyphenyl)-1-(4-nitrophenyl)	181	65·9	4·6	9·1	$C_{17}H_{14}N_2O_4$	65·8	4·5	9·0
2-(2,4-Dimethoxyphenyl)-1-(4-nitrophenyl)	190	65·5	4·3	9·0	$C_{17}H_{14}N_2O_4$	65·8	4·5	9·0
2-(2,5-Dimethoxyphenyl)-1-(4-nitrophenyl)	161	65·8	4·6	9·0	$C_{17}H_{14}N_2O_4$	65·8	4·5	9·0
2-(2,4,5-Trimethoxyphenyl)-1-(4-nitrophenyl)	203	63·5	5·0	8·0	$C_{18}H_{16}N_2O_5$	63·5	4·7	8·2
2-(2,3-Dimethoxyphenyl)-1-(3-pyridyl)	101	72·0	5·2	10·3	$C_{16}H_{14}N_2O_2$	72·2	5·3	10·5
2-(2,4-Dimethoxyphenyl)-1-(3-pyridyl)	123	72·2	5·0	10·5	$C_{16}H_{14}N_2O_2$	72·2	5·3	10·5
2-(2,5-Dimethoxyphenyl)-1-(3-pyridyl)	105	72·2	5·4	10·7	$C_{16}H_{14}N_2O_2$	72·2	5·3	10·5
2-(2,4,5-Trimethoxyphenyl)-1-(3-pyridyl)-	160	68·8	5·4	9·6	$C_{17}H_{16}N_2O_3$	68·9	5·4	9·5

[a] Recrystallised from ethanol, except for the nitro-derivatives (acetic acid); these last were deep yellow or orange-yellow, whereas all the others were colourless or pale yellow.

Although only few hydroxylated 3-arylcoumarins have so far been reported in plants (coumestrol and wedelolactone can be considered as belonging to this

[1] Part XIII, A. Rose and N. P. Buu-Hoï, *J. Chem. Soc.* (*C*), 1968, 2205.

[2] N. P. Buu-Hoï, N. Hoán, and M. Khenissi, *J. Chem. Soc.*, 1951, 2307; N. P. Buu-Hoï and B. Eckert, *J. Org. Chem.*, 1954, **19**, 1391; N. P. Buu-Hoï, B. Eckert, and R. Royer, *ibid.*, p. 1548.

[3] W. Baker and C. S. Howes, *J. Chem. Soc.*, 1953, 119.

[4] It is known that many coumarins employed as anti-vitamins K exhibit these types of activity; see, for instance, H. Newland, *Amer. J. Med. Sci.*, 1968, **256**, 44.

TABLE 2

3-Substituted coumarins

Coumarin [a]	M.p.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
6-Hydroxy-3-phenyl	206°	75·5	4·4	$C_{15}H_{10}O_3$	75·6	4·2
6,7-Dihydroxy-3-phenyl- [b]	258	71·1	4·2	$C_{15}H_{10}O_4$	70·9	4·0
8-Hydroxy-3-(4-hydroxyphenyl)	250	70·8	4·0	$C_{15}H_{10}O_4$	70·9	4·0
7-Hydroxy-3-(4-hydroxyphenyl) [c]	325	70·8	4·0	$C_{15}H_{10}O_4$	70·9	4·0
6-Hydroxy-3-(4-hydroxyphenyl)	273	70·6	4·0	$C_{15}H_{10}O_4$	70·9	4·0
β-Hydroxy-3-(3,4-dihydroxyphenyl) [d]	255	62·8	4·4	$C_{15}H_{10}O_5$–H_2O	62·5	4·2
7-Hydroxy-3-(3,4-dihydroxyphenyl) [d]	308	66·4	3·7	$C_{15}H_{10}O_5$	66·7	3·7
6-Hydroxy-3-(3,4-dihydroxyphenyl)	274	66·5	3·6	$C_{15}H_{10}O_5$	66·7	3·7
8-Hydroxy-3-(4-nitrophenyl) [d]	276	63·8	3·3	$C_{15}H_9NO_5$	63·6	3·2
7-Hydroxy-3-(4-nitrophenyl) [d]	291	63·7	3·3	$C_{15}H_9NO_5$	63·6	3·2
6-Hydroxy-3-(4-nitrophenyl)	281	60·0	3·8	$C_{15}H_9NO_5$–AcOH	59·5	3·8
6,7-Dihydroxy-3-(4-nitrophenyl)	341	59·9	3·3	$C_{15}H_9NO_6$	60·2	3·0
8-Hydroxy-3-(3-pyridyl)	301	70·5	3·8	$C_{14}H_9NO_3$	70·3	3·8
7-Hydroxy-3-(3-pyridyl)	337	70·4	4·0	$C_{14}H_9NO_3$	70·3	3·8
6-Hydroxy-3-(3-pyridyl)	310	70·1	4·0	$C_{14}H_9NO_3$	70·3	3·8
6,7-Dihydroxy-3-(3-pyridyl)	>340	65·6	3·6	$C_{14}H_9NO_4$	65·9	3·6

[a] Recrystallised from methanol or ethanol, save for the nitro- and pyridyl-coumarins, which were recrystallised from acetic acid. All the compounds were colourless to pale yellow prisms, except for the nitrocoumarines which were yellow to orange-yellow. [b] Previously obtained *via* another route by V. K. Ahluwalia, P. L. Sawhney, and T. R. Seshadri (*J. Sci. Ind. Res.*, 1956, **15***B*, 66), who gave m.p. 244—245°. [c] Previously obtained by a Perkin reaction by P. R. Bandhari, L. Bose, and S. Siddiqui (*J. Sci. Ind. Res.*, 1949, **8***B*, 189), who gave m.p. 320—321°. [d] Sublimable compounds.

group),[5] our procedure could prove useful for the structural elucidation of certain naturally occurring oxygen heterocyclics related to the coumarin series: for instance, 7-hydroxy-3-(4-hydroxyphenyl)coumarin (see Table 2) can be readily converted into its dimethyl ether, which is a degradation-product of homopterocarpin.[6]

EXPERIMENTAL

Preparation of the Acrylonitriles (I).—A solution of the aldehyde (0·01 mole) and the arylacetonitrile (0·015 mole) in ethanol (50 c.c.) was heated to 70°; 20% aqueous sodium hydroxide was then added dropwise to the stirred solution until the onset of turbidity. The *acrylonitrile* which precipitated when the solution was cooled, was washed with water and recrystallised from ethanol; yields were in the range 80—90%. This procedure, attempted with allyl cyanide, gave only nondistillable resins and a mixture of allyl and propenyl cyanide.

Cyclisation of the Nitriles (I).—A mixture of the acrylonitrile (1 mol.) and freshly redistilled pyridine hydrochloride (10 mol.) was heated under reflux for 15 min.; the cool solution was treated with water and acidified with acetic acid. The precipitate of the coumarin was washed with water and recrystallised from the appropriate solvent; yields were in the range 80—90%.

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[5] For recent literature see, for instance, F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963.

[6] A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1954, 1440.