[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Bz-HYDROXYLATED-3-ARYL- AND 3,4-DIARYL-COUMARINS

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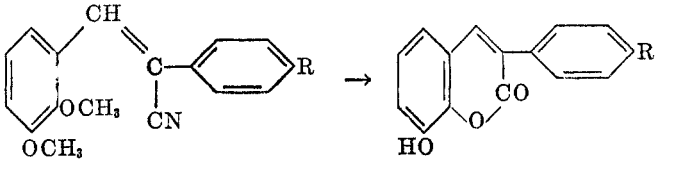
Compounds belonging to the coumarin series have acquired increasing significance in cell biology in recent years. Coumarin, and two of its dihydroxy derivatives (esculetin and daphnetin), possess "blastokolin" (seed-germination inhibiting) properties (1) and impede growth in wheat (2); in animals, several hydroxylated arylcoumarins have shown estrogenic properties (3).

In the framework of a general research in the field of potential carcinostatic and virustatic compounds (4), the preparation of a series of 3-arylcoumarins bearing hydroxy groups on the benzene nucleus has been investigated. The few coumarins of this type hitherto known had been prepared by the three following methods: condensation of α-formylarylacetonitriles (5) or ethyl α-formylarylacetates (6) with polyphenols; the Perkin-type reaction of *o*-hydroxybenzaldehydes with salts of arylacetic acids (7); or the Meerwein coupling of aryldiazonium salts with coumarins having a free 3-position (8). The first method cannot be applied to polyphenols unless these are of the resorcinol type; the second method is inconvenient from the practical point of view and generally leads to poor yields; and the third method lacks generality and requires the preliminary preparation of coumarins.

We have found that these hydroxylated 3-arylcoumarins can be conveniently prepared in excellent yield by the condensation of *o*-methoxybenzaldehydes with arylacetonitriles and demethylation with pyridine hydrochloride of the *trans*-arylacrylonitriles thus obtained (9). Thus, 2,3-dimethoxybenzaldehyde and phenylacetonitrile gave *trans*-α-phenyl-β-(2,3-dimethoxyphenyl)acrylonitrile (I),



I R = H
II R = CH_3
III R = Cl

IV R = H
V R = CH_3
VI R = Cl

which was converted to 8-hydroxy-3-phenylcoumarin (IV). Replacement of phenylacetonitrile by *p*-tolyl- and *p*-chlorophenyl-acetonitrile gave 8-hydroxy-3-*p*-tolylcoumarin (V) and 8-hydroxy-3-*p*-chlorophenylcoumarin (VI), *via* the corresponding acrylonitriles (II) and (III).

In the umbelliferone series, 3-phenyl- (XI), 3-*p*-tolyl- (XII), 3-*p*-chlorophenyl- (XIII), and 3-*p*-hydroxyphenyl-umbelliferone (XIV) were obtained similarly, starting from 2,4-dimethoxybenzaldehyde and the same arylacetonitriles and

TABLE I

trans-DISUBSTITUTED ACRYLONITRILES

Substituents	Formula	M.P., °C.	Analyses			
			Calc'd		Found	
			C	H	C	H
α-Phenyl-β-(2,3-dimethoxyphenyl)...	$C_{17}H_{15}NO_2$	86	77.0	5.7	77.2	5.8
α-*p*-Tolyl-β-(2,3-dimethoxyphenyl)...	$C_{18}H_{17}NO_2$	104	77.4	6.1	77.3	6.3
α-*p*-Chlorophenyl-β-(2,3-dimethoxyphenyl).....	$C_{17}H_{14}ClNO_2$	141	68.1	4.7	67.8	4.9
α-Phenyl-β-(2,4-dimethoxyphenyl)...	$C_{17}H_{15}NO_2$	97	77.0	5.7	76.8	5.8
α-*p*-Tolyl-β-(2,4-dimethoxyphenyl)...	$C_{18}H_{17}NO_2$	124	77.4	6.1	77.2	6.2
α-*p*-Chlorophenyl-β-(2,4-dimethoxyphenyl).....	$C_{17}H_{14}ClNO_2$	148	68.1	4.7	67.9	4.8
α-*p*-Methoxyphenyl-β-(2,4-dimethoxyphenyl).....	$C_{18}H_{17}NO_3$	136	73.2	5.8	73.0	6.0
α-Phenyl-β-(2,3,4-trimethoxyphenyl).	$C_{18}H_{17}NO_3$	145	73.2	5.8	72.9	6.0
α-*p*-Methoxyphenyl-β-(2,3,4-trimethoxyphenyl).....	$C_{19}H_{19}NO_4$	115	70.2	5.8	70.0	5.8

TABLE II

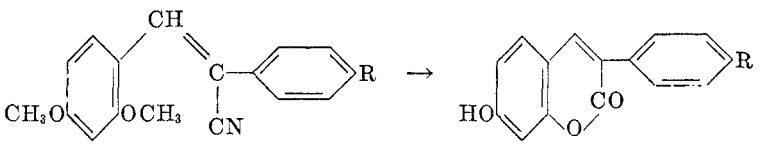
SUBSTITUTED COUMARINS

Substituents	Formula	M.P., °C.	Analyses			
			Calc'd		Found	
			C	H	C	H
8-Hydroxy-3-phenyl....	$C_{15}H_{10}O_3$	202	75.6	4.2	75.3	4.2
8-Hydroxy-3-*p*-tolyl.....	$C_{16}H_{12}O_3$	212	76.2	4.8	76.1	4.7
8-Hydroxy-3-*p*-chlorophenyl....	$C_{15}H_9ClO_3$	214	66.1	3.3	66.4	3.6
7-Hydroxy-3-phenyl[a].....	$C_{15}H_{10}O_3$	209	75.6	4.2	75.4	3.9
7-Hydroxy-3-*p*-tolyl.....	$C_{16}H_{12}O_3$	268 (dec.)	76.2	4.8	76.0	4.7
7-Hydroxy-3-*p*-chlorophenyl....	$C_{15}H_9ClO_3$	289 (dec.)	66.1	3.3	66.4	3.2
7-Hydroxy-3-*p*-hydroxyphenyl[b].	$C_{15}H_{10}O_4$	316 (dec.)	70.9	3.9	70.6	3.9
7,8-Dihydroxy-3-phenyl[c].....	$C_{15}H_{10}O_4$	209–210	70.9	3.9	70.6	4.0
7-Hydroxy-3,4-diphenyl[d].....	$C_{21}H_{14}O_3$	285–286 (dec.)	80.3	4.5	80.0	4.5
3-Phenyl-4-hydroxyphenyl[e].....	$C_{21}H_{14}O_3$	295 (dec.)	80.3	4.5	80.0	4.6
3,4-Di-(*p*-hydroxyphenyl)[e].....	$C_{21}H_{14}O_4$	255 (dec.)	76.4	4.2	76.1	4.4

[a] Literature (6) m.p. 207–208°. [b] Sublimable above 300°; recrystallized from nitrobenzene. [c] Literature (7) m.p. 213–215°. [d] Literature (11) m.p. 288°. [e] Recrystallized from acetic acid.

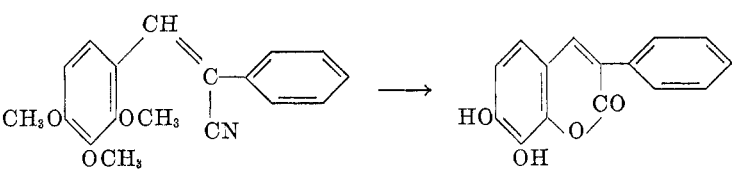
p-methoxyphenylacetonitrile. This method can be extended to the synthesis of 7,8-dihydroxy-3-phenyldaphnetin (XVI), *via* α-phenyl-β-(2,3,4-trimethoxyphenyl)acrylonitrile (XV). The intermediary diarylacrylonitriles are listed in Table I, and the resulting coumarins in Table II. It should be mentioned in passing that 2,4-dimethoxy- and 2,3,4-trimethoxy-benzaldehyde were conveniently prepared from resorcinol dimethyl ether and pyrogallol trimethyl ether by the N-methylformanilide method.

In the group of 3,4-diarylcoumarins, which are the interest as analogs of the estrogenic triphenylethylenes, 7-hydroxy-3,4-diphenylcoumarin (XVIII) was prepared by the pyridine hydrochloride demethylation of *cis*-α,β-diphenyl-β-(2,4-dimethoxyphenyl)acrylonitrile (XVII) according to the method recently devised by Buu-Hoï and Ekert (10); this procedure is far more convenient than



VII R = H
VIII R = CH_3
IX R = Cl
X R = OCH_3

XI R = H
XII R = CH_3
XIII R = Cl
XIV R = OH



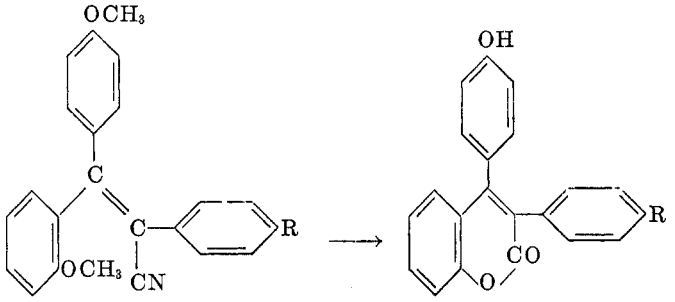
XV XVI

the one used by Ghosh (11), based on the condensation of ω-phenyl-ω-cyanoacetophenone with resorcinol in the presence of hydrogen chloride. 3-Phenyl-4-*p*-hydroxyphenylcoumarin (XXI) and 3,4-di-(*p*-hydroxyphenyl)coumarin (XXII) were similarly prepared by demethylation of 1-*o*-methoxyphenyl-1-*p*-methoxyphenyl-2-phenylacrylonitrile (XIX) and 1-*o*-methoxyphenyl-1,2-di-(*p*-methoxyphenyl)acrylonitrile (XX). These nitriles were prepared by the Bodroux condensation of 2,4′-dimethoxybenzophenone with phenylacetonitrile and *p*-methoxyphenylacetonitrile in the presence of sodium amide (12).

XVII XVIII

Preliminary results of experiments performed on mice infected with influenza virus indicate that 8-hydroxy-3-*p*-chlorophenylcoumarin has some protective activity. In Allen-Doisy tests in spayed rats, compounds IV, V, VI, XII, and

XIII were found to be non-estrogenic at a dose of 10 mg.; 3-phenylumbelliferone (XI) was slightly active at the same dose.



XIX R = H
XX R = OCH_3

XXI R = H
XXII R = OH

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EXPERIMENTAL

Preparation of intermediates. 2,3-Dimethoxybenzaldehyde was prepared by methylation of *o*-vanillin with dimethyl sulfate and aqueous sodium hydroxide. *2,3,4-Trimethoxybenzaldehyde* was prepared, at variance with the literature (13), by heating for five hours on the water-bath a mixture of 55 g. of pyrogallol trimethyl ether, 60 g. of N-methylformanilide, and 60 g. of phosphorus oxychloride; after the usual treatment with an aqueous solution of sodium acetate, and with dilute hydrochloric acid, the aldehyde was taken up in ether, and purified by vacuum-distillation (b.p. 168–170°/12 mm.). Yield: 35 g. *2,3-Dimethoxybenzaldehyde* was prepared from resorcinol dimethyl ether, with similar yield. *2,3,4-Trimethoxybenzaldehyde thiosemicarbazone* crystallized from ethanol in shiny, colorless prisms, m.p. 205°.

Anal. Calc'd for $C_{11}H_{15}N_3O_3S$: C, 49.1; H, 5.6.
Found: C, 48.8; H, 5.6.

p-Methoxyphenylacetonitrile (yield: 100 g., b.p. 150°/12 mm.) was prepared from 135 g. of *p*-methoxybenzyl chloride (b.p. 121°/15 mm., obtained from anisyl alcohol and thionyl chloride) and 75 g. of potassium cyanide in 750 ml. of acetone. *p*-Tolylacetonitrile and *p*-chlorophenylacetonitrile were prepared from the corresponding substituted benzyl chloride and potassium cyanide in ethanol medium.

Condensation of the aldehydes with arylacetonitriles. To a warm, saturated solution of the aldehyde (1 mole) and the appropriate arylacetonitrile (1 mole) in ethanol, a few ml. of a 20% aqueous solution of sodium hydroxide were added with stirring. The condensation product precipitated immediately either as a solid, or as an oil which solidified after a short stay in the refrigerator; it was collected, washed with water, and recrystallized from methanol or ethanol, giving shiny colorless, or pale yellow, prisms. The yields were almost quantitative, and the acrylonitriles obtained gave deep halochromic orange to violet colorations with pure sulfuric acid.

Conversion of the diarylacrylonitriles to the coumarins. A mixture of one part of the appropriate diarylacrylonitrile and five or six parts of redistilled pyridine hydrochloride was gently refluxed for 30 minutes. The precipitate obtained after addition of warm dilute hydrochloric acid [which brought about the hydrolysis of the intermediary iminolactone formed (14)] was collected, washed with water, and recrystallized from methanol, ethanol, or xylene, giving shiny colorless, or gray-tinged, needles. Yields were almost quantitative;

the hydroxycoumarins obtained dissolved in cold aqueous solutions of sodium hydroxide to give yellow solutions. They usually retained crystallization solvents (ethanol, water), and had to be dried carefully above 100° for analysis. All the m.p. were uncorrected, and were taken on a Maquenne block.

cis-1-o-Methoxyphenyl-1-p-methoxyphenyl-2-phenylacrylonitrile (XIX). 2,4′-Dimethoxybenzophenone, m.p. 101°, was prepared in good yield (45 g.) by a Friedel-Crafts reaction with 2-methoxybenzoyl chloride (50 g.), anisole, and aluminum chloride in carbon disulfide; Stoermer (15) obtained this ketone by oxidizing 2,4′-dimethoxybenzhydrol with potassium dichromate and sulfuric acid. A solution of 13 g. of phenylacetonitrile in 150 ml. of anhydrous ether was treated with 5 g. of finely-powdered sodium amide, and the mixture was refluxed on the water-bath until ammonia ceased to evolve; 21 g. of 2,4′-dimethoxybenzophenone was added, and refluxing was continued for two more hours. After cooling, a dilute aqueous solution of acetic acid was added, the ethereal layer was washed with water and dried over sodium sulfate, and the solvent was removed. The *nitrile* obtained had b.p. 235–238°/0.7 mm., and crystallized from methanol in colorless prisms, m.p. 167°. Yield: 60%; no stereoisomer was obtained.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6.

Found: C, 80.7; H, 5.5.

cis-2-o-Methoxyphenyl-1,2-di-(p-methoxyphenyl)acrylonitrile (XX). A solution of 14.4 g. of *p*-methoxyphenylacetonitrile in 150 ml. of anhydrous ether was treated successively with 5 g. of sodium amide and 21 g. of 2,4′-dimethoxybenzophenone as in the previous case; the *reaction product* had b.p. 240–245°/1 mm., and crystallized from methanol in shiny pale yellow needles, m.p. 109°, giving a deep violet coloration with sulfuric acid.

Anal. Calc'd for $C_{24}H_{21}NO_3$: C, 77.6; H, 5.7.

Found: C, 775.; H, 6.0.

SUMMARY

The synthesis, by convenient methods, of a number of *Bz*-hydroxylated 3-arylcoumarins and 3,4-diarylcoumarins is reported. These compounds were prepared for biological evaluation as potential carcinostatic and virustatic agents.

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