511. *A Synthesis of 3-Arylcoumarins and 3-Aryl-5 : 6-Benzocoumarins.*

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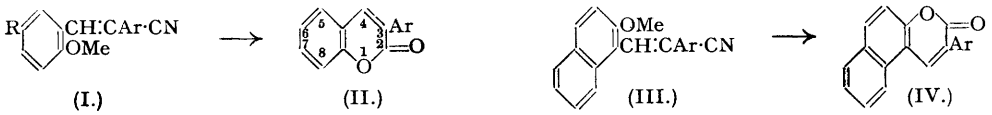
A new and convenient procedure is described for the synthesis of diversely substituted 3-arylcoumarins and 3-aryl-5 : 6-benzocoumarins. A large number of these were new compounds, intended for biological study as potential antagonists of sex hormones and as plant-germination inhibitors. The preparation of many new αβ-diarylacrylonitriles is also reported.

It was recently observed (Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130; Buu-Hoï and Hoán, *J.*, 1951, 251) that demethylation of β-*o*-methoxyphenyl-α-phenylacrylonitrile and some of its thiophen and thionaphthen analogues by means of pyridine hydrochloride, resulted also in hydrolysis of the nitrile group and lactonisation, with formation of 3-substituted coumarins. The present work is an extension of this procedure for coumarin synthesis to the preparation of a large series of 3-arylcoumarins bearing halogen radicals or hydroxyl groups at various positions. Such compounds were needed for investigations into their possible growth-regulating effects upon plants, and for physiological studies of their potential antagonistic action on sex hormones. It may be recalled that coumarin has been found by various workers (Kuhn, *Naturwiss.*, 1943, **31**, 468; Veldstra and Havinga, *Enzymologia*, 1945, **11**, 373) to inhibit plant germination and the formation of the pollen tube in *Antirrhinum*; in animal experiments, Gley and Mentzer (*Compt. rend. Soc. Biol.*, 1945, **139**, 1055) reported the strong œstrogenic activity of some hydroxy-derivatives of 3-phenylcoumarin, and it is now thought that removal, or replacement by halogen groups, of the hydroxyl radicals would abolish that activity.



(I.) (II.) (III.) (IV.)

The α-aryl-β-*o*-methoxyphenylacrylonitriles (I) used as intermediates were readily obtained by condensation of *o*-methoxybenzaldehyde and 5-bromo-2-methoxybenzaldehyde with variously substituted arylacetonitriles in the presence of alkalis. Similar condensation of

Table I.

Acrylonitriles (I) *and* (III).

Substituent α	Substituent β	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
2-Naphthyl	*o*-Methoxyphenyl	104°	$C_{20}H_{15}ON$	84·2	5·0	84·2	4·9
1-Naphthyl	*o*-Methoxyphenyl	132	$C_{20}H_{15}ON$	84·0	5·0	84·2	4·9
p-Fluorophenyl	*o*-Methoxyphenyl	80	$C_{16}H_{12}ONF$	75·6	4·8	75·9	4·7
p-Chlorophenyl	*o*-Methoxyphenyl	116	$C_{16}H_{12}ONCl$	71·1	4·6	71·2	4·4
p-Bromophenyl	*o*-Methoxyphenyl	132	$C_{16}H_{12}ONBr$	61·0	3·9	61·1	3·8
p-Iodophenyl	*o*-Methoxyphenyl	152	$C_{16}H_{12}ONI$	53·0	3·2	53·2	3·3
p-Methoxyphenyl	*o*-Methoxyphenyl	98	$C_{17}H_{15}O_2N$	81·6	6·2	81·9	6·0
p-Tolyl	5-Bromo-2-*o*-methoxyphenyl	100	$C_{17}H_{14}ONBr$	62·0	4·2	62·2	4·3
p-Fluorophenyl	5-Bromo-2-*o*-methoxyphenyl	117	$C_{16}H_{11}ONBrF$	57·5	3·5	57·8	3·3
p-Chlorophenyl	5-Bromo-2-*o*-methoxyphenyl	139	$C_{16}H_{11}ONBrCl$	54·2	3·4	54·5	3·2
p-Bromophenyl	5-Bromo-2-*o*-methoxyphenyl	159	$C_{16}H_{11}ONBr_2$	48·9	2·8	49·0	2·7
p-Iodophenyl	5-Bromo-2-*o*-methoxyphenyl	174	$C_{16}H_{11}ONBrI$	43·4	2·1	43·6	2·3
p-Methoxyphenyl	5-Bromo-2-*o*-methoxyphenyl	150	$C_{17}H_{14}O_2NBr$	59·2	4·6	59·3	4·7
2-Naphthyl	5-Bromo-2-*o*-methoxyphenyl	133	$C_{20}H_{14}ONBr$	65·6	3·9	65·9	3·8
Phenyl	5-Bromo-2-*o*-methoxyphenyl	95	$C_{16}H_{12}ONBr$	61·0	3·8	61·1	3·6
Phenyl	2-Methoxy-1-naphthyl	124	$C_{20}H_{15}ON$	84·0	5·2	84·2	5·3
p-Tolyl	2-Methoxy-1-naphthyl	137	$C_{21}H_{17}ON$	83·9	5·8	84·2	5·7
p-Chlorophenyl	2-Methoxy-1-naphthyl	124	$C_{20}H_{14}ONCl$	74·5	4·3	74·8	4·4
p-Bromophenyl	2-Methoxy-1-naphthyl	135	$C_{20}H_{14}ONBr$	65·7	4·0	65·9	3·8
p-Iodophenyl	2-Methoxy-1-naphthyl	149	$C_{20}H_{14}ONI$	58·1	3·5	58·4	3·4
2-Naphthyl	2-Methoxy-1-naphthyl	149	$C_{24}H_{17}ON$	85·7	5·1	86·0	5·1

2-methoxy-1-naphthaldehyde with arylacetonitriles gave a series of α-aryl-β-(2-methoxy-1-naphthyl)acrylonitriles (III). All these new acrylonitriles are listed in Table I, and the

corresponding 3-arylcoumarins (II) and 3-aryl-5 : 6-benzocoumarins (IV) in Tables II and II*a*, respectively.

The present synthetic route has an advantage, in its simplicity and generality, over those already described for 3-arylcoumarins (von Walther and Wetzlich, *J. pr. Chem.*, 1900, **61**, 178, 194; Funk and von Kostanecki, *Ber.*, 1905, **38**, 939; Meerwein, Büchner, and van Emster, *J. pr. Chem.*, 1939, **152**, 237), and for 3-aryl-5 : 6-benzocoumarins (Bartsch, *Ber.*, 1903, **36**, 1971).

TABLE II.

3-*Substituted coumarins* (II).

Substituent [a]	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
3-β-Naphthyl	174°	$C_{19}H_{12}O_2$	83·5	4·6	83·8	4·4
3-α-Naphthyl	157	$C_{19}H_{12}O_2$	83·8	4·5	83·8	4·4
3-*p*-Fluorophenyl	185	$C_{15}H_9O_2F$	75·1	3·8	75·0	3·7
3-*p*-Chlorophenyl [b]	185	$C_{15}H_9O_2Cl$	—	—	—	—
3-*p*-Bromophenyl	192	$C_{15}H_9O_2Br$	59·5	3·2	59·8	3·0
3-*p*-Iodophenyl	197	$C_{15}H_9O_2I$	51·4	2·6	51·7	2·6
3-*p*-Hydroxyphenyl [c]	202	$C_{15}H_{10}O_3$	75·4	4·4	75·6	4·2
7-Bromo-3-phenyl [d]	196	$C_{15}H_9O_2Br$	57·2	3·1	57·5	2·9
7-Bromo-3-*p*-tolyl	183	$C_{16}H_{11}O_2Br$	60·6	3·6	60·9	3·5
7-Bromo-3-*p*-hydroxyphenyl [c]	230	$C_{15}H_9O_3Br$	56·6	2·9	56·8	2·8
7-Bromo-3-*p*-fluorophenyl [d]	233	$C_{15}H_8O_2BrF$	56·2	2·8	56·4	2·5
7-Bromo-3-*p*-chlorophenyl [d]	235	$C_{15}H_8O_2ClBr$	53·7	2·5	53·7	2·4
7-Bromo-3-*p*-bromophenyl [d]	240	$C_{15}H_8O_2Br_2$	47·1	2·2	47·4	2·1
7-Bromo-3-*p*-iodophenyl [d]	242	$C_{15}H_8O_2BrI$	42·0	2·2	42·2	1·9
7-Bromo-3-β-naphthyl	225	$C_{19}H_{11}O_2Br$	64·9	3·3	65·0	3·1

[a] All these coumarins gave with concentrated sulphuric acid halochromic colours ranging from yellow-green to brown-yellow. [b] Von Walther and Wetzlich (*loc. cit.*) prepared this compound by heating salicylaldehyde with *p*-chlorophenylacetic acid at 300° in a sealed tube and gave m. p. 184°. [c] Soluble in aqueous sodium hydroxide solutions, unlike all the others. [d] Highly sublimable compounds.

TABLE II*a*.

3-*Substituted* 5 : 6-*benzocoumarins* (IV).

Substituent [a]	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
3-Phenyl [b]	145°	$C_{19}H_{12}O_2$	—	—	—	—
3-*p*-Tolyl	160	$C_{20}H_{14}O_2$	83·1	4·9	83·2	4·9
3-β-Naphthyl	210	$C_{23}H_{14}O_2$	85·4	4·5	85·7	4·3
3-*p*-Chlorophenyl [c]	257	$C_{19}H_{11}O_2Cl$	74·3	3·9	74·4	3·9
3-*p*-Bromophenyl [c]	276	$C_{19}H_{11}O_2Br$	64·6	3·2	64·9	3·1
3-*p*-Iodophenyl [c]	283	$C_{19}H_{11}O_2I$	57·2	2·9	57·3	2·8

[a] All these compounds gave with concentrated sulphuric acid, greenish-yellow to golden-yellow, strongly fluorescent solutions. [b] Bartsch (*loc. cit.*) prepared this compound by heating 2-hydroxy-1-naphthaldehyde with sodium phenylacetate and acetic anhydride, and gave m. p. 142°. [c] Highly sublimable compounds.

None of the coumarins and benzocoumarins reported here has been found to be œstrogenic in the Allen–Doisy test in mice; Gley and Mentzer (*loc. cit.*) reported the activity of 7-hydroxy-3-(*p*-hydroxyphenyl)-4-*n*-propylcoumarin to be only 50 times less than that of œstradiol.

EXPERIMENTAL.

Preparation of Intermediates.—2-Methoxy-1-naphthaldehyde was prepared from neroline by the *N*-methylformanilide reaction (*Org. Synth.*, 1940, **20**, 12), toluene being used in place of the prescribed *o*-dichlorobenzene; 5-bromo-2-methoxybenzaldehyde was obtained by methylation of 5-bromosalicylaldehyde (Auwers and Bürger, *Ber.*, 1904, **37**, 3934) with methyl sulphate in alkaline medium (Wentworth and Brady, *J.*, 1920, **117**, 1043). *p*-Methyl-, *p*-fluoro-, *p*-chloro-, *p*-bromo-, and *p*-iodophenylacetonitrile were prepared by chloromethylation of toluene, *p*-fluoro-, *p*-chloro-, *p*-bromo-, and *p*-iodo-benzene, and treatment of the corresponding chloromethyl compounds with sodium cyanide in ethanol–water. *p*-Methoxyphenylacetonitrile was similarly obtained from the reaction product of *p*-methoxybenzyl alcohol with dry hydrogen chloride. α- and β-Naphthylacetonitrile were prepared from α- and β-methylnaphthalene by side-chain bromination with *N*-bromosuccinimide (Buu-Hoï, *Annalen*, 1944, **556**, 1), and subsequent treatment with sodium cyanide.

Preparation of Acrylonitriles of Types (I) *and* (III).—These were prepared in almost quantitative yield by shaking a mixture of the aldehyde and the arylacetonitrile in warm ethanol with a few drops of 30% aqueous potassium hydroxide. Generally, an oil separated, which readily solidified; the solid was collected, washed with water, and recrystallised from ethanol. The *diarylacrylonitriles* (I) thus

obtained formed long colourless prisms, and their *analogues* of general formula (III) were pale yellow; all gave with concentrated sulphuric acid halochromic colours ranging from yellow to red.

Cyclisation of Acrylonitriles (I) *and* (III) *to Coumarins.*—This was effected by refluxing a mixture of one part of the acrylonitrile and five parts of pyridine hydrochloride until a clear solution was obtained (*ca.* 15 mins.); after cooling, the reaction product was treated with water, and the solid precipitate thus obtained was collected and washed with water, then with methanol. Recrystallisation from benzene or toluene gave the *coumarin* or *benzocoumarin* as well-formed colourless prisms, or shiny needles, resistant to cold alkaline solutions.

The yields obtained in the demethylation-cyclisation reaction were almost quantitative in all cases; those in the acrylonitrile syntheses exceeded 80% except from 1-naphthylacetonitrile, in which case it was probably decreased by steric hindrance.

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