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

3,4-DIARYLCOUMARINS

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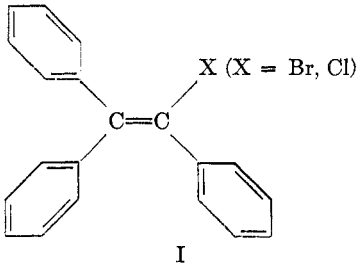
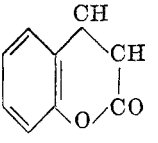
The 1,1,2-triarylethylenes form an interesting family of estrogenic substances (1), and some of them, such as 2-bromo- and 2-chloro-1,1,2-triarylethylene (I) have been successfully used as chemotherapeutic agents against cancer of the prostate (2) and of the breast (3). On the other hand, coumarin (II) possesses growth-inhibiting properties on certain plant tissues (4), and in animal physiology certain of its derivatives, such as the amides of coumarin-3-decarboxylic acid, show sedative properties (5).

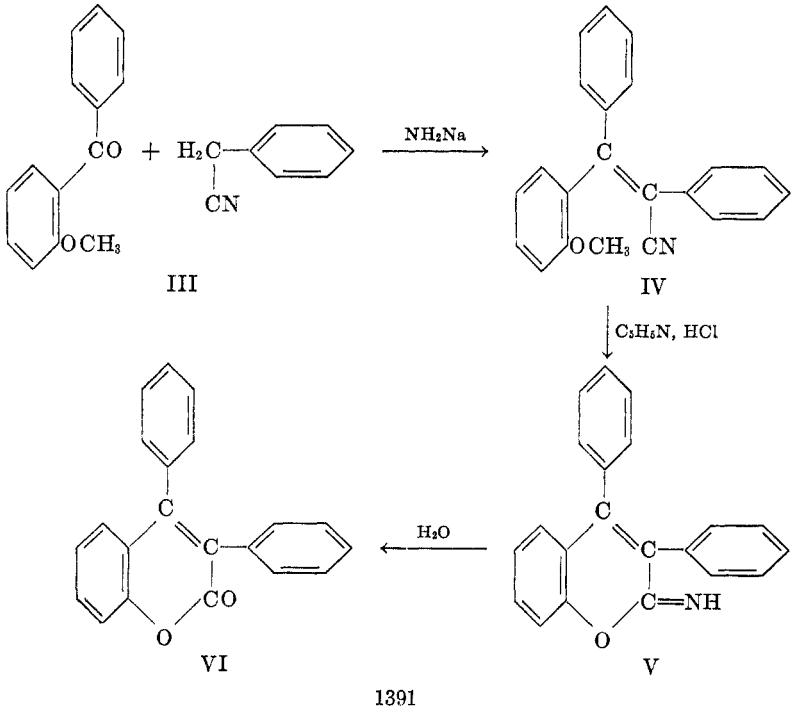


I



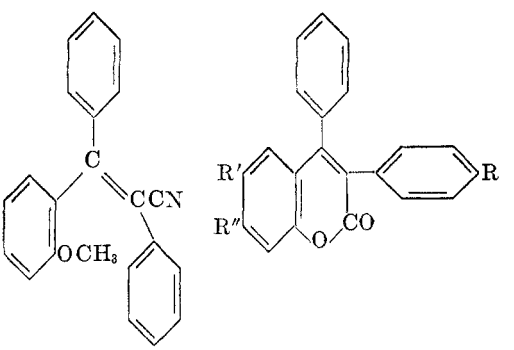
II

It was therefore deemed of interest to combine in the same molecule the chemical structure of the 1,1,2-triarylethylenes and that of coumarin, with a view to obtaining substances to be tested as chemotherapeutic agents against cancer.



III IV V VI

The most simple substance of this group is 3,4-diphenylcoumarin (VI). No general method for the preparation of either this compound or its substitution products had been reported in the literature. It has now been synthesized by the pyridine hydrochloride demethylation of *cis*-α,β-diphenyl-β-*o*-methoxyphenylacrylonitrile (IV), this nitrile being prepared by condensation of 2-methoxybenzophenone (III) with benzyl cyanide in the presence of sodium amide (6). Whereas such Bodroux reactions generally lead to a mixture of *cis*- and *trans*-α,β,β-triarylacrylonitriles, no *trans*- form (VII) was obtained in the present case, probably on account of steric hindrance, as in the *trans*- form a bulky phenyl radical would be in the vicinity of the *ortho*-methoxy group. This is in line with previous observations of Buu-Hoï and Lecocq (7), who found that the Bodroux condensation of benzyl cyanide with another *ortho*-substituted ketone, 2,4-dimethoxybenzophenone, yielded only one of the two possible stereoisomeric α,β-diphenyl-β-3,4-dimethoxyphenylacrylonitriles, and that this substance did not undergo stereomutation on heating.



VII

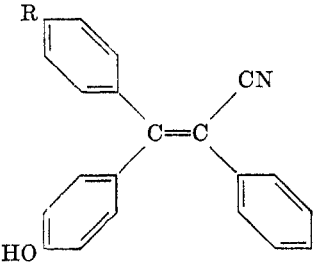
VIII R = R″ = H, R′ = CH_3
IX R = R′ = H, R″ = CH_3
X R = OH, R′ = CH_3, R″ = H

With respect to the conversion of the nitrile (IV) to 3,4-diphenylcoumarin under the influence of pyridine hydrochloride, the transitory formation of an iminolactone (V) could be postulated, according to the reaction scheme devised by Baker and Howes (8) to account for a similar synthesis, by Buu-Hoï and coworkers (9), of 3-arylcoumarins from *o*-methoxybenzaldehyde and arylacetonitriles; the iminolactone (V) would undergo instantaneous conversion to 3,4-diphenylcoumarin on treatment with water.

This method for the synthesis of 3,4-diphenylcoumarin could easily be generalized to provide a variety of diversely substituted 3,4-diarylcoumarins. Thus, the condensation of 2-methoxy-5-methylbenzophenone with benzyl cyanide afforded *cis*-α,β-diphenyl-β-(2-methoxy-5-methylphenyl)acrylonitrile, which was converted by pyridine hydrochloride to 6-methyl-3,4-diphenylcoumarin (VIII); similarly, 7-methyl-3,4-diphenylcoumarin (IX) was prepared from 2-methoxy-4-methylbenzophenone, *via* *cis*-α,β-diphenyl-β-(2-methoxy-4-methylphenyl)acrylonitrile. An example of synthesis of a hydroxylated coumarin is afforded by the Bodroux condensation of 2-methoxy-5-methylbenzophenone with 4-methoxyphenylacetonitrile to give *cis*-α-(4-methoxyphenyl)-β-phenyl-β-(2-methoxy-5

methylphenyl)acrylonitrile, which underwent double demethylation to 6-methyl-3-(*p*-hydroxyphenyl)-4-phenylcoumarin (X).

It is worth noting that, unlike the acrylonitriles mentioned above, triarylacrylonitriles bearing alkyloxy groups in the *para*-position undergo normal conversion to the corresponding hydroxy acrylonitriles by treatment with pyridine hydrochloride. Thus, α,β-diphenyl-β-(4-methoxyphenyl)acrylonitrile and α-phenyl-β,β-di(4-ethoxyphenyl)acrylonitrile were readily dealkylated to the phenolic acrylonitriles XI and XII.



XI R = H
XII R = CH

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EXPERIMENTAL

Preparation of intermediates. 2-Methoxybenzophenone (m.p. 41°) was obtained only in very poor yield (5 g.) by the Friedel-Crafts condensation of 2-methoxybenzoyl chloride (120 g.) with benzene in the presence of aluminum chloride; it was best prepared by oxidation of 2-methoxybenzhydrol with potassium dichromate (10); *2-methoxy-4-methylbenzophenone* was prepared as described by Buu-Hoï, Royer, and Eckert (11).

cis-α,β-Diphenyl-β-o-methoxyphenylacrylonitrile (IV). A solution of 6 g. of benzyl cyanide in 50 ml. of dry ether was heated with 2.5 g. of sodium amide for two hours on the water-bath; after cooling, 5 g. of 2-methoxybenzophenone was added, and the mixture, which took on a deep red color, was refluxed for a further two hours. After careful addition of water and a few drops of acetic acid, the ethereal layer was collected, washed with water, dried over sodium sulfate, and the solvent was evaporated off. Vacuum-fractionation of the residue (b.p. 220–222°/1 mm.) yielded 4 g. of nitrile (IV), which crystallized from methanol in shiny colorless leaflets, m.p. 116°; no stereoisomer could be isolated.

Anal. Calc'd for $C_{22}H_{17}NO$: C, 84.9; H, 5.5.
Found: C, 84.6; H, 5.5.

3,4-Diphenylcoumarin (VI). A mixture of one part of the foregoing nitrile and four parts of redistilled pyridine hydrochloride was refluxed for 15 minutes, after which a homogeneous solution was obtained; after cooling, dilute hydrochloric acid was added, and the precipitate which formed was washed and dried. Upon recrystallization from ethanol it gave fine colorless needles, m.p. 231°. These were insoluble in cold aqueous solutions of sodium hydroxide, and gave a yellow coloration with sulfuric acid. Yield, 92%.

Anal. Calc'd for $C_{21}H_{14}O_2$: C, 84.7; H, 4.7.
Found: C, 84.6; H, 4.9.

cis-α,β-Diphenyl-β-(2-methoxy-5-methylphenyl)acrylonitrile was prepared as above from 16 g. of benzyl cyanide, 6.8 g. of sodium amide, and 25 g. of 2-methoxy-5-methylbenzophenone in 100 ml. of dry ether. The acrylonitrile, purified by vacuum-distillation, crystallized

from methanol in shiny colorless leaflets, m.p. 107°; it gave a dark red coloration with sulfuric acid. Yield, 9 g.; as in the previous case, no stereoisomer was isolated.

Anal. Calc'd for $C_{23}H_{19}NO$: C, 84.9; H, 5.8.
Found: C, 84.7; H, 5.7.

6-Methyl-3,4-diphenylcoumarin (VIII) was obtained in almost quantitative yield by refluxing for 30 minutes a mixture of one part of the foregoing acrylonitrile and four parts of pyridine hydrochloride; the demethylation product crystallized from a mixture of ethanol and benzene in shiny colorless needles, m.p. 214°; it gave a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{16}O_2$: C, 84.6; H, 5.1.
Found: C, 84.6; H, 5.4.

cis-α,β-Diphenyl-β-(2-methoxy-4-methylphenyl)acrylonitrile was prepared from 32 g. of benzyl cyanide, 50 g. of 2-methoxy-4-methylbenzophenone, and 14 g. of sodium amide in 200 ml. of anhydrous ether; it crystallized, after vacuum-distillation, from ethanol in colorless leaflets, m.p. 154°, which gave a dark red coloration with sulfuric acid. Yield, 17 g.

Anal. Calc'd for $C_{23}H_{19}NO$: C, 84.9; H, 5.8.
Found: C, 84.6; H, 6.0.

7-Methyl-3,4-diphenylcoumarin (IX) crystallized from a mixture of ethanol and benzene in long, shiny, colorless needles, m.p. 243°; it gave a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{16}O_2$: C, 84.6; H, 5.1.
Found: C, 84.5; H, 5.1.

cis-α-(4-Methoxyphenyl)-β-phenyl-β-(2-methoxy-5-methylphenyl)acrylonitrile was prepared from 6.6 g. of sodium amide, 20 g. of 4-methoxyphenylacetonitrile, and 24 g. of 2-methoxy-5-methylbenzophenone in 150 ml. of ether. The reaction product crystallized in part after the usual treatment with acidified water. Recrystallization from methanol gave shiny, pale yellow needles, m.p. 108°, which gave a deep violet coloration with sulfuric acid. The mother liquors on vacuum-fractionation (b.p. 240–242°/1 mm.) gave a further amount of the same compound. Yield, 12 g.

Anal. Calc'd for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.9.
Found: C, 80.9; H, 5.9.

6-Methyl-3-(p-hydroxyphenyl)-4-phenylcoumarin (X). This compound crystallized from aqueous ethanol in fine colorless prisms, m.p. 256°, which were soluble in aqueous sodium hydroxide.

Anal. Calc'd for $C_{22}H_{16}O_2$: C, 84.6; H, 5.1.
Found: C, 84.3; H, 5.2.

α,β-Diphenyl-β-(4-hydroxyphenyl)acrylonitrile (XI). A mixture of 3.1 g. of α,β-diphenyl-β-(4-methoxyphenyl)acrylonitrile and 3.5 g. of pyridine hydrochloride in 30 ml. of nitrobenzene was refluxed for five hours; the solvent was distilled off with steam, and the solid residue was purified by dissolution in an aqueous solution of sodium hydroxide and reprecipitated with acetic acid. Recrystallization from aqueous ethanol gave 2.5 g. of colorless needles, m.p. 203–204°.

Anal. Calc'd for $C_{21}H_{15}NO$: C, 84.8; H, 5.1.
Found: C, 84.5; H, 5.0.

α-Phenyl-β,β-di(4-hydroxyphenyl)acrylonitrile (XII) was prepared similarly from α-phenyl-β,β-di(4-ethoxyphenyl)acrylonitrile (12); it crystallized from aqueous acetic acid in colorless needles, m.p. 241–242°; it gave a red coloration with sulfuric acid, which turned green on heating.

Anal. Calc'd for $C_{21}H_{15}NO_2$: C, 80.5; H, 4.8.
Found: C, 80.4; H, 5.0.

SUMMARY

1. A general method has been devised for the synthesis of 3,4-diarylcoumarins, and several of these substances have been prepared for biological evaluation as potential carcinolytic agents.

2. Triarylacrylonitriles bearing alkyloxy groups in the *para*-position are shown to undergo normal pyridine hydrochloride demethylation.

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