347. *A Synthesis of Certain Naphtha*(1 : 2 : 4′ : 3′)*coumarin Derivatives.*

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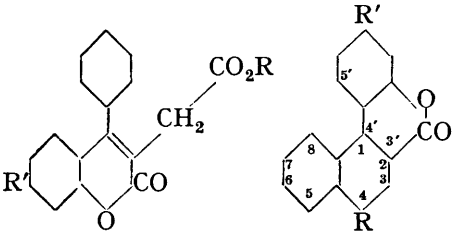
In recent years a considerable number of tricyclic and tetracyclic substances with one or two aromatic nuclei and other nuclei of various types, including the heterocyclic rings, have been found to possess physiological activity. Interest attaches, therefore, to the synthesis of similar compounds, especially if the methods are of general applicability. The preparation in a simple manner of some phenolic naphthacoumarins which have points of constitutional analogy with certain fish-poisons is now described.

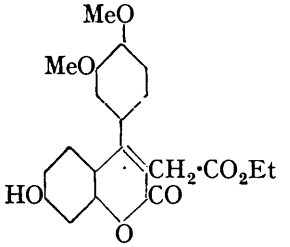
The method adopted involves a remarkably facile ring-closure to a naphthalene derivative. Ethyl benzoylsuccinate and resorcinol are condensed with the help of 85% sulphuric acid to the *coumarin* derivative (I; R = Et, R′ = OH), which on hydrolysis furnishes the corresponding *acid* (I; R = H, R′ = OH). The *methyl* ethers of this ester and acid (R′ = MeO) were readily obtained.

Condensation between the phenyl and the carboxyl group of substances of type (I) was effected under a variety of conditions, most smoothly by simple boiling with acetic



(I.)

(II.)



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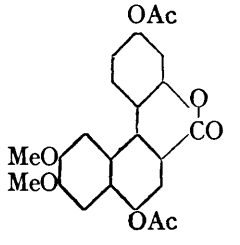

(IV.)

anhydride; the products were naphthacoumarins * of type (II; R = OAc). This ring-closure is accompanied by a striking change in the fluorescence properties. Dissolved in sulphuric acid, the phenylcoumarins (I) exhibit an intense bluish-violet fluorescence, and the naphthacoumarins an even more vivid green fluorescence.

In order to approach more closely a structure analogous to rotenone, *ethyl 7-hydroxy-4-veratrylcoumarin-3-acetate* (III) and the *diacetoxydimethoxynaphthacoumarin* (IV) were synthesised by the general method.

Certain of the physiological properties of these substances are under examination.

Experimental.

Ethyl 7-Hydroxy-4-phenylcoumarin-3-acetate (I; R = Et, R′ = OH).—A fused mixture of resorcinol (20 g.) and ethyl benzoylsuccinate (15 g.) was distributed on the walls of a flask and allowed to solidify, sulphuric acid (225 c.c. of 85%) was then added during 30 minutes in portions

* These are the true naphthacoumarins. The tricyclic substances termed "naphthacoumarins" in the literature should have been named "naphthapyrones."

of *ca.* 20 c.c. with constant shaking and cooling in running water, and the clear red solution was kept for 24 hours at room temperature. The mixture was poured with stirring into ice-water (2000 c.c.) and kept for some hours; the solid (20 g.) crystallised from alcohol in colourless flat prisms, m. p. 177° (Found: C, 70·3; H, 5·0; EtO, 18·3; *M*, cryoscopic in camphor, 323, 317. $C_{19}H_{16}O_5$ requires C, 70·3; H, 4·9; 1EtO, 18·0%; *M*, 324). The *substance* is readily soluble in acetic acid or alcohol, gives a brown coloration with alcoholic ferric chloride, and forms a pale yellow solution exhibiting a dark green fluorescence in aqueous sodium hydroxide and a yellow solution with bright violet fluorescence in sulphuric acid.

7-*Hydroxy*-4-*phenylcoumarin*-3-*acetic Acid* (I; R = H, R′ = OH).—The ester (5 g.) was refluxed with aqueous sodium hydroxide (40 c.c. of 5%) for 1 hour; the *acid* (4·5 g.) precipitated by hydrochloric acid crystallised from acetic acid in colourless hexagonal plates, m. p. 249—250° after darkening at 205° (Found in material dried at 110° in a high vacuum over phosphoric oxide: C, 68·1, 67·9; H, 4·4, 4·2. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%). Low values for content of carbon were obtained in many estimations, and this may be due to contamination with a substituted *trans-o*-coumaric acid. The colour reactions of the acid resemble those of its ester described above. When the acid was refluxed with 10% alcoholic sulphuric acid, it was reconverted into its ethyl ester (m. p. and mixed m. p. 177°).

7-*Methoxy*-4-*phenylcoumarin*-3-*acetic Acid* (I; R = H, R′ = OMe).—Ethyl hydroxyphenylcoumarinacetate (60 g.) was dissolved in the minimum of 10% aqueous sodium hydroxide, and methyl sulphate (45 g.) added with vigorous stirring; sodium hydroxide was added when necessary in order to preserve an alkaline reaction. The mixture was finally refluxed for 2 hours and the hot clear liquid was acidified with hydrochloric acid. The precipitate crystallised from acetic acid in long needles (25 g.), m. p. 209° (Found: C, 69·5; H, 4·6; MeO, 9·8. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5; 1MeO, 10·0%). This *acid* is sparingly soluble in water or in hot xylene and readily soluble in hot glacial acetic acid. The fluorescence of a solution in sulphuric acid is bright bluish-violet.

1-*Methyl* 2-*Ethyl Phenyl*-2 : 4-*dimethoxyphenylmethylenesuccinate*.—This ester results from the methylation of ethyl 7-hydroxy-4-phenylcoumarin-3-acetate under the following conditions and it is apparent that the coumarin ring is opened before the carbethoxyl group is hydrolysed. A solution of the coumarin ester (2 g.) in the minimum of aqueous sodium hydroxide (10%) was shaken vigorously with methyl sulphate (5 g.), further addition of sodium hydroxide being made when necessary to preserve an alkaline reaction. A white solid which separated crystallised from alcohol in small plates (0·8 g.), m. p. 93° (Found: C, 68·8; H, 6·2. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·3%). The *ester* dissolved in sulphuric acid to a non-fluorescent solution.

On similar methylation of 7-hydroxy-4-phenylcoumarin-3-acetic acid by means of aqueous sodium hydroxide and an excess of methyl sulphate, *methyl phenyl*-2 : 4-*dimethoxyphenylmethylenesuccinate* was obtained; this crystallised from aqueous alcohol in small rectangular plates, m. p. 101° (Found: C, 67·7; H, 5·8; MeO, 33·1. $C_{21}H_{22}O_6$ requires C, 68·1; H, 5·9; 4MeO, 33·5%).

4 : 7′-*Diacetoxynaphtha*(1 : 2 : 4′ : 3′)*coumarin* (II; R, R′ = OAc).—A mixture of 7-hydroxy-4-phenylcoumarin-3-acetic acid (18 g.) and acetic anhydride (100 c.c.) was refluxed for 12 hours; on cooling, white crystals (8 g.) separated, and a further quantity was obtained from the mother-liquor after the excess of acetic anhydride had been decomposed with water. The *substance* crystallised from acetic acid in long colourless needles, m. p. 230° (Found: C, 69·7; H, 3·9. $C_{21}H_{14}O_6$ requires C, 69·6; H, 3·8%). The solution in sulphuric acid exhibits an intense green fluorescence and rapidly acquires a scarlet coloration.

4 : 7′-*Dihydroxynaphtha*(1 : 2 : 4′ : 3′)*coumarin* (I; R, R′ = OH).—The diacetate (8 g.) was refluxed for 1 hour with alcoholic potash (50 c.c. of 5%), and the solution acidified hot with hydrochloric acid and added to water (200 c.c.). The yellow powder (6 g.) obtained crystallised from *n*-butyl alcohol in microscopic prisms which charred but did not melt at 360° (Found: C, 70·9; H, 3·9. $C_{17}H_{10}O_4,0{\cdot}5H_2O$ requires C, 71·1; H, 3·8%). This *substance* is sparingly soluble in organic solvents; its solution in sulphuric acid exhibits a phenomenal green fluorescence and, on keeping, a crimson coloration is developed. On acetylation with boiling acetic anhydride for 30 minutes, the diacetate, m. p. 230° (undepressed mixed m. p.), was obtained.

4-*Acetoxy*-7′-*methoxynaphtha*(1 : 2 : 4′ : 3′)*coumarin* (II; R = OAc, R′ = OMe).—7-Methoxy-4-phenylcoumarin-3-acetic acid (5 g.) was refluxed for 6 hours with acetic anhydride (20 c.c.). The cooled solution deposited hair-like crystals (1·9 g.) and a further quantity (2·9 g.) was obtained from the mother-liquor. The *substance* crystallised from acetic acid in long, slender, pale yellow needles, m. p. 184° (Found: C, 71·7; H, 4·3; MeO, 9·0. $C_{20}H_{14}O_5$ requires C, 71·6; H, 4·2; MeO, 9·6%). This derivative is sparingly soluble in hot alcohol and in cold

benzene or acetic acid; it is readily soluble in hot benzene. In sulphuric acid the usual brilliant green fluorescence and yellow solution, changing to crimson, were observed.

The related phenol (II; R = OH, R′ = OMe) was obtained by hydrolysis with boiling alcoholic potassium hydroxide as in a previous case. The crude product (1·5 g. from 2 g. of the acetate) crystallised from a relatively large volume of alcohol in long *yellow* needles, m. p. 266—267° (decomp.) (Found: C, 73·6; H, 4·1. $C_{18}H_{12}O_4$ requires C, 73·9; H, 4·1%). *4-Hydroxy-7′-methoxynaphtha*(1 : 2 : 4′ : 3′)*coumarin* is very sparingly soluble in most organic solvents, but is moderately readily soluble in hot alcohol or tetrachloroethane. The solution in sulphuric acid exhibits the usual properties and the sodium salt is sparingly soluble in alcohol. On boiling with acetic anhydride the acetate (above) is regenerated.

7′-Methoxy-4-(*7″-methoxy-4″-phenylcoumarin-3″-acetoxy*)*naphtha*(1 : 2 : 4′ : 3′)*coumarin* (?). —A mixture of 7-methoxy-4-phenylcoumarin-3-acetic acid (1·5 g.), phosphoric oxide (5 g.), and xylene (40 c.c.) was refluxed for 4 hours, and light petroleum added to the clear solution decanted from the black residue. The deposited yellow powder (0·7 g.) crystallised from xylene in elongated diamond-shaped plates, m. p. 237° (Found: C, 73·9; H, 4·1; MeO, 9·9. $C_{36}H_{24}O_8$ requires C, 73·9; H, 4·1; 2MeO, 10·6%). This sparingly soluble *substance* dissolves in sulphuric acid to a solution exhibiting the behaviour of one of the dihydroxynaphthacoumarin derivatives. Hydrolysis by means of alcoholic sodium hydroxide resulted in the formation of 4-hydroxy-7′-methoxynaphtha(1 : 2 : 4′ : 3′)coumarin (above) in 25—30% yield. It appears probable that the compound is, as suggested in the heading, an ester derived from methoxyphenylcoumarinacetic acid and hydroxymethoxynaphthacoumarin; the note of interrogation is added on account of our failure to synthesise the supposed ester from the acid and the phenolic component named.

4 : 7′-Diacetoxy-5 : 6-dimethoxynaphtha(1 : 2 : 4′ : 3′)*coumarin* (IV).—Veratroyl chloride (50 g., b. p. 180°/40 mm., m. p. 70°), prepared by the interaction of equal weights of dry veratric acid and thionyl chloride at the b. p. of the latter, was dissolved in ether (700 c.c.). Sodium (12·5 g.) and alcohol (400 c.c.) were used for the preparation of a sodium ethoxide solution, to half of which ethyl acetoacetate (31 g.) was added. After cooling to 5°, the veratroyl chloride (350 c.c.) was introduced and after 1 hour successive additions of sodium ethoxide solution (100 c.c.) and veratroyl chloride solution (175 c.c.) were made. At suitable intervals half of the residual ethoxide and of the chloride solution were added until the volumes were small. After 24 hours the sodio-derivative of ethyl veratroylacetoacetate mixed with sodium chloride was collected.

A small portion of the salt was suspended in ice-water, and acetic acid used to precipitate free *ethyl veratroylacetoacetate*, which crystallised from alcohol in long colourless needles, m. p. 82° (Found: C, 60·8; H, 6·1. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%).

The main quantity of the salt (75 g.) was mixed with water (150 c.c.), ammonium chloride (12 g.), and aqueous ammonia (40 c.c. of 10%), and the whole heated to 45° and vigorously shaken. The heavy brown oil (45 g.) that was isolated by means of ether could not be crystallised or distilled. It was regarded as ethyl veratroylacetate and converted into ethyl veratroylsuccinate, also a viscous oil, by means of sodium ethoxide and ethyl bromoacetate in the usual manner. The increase of weight indicated that the reaction had succeeded (40 g. from 32 g.).

Alternatively, ethyl veratroylsuccinate was prepared by interaction of the sodio-derivative of ethyl acetylsuccinate (50 g.) with veratroyl chloride (47 g.) in ethereal alcoholic solution. The product was hydrolysed by means of aqueous ammonium chloride and ammonia, and afforded a yellow oil (69 g.), doubtless consisting largely of ethyl veratroylsuccinate. After some days, the oil deposited a white solid, which crystallised from alcohol in needles, m. p. 98° (Found: C, 59·8; H, 6·3. $C_{19}H_{24}O_8$ requires C, 60·0; H, 6·3%). This substance, which gives no coloration with ferric chloride in alcoholic solution, is certainly *ethyl αα-veratroylacetylsuccinate*, the hydrolysis having been incomplete. A mixture of ethyl veratroylsuccinate (crude oil, 5 g.), resorcinol (6 g.), and sulphuric acid (150 c.c. of 84%) was kept for 12 hours and added to water. The dark red tar was taken up in acetic acid and, on keeping, this solution deposited a solid which, recrystallised from acetic acid, formed small diamond-shaped plates, m. p. 172° (Found in material dried at 110°/20 mm. over phosphoric oxide: C, 63·1; H, 5·5. $C_{20}H_{20}O_8,H_2O$ requires C, 62·7; H, 5·5%). The substance exhibits only pseudo-acidic properties and so appears to be *ethyl 7-hydroxy-4-veratroylcoumarin-3-acetate*, crystallising with $1H_2O$ very firmly held, rather than the corresponding coumaric acid. Its solution in sulphuric acid is non-fluorescent.

This substance (2 g.) was hydrolysed as in a previous case with alcoholic potash, and the product boiled for 6 hours with acetic anhydride (8 c.c.); white crystals (0·5 g.) were obtained

from the cooled solution. The substance crystallised from acetic acid in long colourless needles, m. p. 256—257° (Found : C, 65·3; H, 4·3. $C_{23}H_{18}O_8$ requires C, 65·4; H, 4·3%). This *compound* has the usual properties of a naphthacoumarin; its yellow solution in sulphuric acid exhibits a brilliant green fluorescence and the liquid becomes bright red on keeping.

Ethyl m-*Methoxybenzoylsuccinate.*—*m*-Methoxybenzoic acid (50 g.) and thionyl chloride (60 g.) were refluxed for 2 hours and afforded *m*-methoxybenzoyl chloride, b. p. 148°/24 mm. (yield, 54 g.).

By the method described above for ethyl veratroylacetate, ethyl acetoacetate (40 g.) and *m*-methoxybenzoyl chloride (54 g.) gave ethyl *m*-methoxybenzoylacetate (51 g.). This ester (50 g.), sodium (5 g.), alcohol (100 c.c.), and ethyl bromoacetate (37 g.) were used in the preparation of *ethyl* m-*methoxybenzoylsuccinate* (26 g. of b. p. 227°/17 mm.) (Found : C, 62·2; H, 6·4. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·4%). Attempts to condense this ester with resorcinol to a coumarin derivative were fruitless.

The authors thank Imperial Chemical Industries Ltd. for assistance.

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