59. *Furano-compounds. Part I. A Synthesis of Bergapten.*

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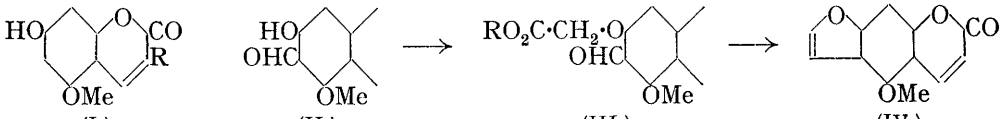
The accepted structure of bergapten, which depends on the analytical evidence of Thoms and Baetcke (*Ber.*, 1912, **45**, 3705), has now been confirmed by a synthesis of the compound from *apo*xanthoxyletin, the orientation of which has been established (preceding paper).



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

Interaction of (II) and ethyl bromoacetate in boiling acetone containing potassium carbonate gave an unexpectedly poor yield of the *ethyl* ester (III, R = Et), which was not improved by varying the relative amounts of the reactants. On hydrolysis this ester furnished the *acid* (III, R = H), which on cyclisation and simultaneous decarboxylation by means of boiling acetic anhydride containing sodium acetate yielded the furanocoumarin (IV), identical in every respect with natural bergapten.

The parent *coumarin* (I, R = H) has been obtained by decarboxylation of the *acid* (I, R = CO_2H), which was prepared by the cyanoacetic acid method, but the conversion of (I, R = H) into (II), the remaining step required to complete the synthesis of bergapten, has not yet been achieved.

Experimental.

7-Hydroxy-5-methoxycoumarin.—Interaction of 2 : 4-dihydroxy-6-methoxybenzaldehyde (2 g.) with cyanoacetic acid (12 c.c. of Phelps and Tillotson's solution; *Amer. J. Sci.*, 1908, **26**, 267) in 20% aqueous sodium hydroxide (12 c.c.) during 16 hours yielded 4-hydroxy-6-methoxysalicylidenecyanoacetic acid, which on hydrolysis with boiling 4% hydrochloric acid (200 c.c.) for ½ hour gave *7-hydroxy-5-methoxycoumarin-3-carboxylic acid* (1·8 g.); this formed needles, m. p. 264°, from 90% alcohol, insoluble in water (Found : C, 55·9; H, 3·3. $C_{11}H_8O_6$ requires C, 55·9; H, 3·4%). A solution of the acid in alcohol exhibited a blue fluorescence.

A mixture of the acid (1 g.) and quinoline (15 c.c.) containing copper-bronze (1 g.) was gently refluxed for ½ hour, cooled, filtered, and mixed with chloroform (600 c.c.). After the removal of the quinoline by means of dilute hydrochloric acid the chloroform solution was washed with aqueous sodium bicarbonate and dried. The *coumarin*, isolated from the product left on evaporation of the solvent by sublimation in a high vacuum, crystallised from 50% alcohol in slender needles, m. p. 246°, easily soluble in alcohol and sparingly soluble in chloroform or ether (Found : C, 62·9; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%). An alcoholic solution of the compound does not fluoresce and does not give a ferric reaction.

7-Hydroxy-5-methoxy-6-formylcoumarin-7-O-acetic Acid (III, R = H).—The yield of *apo*xanthoxyletin obtained by ozonolysis of xanthoxyletin (*loc. cit.*) was improved by passing the stream of ozone and oxygen through the chloroform solution until the yellow colour was discharged; yield, 0·4 g. from 1 g. of xanthoxyletin.

A solution of *apo*xanthoxyletin (1 g.) and ethyl bromoacetate (1 g.; 1·3 mols.) in acetone (150 c.c.), containing excess of potassium carbonate, was refluxed for 18 hours and after the addition of more acetone (100 c.c.) the warm solution was filtered (wash potassium salts with acetone) and evaporated, leaving the *ester* (III, R = Et), which separated from alcohol in slender needles (0·2 g.), m. p. 136°, sparingly soluble in light petroleum and having a negative ferric reaction (Found : C, 58·9; H, 4·7. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%).

Acidification of an aqueous solution of the yellow potassium salts with hydrochloric acid gave unchanged *apo*xanthoxyletin (0·4 g.).

Hydrolysis of the ester (0·3 g.) with boiling 5% methyl-alcoholic potassium hydroxide (7 c.c.) for ½ hour gave rise to the *acid* (III, R = H), which separated from a small volume of acetone in tiny clusters of colourless needles (0·24 g.), m. p. 242° (decomp.), sparingly soluble in water, benzene, or carbon tetrachloride (Found : C, 56·4; H, 3·9. $C_{13}H_{10}O_7$ requires C, 56·1; H, 3·6%).

Bergapten (IV).—A mixture of the foregoing acid (0·3 g.), sodium acetate (1·5 g.), and acetic anhydride (15 c.c.) was refluxed for ½ hour, and, after decomposition of the anhydride with water, the mixture was neutralised with sodium bicarbonate and repeatedly extracted with ether.

Evaporation of the combined, dried extracts left bergapten, which was purified by recrystallisation from methyl alcohol, then aqueous alcohol, and finally benzene–light petroleum (b. p. 60—80°) with or without previous sublimation in a high vacuum and obtained in slender prisms, m. p. 188—189°, identical in every way with a natural specimen, m. p. 189° (Found : C, 66·7; H, 3·7. Calc. for $C_{12}H_8O_4$: C, 66·7; H, 3·7%).

A natural specimen was isolated from a fraction of bergamot oil rich in bergapten which was kindly presented to us by Messrs. Bush & Co., of London. This fraction was mixed with excess of light petroleum (b. p. 40—60°) and 48 hours later the precipitate was collected and repeatedly crystallised from methyl alcohol and then ethyl alcohol. The resulting bergapten had m. p. 189°.

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