197. *Furano-compounds. Part IV. A Synthesis of* allo*Bergapten.*

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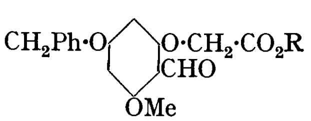
A synthesis of *allo*bergapten (VII), suggested by the results described in Part II, has been effected by way of the stages (I, R = Et), (II, R = CH_2Ph), (II, R = H), (III, R = Et), (III, R = H), (V) and (VI). The orientation of the intermediate aldehyde (III, R = Et) is established by the fact that on hydrogenation, and methylation of the product, it gave rise to ethyl 4 : 6-dimethoxy-7-methylcoumarone-2-carboxylate.

By the condensation of 3 : 4 : 6-triacetoxycoumaran with ethyl sodioformylacetate and distillation of the product Späth and his co-workers (*Ber.*, 1937, **70**, 243, 478) have obtained two of the three possible hydroxyfurocoumarins, *viz.*, *allo*bergaptol along with a smaller amount of bergaptol, which on methylation furnished *allo*bergapten and bergapten respectively, but the procedure employed did not in itself serve to establish the orientation of the products. In the present communication there is described a rational synthesis of *allo*bergapten which is based on the conclusions deduced in Part II (this vol., p. 921).

The *phenoxyacetic* ester (I, R = Et) was prepared from 2-hydroxy-4-benzyloxy-6-methoxybenzaldehyde and ethyl bromoacetate by the potassium carbonate method and on cyclisation with alcoholic sodium ethoxide gave, along with small amounts of the *acid* (I, R = H), *ethyl 6-benzyloxy-4-methoxycoumarone-2-carboxylate* (II, R = CH_2Ph), which on debenzylation with hydrogen and a palladium catalyst furnished a quantitative yield of *ethyl 6-hydroxy-4-methoxycoumarone-2-carboxylate.* Application of Gattermann's reaction to the latter substance gave rise to the *aldehyde* (III, R = Et) in good yield, the orientation of which was established by the fact that on catalytic reduction, and methylation of the product (IV, R = H), it gave rise to ethyl 4 : 6-dimethoxy-7-methylcoumarone-2-carboxylate (IV, R = Me), identical with an authentic specimen.



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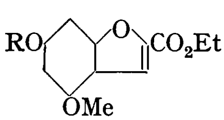

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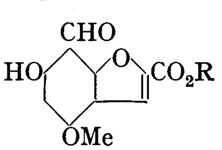

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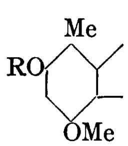

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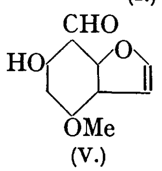

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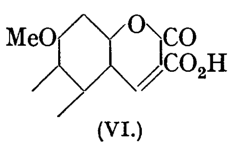

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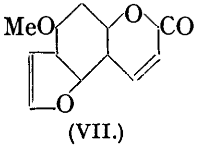
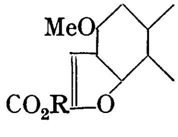


(VII.)



(VIII.)

Having found that application of the Perkin reaction to the aldehydo-ester (III, R = Et) gave a satisfactory yield of the *furocoumarin* (VIII, R = Et), we applied the same reaction to the *aldehydo-acid* (III, R = H), expecting that coumarin formation would be accompanied by simultaneous elimination of the carboxyl group in the furan residue and thus lead to the direct production of (VII). The product, however, was acidic and appeared to be difficult to purify, but on being heated with copper-bronze in a high vacuum the partly purified material gave a small amount of a substance, m. p. 195°, which is almost certainly impure *allo*bergapten. Although these experiments indicated the possibility of attaining our objective by this route if sufficient starting material were employed, we abandoned the method when it was discovered that the following alternative route proved successful.

Decarboxylation of the aldehydo-acid (III, R = H) by means of boiling quinoline containing copper-bronze gave a satisfactory yield of 6-*hydroxy*-4-*methoxy*-7-*formylcoumarone* (V) and on condensation with cyanoacetic acid in alkaline solution and hydrolysis of the resulting salicylidenecyanoacetic acid this aldehyde gave rise to a good yield of the *coumarin*-3-*carboxylic acid* (VI), from which *allo*bergapten (VII) was obtained by elimination of the carboxyl group.

In connexion with the results described in Part II (*loc. cit.*) it is of interest to note that in the formation of (II, R = H) from (II, R = CH_2Ph) and of (IV, R = H) from (III) by means of hydrogen and a palladium catalyst the presence of the carbethoxy-group in the α-position serves to inhibit hydrogenation of the furan residue, whereas under the same conditions 6-*benzyloxy*-4-*methoxycoumarone* is quantitatively converted into 6-hydroxy-4-methoxycoumaran, a low-melting solid which is conveniently characterised by the formation of the p-*nitrobenzoate*.

EXPERIMENTAL.

Ethyl 5-*Benzyloxy*-3-*methoxy*-2-*formylphenoxyacetate* (I, R = Et).—A mixture of 2-hydroxy-4-benzyloxy-6-methoxybenzaldehyde (J., 1931, 2676) (6 g.), ethyl bromoacetate (4·5 g.), anhydrous potassium carbonate (6 g.), and acetone (75 c.c.) was heated on the steam-bath for 4 hours, diluted with more acetone (75 c.c.), filtered (wash salts with acetone), and evaporated in a vacuum. The viscous *product* solidified on being triturated with a little ether and then separated from light petroleum (b. p. 60—80°) in colourless, elongated, rectangular prisms (6 g.), m. p. 74° (Found : C, 66·1; H, 5·8. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%). The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 220°, from methyl alcohol (Found : C, 57·3; H, 4·6; N, 10·8. $C_{25}H_{24}O_9N_4$ requires C, 57·3; H, 4·6; N, 10·7%).

Ethyl 6-*Benzyloxy*-4-*methoxycoumarone*-2-*carboxylate* (II, R = CH_2Ph).—When the foregoing aldehyde (15 g.) was dissolved in an alcoholic solution of sodium ethoxide (from 1·16 g. of sodium and 150 c.c. of alcohol) (agitate), crystalline material quickly began to separate from the resulting yellow solution and one hour later the *product* (II, R = CH_2Ph) was collected, washed with water, and crystallised from 60% alcohol, forming long, colourless, rectangular prisms (9—10 g.), m. p. 111° (Found : C, 69·9; H, 5·7. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%). When the yellow solution of this compound in concentrated sulphuric acid was warmed on the steam-bath, it became brown, then purple, and finally red-brown.

On being acidified with dilute hydrochloric acid, the alkaline liquor left on removal of the foregoing ester gave a precipitate of 5-*benzyloxy*-3-*methoxy*-2-*formylphenoxyacetic acid* (I, R = H), which separated from warm water in colourless needles (2 g.), m. p. 136°, identical with a specimen obtained by hydrolysis of the ethyl ester with hot 5% aqueous-alcoholic potassium hydroxide during ½ hour (Found : C, 64·7; H, 5·2. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%).

Ethyl 6-*Hydroxy*-4-*methoxycoumarone*-2-*carboxylate* (II, R = H).—Debenzylation of ethyl 6-benzyloxy-4-methoxycoumarone-2-carboxylate (2 g.), dissolved in acetic acid (75 c.c.), was effected with hydrogen (120 c.c. absorbed) at atmospheric pressure and a palladium–charcoal catalyst (from 2 g. of charcoal and 0·2 g. of palladium chloride) in the course of 15 minutes. The filtered liquid was evaporated in a vacuum; the residual *product* (1·4 g.) crystallised from aqueous alcohol in colourless rectangular prisms, m. p. 193°, moderately readily soluble in acetic acid or benzene and insoluble in light petroleum (Found : C, 61·1; H, 5·2. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The sulphuric acid reaction was purple, changing to red-brown.

Ethyl 6-*Hydroxy*-4-*methoxy*-7-*formylcoumarone*-2-*carboxylate* (III, R = Et).—A solution of the foregoing compound (1 g.) in ether (250 c.c.), containing hydrogen cyanide (1 c.c.) and zinc cyanide (2 g.), was saturated with hydrogen chloride, 12 hours later the ether was decanted from the purple oil which had separated, and the latter material was well washed with ether to remove hydrogen chloride and then heated on the steam-bath with water (50 c.c.) for 15 minutes. The resulting *aldehyde* separated from dilute alcohol in rectangular plates (0·7 g.), m. p. 178°, giving a red-brown ferric reaction and a yellow sulphuric reaction which became blue and then brown (Found : C, 59·2; H, 4·6. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%). The 2 : 4-*dinitrophenylhydrazone* formed scarlet needles, m. p. 252°, from alcohol (Found : N, 13·0. $C_{19}H_{16}O_9N_4$ requires N, 12·6%).

This aldehyde (0·4 g.), dissolved in acetic acid (50 c.c.), was reduced with hydrogen (approx. 2 mols. absorbed) and a palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 2 g. of charcoal) in the course of 30 minutes and after neutralisation of the filtered solution with sodium bicarbonate the substance (IV, R = H) (0·2 g.) was isolated with ether, crystallised once from alcohol (m. p. 191—193°), and methylated with methyl iodide (1 c.c.) and potassium carbonate (0·5 g.) in boiling acetone (10 c.c.) during 6 hours. On isolation the resulting ethyl 4 : 6-dimethoxy-7-methylcoumarone-2-carboxylate (IV, R = Me) separated from aqueous alcohol in colourless, elongated, rectangular prisms, m. p. 125°, which on admixture with an authentic specimen had m. p. 126° (Part II, *loc. cit.*); mixed with ethyl 4 : 6-dimethoxy-5-methylcoumarone-2-carboxylate, m. p. 115° (Part II, *loc. cit.*), the ester (IV, R = Me) melted at about 85°.

Ethyl 7-*Methoxy*-5 : 6 : 4′ : 5′-*furocoumarin*-2′-*carboxylate* (VIII, R = Et).—A mixture of the foregoing aldehyde (0·2 g.), acetic anhydride (10 c.c.), and sodium acetate (5 g.) was refluxed for 5 hours, cooled, treated with water, and neutralised with sodium bicarbonate. On isolation with ether the resulting *furocoumarin* (0·1 g.) separated from alcohol in stout needles, m. p. 240°, soluble in benzene (Found : C, 62·3; H, 4·2. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%).

6-*Hydroxy*-4-*methoxy*-7-*formylcoumarone* (V).—Ethyl 6-hydroxy-4-methoxy-7-formylcoumarone-2-carboxylate (1 g.) was boiled with aqueous-alcoholic potassium hydroxide (from 1 g. of potassium hydroxide, 15 c.c. of alcohol, and 10 c.c. of water) for ½ hour and, after being diluted with water (40 c.c.), the cooled solution was acidified with dilute hydrochloric acid. The *acid* (0·85 g.) thus precipitated formed colourless rectangular prisms, m. p. 281° (decomp.), from aqueous acetone, which gave a greenish-brown ferric reaction in alcohol [Found : C, 55·9; H, 3·4; OMe, 13·0. $C_{10}H_5O_5(OMe)$ requires C, 55·9; H, 3·5; OMe, 13·1%]. The sulphuric reaction was yellow, becoming blue, then purple, and finally brown.

A solution of this acid (1 g.) in quinoline (10 c.c.), containing copper-bronze (1 g.), was refluxed for 10 minutes, cooled, diluted with ether (100 c.c.), filtered, and washed with dilute hydrochloric acid to remove the quinoline and then with aqueous sodium bicarbonate to remove traces of acidic material. The *formylcoumarone* (V) was isolated from the ethereal solution by extraction with N-sodium hydroxide, followed by acidification of the combined extracts with dilute hydrochloric acid, and was crystallised from warm aqueous alcohol, forming rectangular prisms (0·65 g.), m. p. 135°, having a green ferric reaction in alcohol [Found : C, 62·4; H, 4·4; OMe, 15·9. $C_9H_5O_3(OMe)$ requires C, 62·5; H, 4·2; OMe, 16·1%]. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m. p. 253° (Found : N, 14·7. $C_{16}H_{12}O_7N_4$ requires N, 14·6%).

7-*Methoxy*-5 : 6 : 4′ : 5′-*furocoumarin*-3-*carboxylic Acid* (VI).—A solution of the foregoing aldehyde (1 g.) and cyanoacetic acid (7 c.c. of a solution prepared according to Phelps and Tillotson, *Amer. J. Sci.*, 1908, **26**, 267) in 20% aqueous sodium hydroxide (20 c.c.) was kept for 24 hours, acidified (Congo-red) with dilute hydrochloric acid, and diluted with water (50 c.c.). On being boiled with 4% hydrochloric acid for ½ hour, the resulting yellow precipitate of the salicylidenecyanoacetic acid, m. p. 206—208° (decomp.), was converted into the insoluble *coumarin*-3-*carboxylic acid* (VI), which separated from aqueous acetone in rectangular prisms (0·7 g.), m. p. 242° [Found : C, 60·0; H, 3·4; OMe, 11·8. $C_{12}H_5O_5(OMe)$ requires C, 60·0; H, 3·1; OMe, 11·9%]. A solution of this acid in alcohol or acetone exhibited a bluish-purple fluorescence.

7-*Methoxy*-5 : 6 : 4′ : 5′-*furocoumarin* (allo*Bergapten*) (VII).—The aforementioned carboxylic acid (VI) (0·6 g.) was decarboxylated with boiling quinoline (10 c.c.) containing copper-bronze (0·8 g.) in the course of 5 minutes, and the reaction mixture diluted with ether (100 c.c.) and filtered. After the separation of the quinoline by extraction with dilute hydrochloric acid and subsequently of traces of acidic material with 2% aqueous sodium hydroxide the ethereal solution was washed, dried, and evaporated, and the residual *allo*bergapten purified by sublimation in a high vacuum (140—150°/0·01 mm.) and then by crystallisation from methyl alcohol, forming colourless, rectangular prisms (0·2 g.), m. p. 207°, identical in every way with the material, m. p. 207°, described by Späth and co-workers (*loc. cit.*) [Found : C, 66·6; H, 3·8; OMe, 14·3. Calc. for $C_{11}H_5O_3(OMe)$: C, 66·7; H, 3·7; OMe, 14·4%].

6-*Hydroxy*-4-*methoxycoumaran*.—A mixture of 5-benzyloxy-3-methoxy-2-formylphenoxyacetic acid (I, R = H) (0·4 g.), sodium acetate (1·5 g.), and acetic anhydride (15 c.c.) was refluxed for ½ hour, the greater part of the anhydride removed in a vacuum, and the residue treated with water. On neutralisation of the aqueous liquors with sodium bicarbonate 24 hours later, the oily product, consisting of 6-*benzyloxy*-4-*methoxycoumarone*, solidified and then separated from 70% alcohol in colourless plates, m. p. 55—56° (Found: C, 75·6; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

Hydrogenation and simultaneous debenzylation of this coumarone (1 g.), dissolved in acetic acid (50 c.c.), with hydrogen and a palladium–charcoal catalyst (from 0·1 g. of palladium chloride and 1 g. of charcoal) was complete in about 20 minutes. The filtered solution was neutralised with aqueous sodium bicarbonate and on isolation with ether the resulting 6-hydroxy-4-methoxycoumaran was obtained as a low-melting solid which, owing to its solubility in the usual organic solvents, except aqueous alcohol, could not be conveniently recrystallised and was directly converted into the p-*nitrobenzoate* by treatment with an excess of *p*-nitrobenzoyl chloride and pyridine. This derivative separated from alcohol in needles, m. p. 159—160° (Found: C, 61·0; H, 4·4; N, 4·7. $C_{16}H_{13}O_6N$ requires C, 61·0; H, 4·2; N, 4·4%).

The authors are indebted to Imperial Chemical Industries, Limited, for a grant in aid of this investigation.

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[*Received, March* 29*th*, 1939.]