184. *Experiments on the Synthesis of Bergapten and its Derivatives. Part I. Furocoumarins.*

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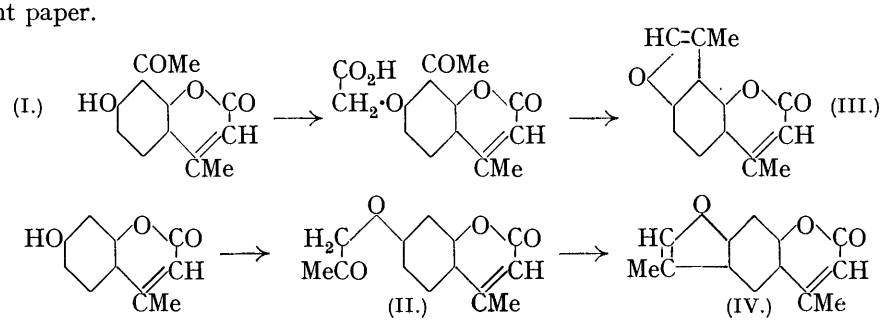
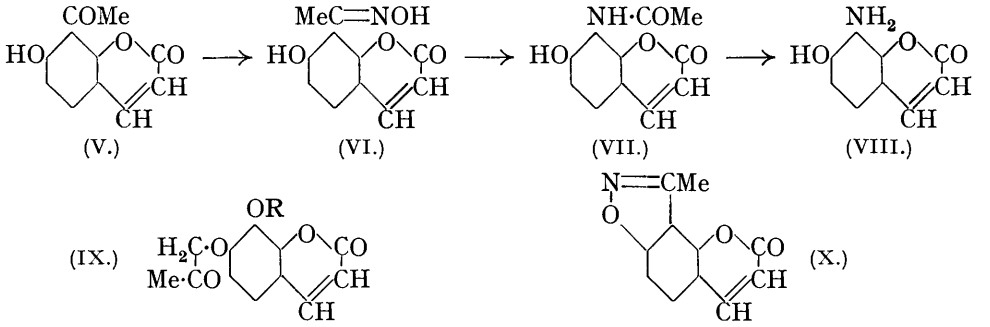
BERGAPTEN has been formulated as a linear furocoumarin derivative. Karrer (*Helv. Chim. Acta*, 1920, **3**, 541) attempted the synthesis of furocoumarin from hydroxycoumarone-acrylic acid, but could not close the ring. This was obviously due to the *trans*-configuration of his acid. It has now been found that 7-hydroxycoumarin condenses with chloroacetone and ω-bromoacetophenone in alkaline solution and the resulting *acetonyl* and

phenacyl derivatives are readily cyclised to furocoumarins by sodium ethoxide, since the intermediate hydroxycoumaroneacrylic acids have the *cis*-configuration.

Limaye (*Ber.*, 1932, **65**, 375) has prepared the angular furocoumarin (III), m. p. 176°, from the ketone (I) obtained by the Fries migration of 7-acetoxy-β-methylumbelliferone, by condensation with chloroacetic acid, subsequent ring closure with acetic anhydride, and decarboxylation. We have found that β-methylumbelliferone on condensation with chloroacetone gives a product (II), which is easily cyclised to a furocoumarin, m. p. 220°; we incline to the view that it has the linear structure (IV). Its degradation to 4 : 6-dihydroxy-*iso*phthalic acid was not successful owing to the small amount of material available, but the similar product from 7-hydroxycoumarin has been transformed into the related *trans*-coumarilic acid (the 5-hydroxy-2-methylcoumarone-4-acrylic acid of Karrer). Therefore there is no doubt as to the linear configuration of the furocoumarins described in the present paper.



Späth and Pailer (*Ber.*, 1934, **67**, 1212), condensing sodioumbelliferone with bromoacetal in xylene at 175—180°, obtained umbelliferone ethyl ether along with angelicin—an angular furocoumarin. In view of our results it cannot be definitely taken that in this reaction an angular condensation always occurs. However, there is some uncertainty as to the structure of our product (V), as we obtained a small quantity of a second substance in its preparation. The main product of the reaction was converted into the *oxime* and transformed by the reactions indicated below into daphnetin (m. p. and mixed m. p.).



The *iso*oxazole (X) was formed along with (VII) in the Beckmann transformation; their separation was effected by means of cold dilute alkali solution.

The sodium salt of (V) does not condense with chloroacetone or chloroacetal under ordinary conditions. Therefore the smooth formation of the chloroacetic acid condensation product from (I) observed by Limaye is difficult to understand. However, we are engaged in finding the conditions for condensing (V) with chloroacetal, so that, after formation of the furocoumarin, the replacement of the acylamido-group by hydroxyl may be effected.

Daphnetin condensed with chloroacetone in presence of one molecular equivalent of alkali to give a homogeneous product, formulated as (IX; R = H), which was methylated to (IX; R = Me); this gave a furocoumarin only with difficulty. The justification for the structure (IX) is that the product is homogeneous and is dehydrated to a furocoumarin, the isomeric substance being incapable of dehydration.

Experimental.

Condensation of 7-Hydroxycoumarin with ω-Bromoacetophenone and with Chloroacetone.—A mixture of umbelliferone (3 g.) and alcoholic sodium ethoxide (0·55 g. of sodium) was mixed with bromoacetophenone (4·7 g.) in alcohol (10 c.c.) and was refluxed for 2½ hours after the addition of a further 15 c.c. of alcohol. The removal of the solvent left a solid, which was washed with dilute aqueous ammonia and crystallised from hot alcohol; m. p. 167° (Found: C, 72·9; H, 4·7. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%).

A solution of the foregoing *7-phenacyloxycoumarin* in alcohol was treated with sodium ethoxide (1 mol.) and kept at 60° for some time. On removal of the solvent and acidification, *3′-phenyl-7 : 6-furocoumarin*, m. p. 200°, was obtained; it was crystallised from hot alcohol (Found: C, 77·8; H, 3·9. $C_{17}H_{10}O_3$ requires C, 77·9; H, 3·8%). It often accompanies the substance, m. p. 167°, in the preparation of the latter.

Similarly, 7-hydroxycoumarin (3 g.), dissolved in alcohol (25 c.c.), was treated with a solution of sodium (0·45 g.) in alcohol, and the mixture refluxed with chloroacetone (2 c.c.) for 2 hours. The residue after the removal of solvent was treated with dilute aqueous ammonia, and the product crystallised from alcohol; m. p. 167° (Found: C, 65·9; H, 4·3. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%).

The foregoing *7-acetonyloxycoumarin* (2 g.) in pure absolute alcohol (10 c.c.) was treated with sodium ethoxide (1 mol.) for 1 hour at 60°, and the product worked up as before; *3′-methyl-7 : 6-furocoumarin* had m. p. 188° after crystallisation from alcohol (Found: C, 72·2; H, 3·7. $C_{12}H_8O_3$ requires C, 72·0; H, 4·0%).

A solution of this furocoumarin in hot aqueous potassium hydroxide (2 mols.) was concentrated to small bulk and exposed to ultra-violet light from a mercury vapour lamp for ½ hour. Dilute hydrochloric acid then precipitated a mixture of the coumarin and 5-hydroxy-2-methylcoumarone-4-acrylic acid, which were separated by means of dilute sodium bicarbonate solution. The acid had m. p. 199—200° after crystallisation from benzene, dissolved to a yellowish solution in sodium carbonate solution, and gave an intense bluish-violet colour with ferric chloride (Found: C, 59·9; H, 4·6. Calc. for $C_{12}H_{10}O_4$: C, 66·1; H, 4·6%).

Condensation of β-Methylumbelliferone and Chloroacetone.—β-Methylumbelliferone (3 g.), dissolved in alcohol (35 c.c.), was treated with sodium (0·4 g.) dissolved in alcohol (5 c.c.), and the resulting solution heated with chloroacetone (2 c.c.) on the steam-bath for 2 hours. *7-Acetonyloxy-4-methylcoumarin* (II), isolated as before, had m. p. 157° after crystallisation from dilute alcohol (Found: C, 67·3; H, 5·0. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). It (5 g.) was treated in hot absolute alcohol (15 c.c.) with 1% alcoholic sodium ethoxide (5 c.c.), then cooled to 30—35°, and occasionally warmed during the next ½ hour. After acidification, the resulting *4 : 3′-dimethyl-7 : 6-furocoumarin* (IV) was dried at 100—105° and crystallised from hot 75% alcohol; m. p. 220° (Found: C, 72·6; H, 4·5. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·6%).

7-Hydroxy-8-acetylcoumarin (V).—Acetylumbelliferone, m. p. 147° (4·8 g.), was powdered with aluminium chloride (11 g.), and heated for 10 minutes at 130°, 15 minutes at 135°, 15 minutes at 135—140°, and 20 minutes at 140—145°. The product was decomposed with ice and the substance was collected, boiled with 20 c.c. of water, and dissolved in a boiling mixture of alcohol (25 c.c.) and water (15 c.c.) with charcoal; *7-hydroxy-8-acetylcoumarin*, m. p. 167°, crystallised from the filtered solution (Found: C, 64·6; H, 3·6. $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%); yield, 2 g.

The *oxime* (VI) had m. p. 223° after crystallisation from alcohol (Found: N, 6·6. $C_{11}H_9O_4N$ requires N, 6·4%). It (2 g.) was dissolved in phosphoryl chloride (20 c.c.) and occasionally warmed during ½ hour; the solution was then poured on ice. Treatment with alkali separated the product into two substances. The alkali-insoluble *iso*oxazole (X), crystallised from dilute alcohol, had m. p. 247° (Found: N, 6·9. Calc.: N, 6·9%). *8-Acetamido-7-hydroxycoumarin* (VII), isolated from the alkaline solution, had m. p. 251° after crystallisation from hot dilute alcohol (Found: N, 6·6. $C_{11}H_9O_4N$ requires N, 6·4%). The substance after hydrolysis with dilute acid showed a diazo-reaction indicating that it is not the methylamide of 7-hydroxycoumarin-8-carboxylic acid.

The foregoing substance (1 g.) was boiled with hydrochloric acid (*d* 1·14, 25 c.c.) and water (15 c.c.) for 3 hours. The *amine* (VIII) crystallised from dilute alcohol in fine yellow needles, m. p. 278° (Found: N, 7·9. $C_9H_7O_3N$ requires N, 7·9%). After diazotisation and decomposition it furnished a small amount of a substance having the characteristic properties of daphnetin (m. p. and mixed m. p.).

Daphnetin-3-carboxylic Acid.—A mixture of pyrogallaldehyde (1·5 g.), malonic acid (3 g.),

pyridine (10 c.c.), and a drop of piperidine was heated on the steam-bath for 1 hour and over a free flame for 2 minutes. The mixture was diluted with water (20 c.c.) and acidified. The pale greenish-yellow substance obtained, recrystallised from hot dilute acetone, gave *daphnetin-3-carboxylic acid*, m. p. 228° (Found: C, 54·3; H, 2·6. $C_{10}H_6O_6$ requires C, 54·0; H, 2·7%).

The preparation of daphnetin from pyrogallol and malic acid was advantageous from the point of view of yield but not of purity.

Condensation of Daphnetin and Chloroacetone.—Daphnetin (1·0 g.) was dissolved in alcohol (10 c.c.), treated with sodium ethoxide solution (0·13 g. of sodium), mixed with a solution of chloroacetone (0·5 g.) in alcohol, and heated for 3 hours on the steam-bath. After removal of the solvent, water precipitated *8-hydroxy-7-acetonyloxycoumarin* (IX, R = H), which was crystallised from hot benzene; m. p. 132—133°. It was soluble in dilute alkali solution (Found: C, 61·5; H, 4·4. $C_{12}H_{10}O_5$ required C, 61·5; H, 4·3%).

The foregoing substance (0·5 g.) was dissolved in alcohol (10 c.c.) by heating, cooled, mixed with a solution of 0·05 g. of sodium in alcohol, and shaken with methyl sulphate (0·35 g.) for ½ hour. After warming on the steam-bath for ½ hour, the solvent was removed, water added, and the mixture extracted with benzene. The extract was freed from alkali-soluble substances and evaporated; the resulting crystalline material, recrystallised from boiling benzene–ligroin, formed silky needles, m. p. 81—82°, of *8-methoxy-7-acetonyloxycoumarin* (Found: C, 62·65; H, 5·3. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%). This substance (0·2 g.) was dissolved in alcohol (8 c.c.) and kept with sodium ethoxide solution (1 mol.) at 70° for 2 hours. After removal of alcohol, water (4 c.c.) was added; the precipitated *8-methoxy-3′-methyl-7 : 6-furocoumarin* crystallised from hot dilute alcohol in very pale yellow needles, m. p. 155° [Found (microanalysis by Dr. Weiler) after drying at 90°: C, 63·2; H, 5·2. $C_{13}H_{10}O_4,H_2O$ requires C, 62·9; H, 4·8%], insoluble in alkali solution.

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