

HETEROCYCLIC COMPOUNDS.

Part VII. Coumarins from Resacetophenone and Cyclic- β -ketonic Esters.

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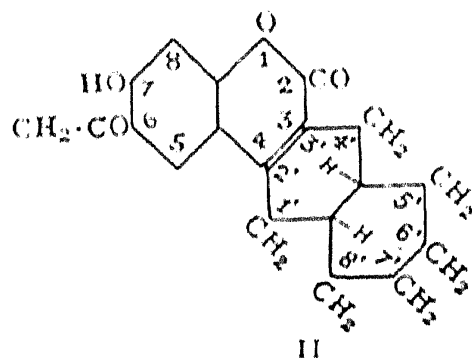
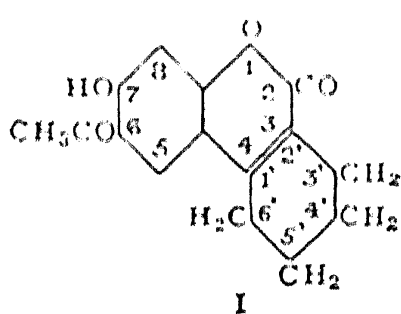
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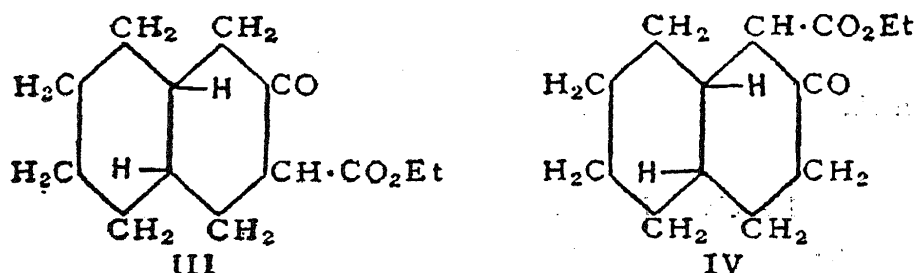
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DESAI AND AHMAD¹ showed that resacetophenone condensed with acetoacetic ester in the presence of phosphorus oxychloride with the formation of 7-hydroxy-6-acetyl-4-methylcoumarin. Extending this reaction to ethylcyclohexanone-2-carboxylate, we find that resacetophenone under similar conditions, gives 7-hydroxy-6-acetyl-(1' : 2' : 4 : 3)-cyclohexenocoumarin (I). Its constitution was established by the fact that it gave a strong ferric chloride reaction showing the *ortho*-position of OH and $-\text{COCH}_3$ groups. Further, reduction by Clemmensen's method gave 7-hydroxy-6-ethyl-(1' : 2' : 4 : 3)-cyclohexenocoumarin which was also prepared for comparison by condensing 4-ethyl-resorcinol with cyclohexanone-2-carboxylate in the presence of concentrated sulphuric acid.



Other cyclic- β -ketonic esters like 4-methylcyclohexanone-2-carboxylate, 5-methylcyclohexanone-2-carboxylate and *trans*- β -decalone-3-carboxylate condensed similarly with resacetophenone with the formation of 7-hydroxy-6-acetyl-4'-methylcyclohexeno-(1' : 2' : 4 : 3); 7-hydroxy-6-acetyl-5'-methylcyclohexeno-(1' : 2' : 4 : 3)-, and 7-hydroxy-6-acetyl-*trans*-octalino-(2' : 3' : 4 : 3)-coumarins (II). As each of them was reducible by zinc amalgam to their 7-hydroxy-6-ethyl analogues which could be easily prepared from 4-ethylresorcinol and the respective β -ketonic esters, the constitution of these coumarins was clearly established.

Ethyl-2-keto-*trans*-decalin-3-carboxylate was prepared by the method of Kötzt's² method; according to Hückel and Goth,³ but the investigators have not determined the constitution. We found that oxidation with alkaline potassium permanganate gave a quantitative *trans*-cyclohexane-1:2-diacetic acid; which could arise only from 3-carboxylate (III) and not from 1-carboxylate (IV).



6-Methylcyclohexanone-2-carboxylate did not react with resacetophenone in the presence of phosphorus oxychloride. We are busy with these esters with substituted resacetophenones as well as the preparation of coumarino-chromones from these coumarins.

Experimental.

7-Hydroxy-6-acetyl-cyclohexeno-(1' 2' : 4 : 3)-coumarin.—A mixture of 6-methylcyclohexanone-2-carboxylate (5 g.), resacetophenone (4.5 g.), phosphorus oxychloride (3 c.c.) and dry benzene (25 c.c.) was heated on the water-bath under reflux for three hours. The benzene solution was poured into water, the sticky, black residue was thrice extracted with benzene (15 c.c.). The residue left after the removal of benzene crystallised from dilute alcohol in needles, m.p. 237° C. (Found: C, 69.5; H, 5.5; $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4 per cent.) The coumarin is soluble in alcohol, benzene and glacial acetic acid but sparingly soluble in hexane and ether. Its alcoholic solution gives a reddish-violet colouration with ferric chloride.

The *acetyl derivative* prepared by heating the coumarin (0.5 g.) with acetic anhydride (5 c.c.) on a sand-bath for three hours, crystallised from dilute alcohol in needles melting at 199° C. (Found: C, 67.9; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3 per cent.)

Reduction to 7-hydroxy-6-ethyl-cyclohexeno-(1' : 2' : 4 : 3)-coumarin.—An alcoholic solution of the above coumarin (0.5 g.) was added to ammonia solution of zinc dust (5 g.) covered with hydrochloric acid (15 c.c.) and the mixture heated under reflux on sand-bath for three hours. The precipitate on cooling was filtered off, extracted with alcohol to get rid of zinc. The alcoholic solution concentrated, when prismatic needles melting at 218° C. were obtained. This was identical in m.p. and mixed m.p.

coumarin obtained from 4-ethylresorcinol and cyclohexanone-2-carboxylate, by Z. Ahmad and Desai.⁴

7-Hydroxy-6-acetyl-4'-methylcyclohexano-(1' : 2' : 4 : 3)-coumarin, was similarly prepared from resacetophenone (5 g.), 4-methylcyclohexanone-2-carboxylate (5 g.), POCl_3 (3 c.c.), and dry benzene (20 c.c.) as usual, and crystallised from dilute alcohol in fine needles melting at 262°C . Its alcoholic solution gave a reddish-brown colour with ferric chloride. (Found: C, 70.4; H, 5.8; $\text{C}_{16}\text{H}_{16}\text{O}_4$ requires, C, 70.6; H, 5.9 per cent.) Reduction with amalgamated zinc dust gave *7-hydroxy-6-ethyl-4'-methylcyclohexeno-(1' : 2' : 4 : 3)-coumarin*, identified by m.p. and mixed m.p. with an authentic specimen.

A mixture of 4-ethylresorcinol (3 g.), 4-methylcyclohexanone-2-carboxylate (3 g.) and concentrated sulphuric acid (10 c.c.) was left overnight and poured over ice. The solid crystallised from dilute alcohol in tiny plates melting at 252°C . It dissolved in alkali with a yellow colour and blue fluorescence. (Found: C, 74.1; H, 7.1; $\text{C}_{16}\text{H}_{18}\text{O}_3$ requires C, 74.4; H, 7.0 per cent.) The *acetyl derivative* crystallised from dilute alcohol in lustrous plates melting at 146°C . (Found: C, 72.1; H, 6.8; $\text{C}_{18}\text{H}_{20}\text{O}_4$ requires C, 72.0; H, 6.7 per cent.) The *methyl ether* prepared by shaking the alkaline solution of the coumarin with dimethyl sulphate crystallised from dilute alcohol in flat needles melting at 158°C . (Found: C, 74.8; H, 7.6; $\text{C}_{17}\text{H}_{20}\text{O}_3$ requires C, 75.0; H, 7.6 per cent.)

7-Hydroxy-6-acetyl-5-methylcyclohexeno-(1' : 2' : 4 : 3)-coumarin, was prepared from resacetophenone (3 g.), 5-methylcyclohexanone-2-carboxylate (3 g.), POCl_3 (3 c.c.) and dry benzene (20 c.c.) by the usual method and crystallised from dilute alcohol in small needles melting at 258°C . Its alcoholic solution gave a reddish colour with ferric chloride. (Found: C, 70.6; H, 6.0; $\text{C}_{16}\text{H}_{16}\text{O}_4$ requires C, 70.6; H, 5.9 per cent.) It could be reduced to *7-hydroxy-6-ethyl-5'-methylcyclohexeno-(1' : 2' : 4 : 3)-coumarin*, identified by m.p. and mixed m.p. with an authentic specimen.

7-Hydroxy-6-ethyl-5'-methylcyclohexeno-(1' : 2' : 4 : 3)-coumarin, was obtained by the usual method from 4-ethylresorcinol and 5-methylcyclohexanone-2-carboxylate and crystallised from dilute alcohol in small plates melting at 202°C . The yellowish alkaline solution gave blue fluorescence, while its solution in concentrated sulphuric acid gave violet fluorescence. (Found: C, 74.2; H, 6.9; $\text{C}_{18}\text{H}_{20}\text{O}_3$ requires C, 74.4; H, 7.0 per cent.) The *acetyl derivative* crystallised from dilute alcohol in fine needles melting at 167°C . (Found: C, 71.8; H, 6.9; $\text{C}_{18}\text{H}_{20}\text{O}_4$ requires C, 72.0; H, 6.7 per cent.) The *methyl ether* crystallised from alcohol in lustrous plates.

melting at 127° C. (Found : C, 74.9 ; H, 7.7 ; $C_{17}H_{20}O_3$ requires C, 75.0 ; H, 7.6 per cent.)

Preparation of trans-β-decalone-3-carboxylate.—This was prepared by a slight modification of the method of Hückel and Goth (*loc. cit.*)

To a cooled solution of sodium ethoxide (6.6 g. Na ; 80 c.c. absolute alcohol) a mixture of *trans*-β-decalone (42 g.) and absolute ethyl oxalate (42 g.) was slowly added with constant shaking, and the mixture allowed to stand in ice-cold water for six hours and then at the ordinary temperature for four days. The mixture was freely diluted with water, and made slightly acidic with ice-cold hydrochloric acid, when a thick oil was precipitated. This was extracted with ether, and the ethereal solution was extracted with 5 per cent. NaOH solution to remove the unreacted decalone. The alkaline solution on acidification gave almost pure *trans*-β-decalone-3-glyoxalate which was extracted with ether, dried and recovered. Its alcoholic solution gave a blood-red coloration with ferric chloride. It was heated in an oil-bath at 180° C. for two hours, taken up in ether, and the ethereal solution extracted with 5 per cent. NaOH solution to remove β-decalone which was also formed as a by-product during heating. The alkaline solution on acidification, gave *trans*-β-decalone-3-carboxylate which was extracted with ether, dried and distilled. It boiled at 145–50° C./6 mm. and immediately solidified on cooling to large, beautiful, rectangular plates, melting at 46° C. It could be easily crystallised from hexane. Its alcoholic solution gave indigo-blue colour with ferric chloride.

Oxidation to trans-cyclohexane-1:2-diacetic acid.—To the ester (0.5 g.) dissolved in N/10 NaOH (20 c.c.) 5 per cent. potassium permanganate (40 c.c.) was gradually added, and thoroughly shaken. Sulphur dioxide was passed to remove the excess of permanganate and the precipitated manganese dioxide was filtered off. The alkaline solution was concentrated on the sand-bath, and strongly acidified with concentrated hydrochloric acid, when a crystalline acid melting at 164° C. was obtained. This was identified as *trans*-cyclohexane-1:2-diacetic acid by mixed melting point with an authentic specimen obtained by oxidising *trans*-β-decalone with concentrated nitric acid according to the instructions of Kandiah.⁵

7-Hydroxy-6-acetyl-trans-octalino-(2' : 3' : 4 : 3)-coumarin, was prepared by the usual method from resacetophenone (3 g.), *trans*-β-decalone-3-carboxylate (3 g.), $POCl_3$ (2 c.c.) and dry benzene (15 c.c.). The coumarin crystallised from dilute alcohol in fine needles melting at 250° C. Its alcoholic solution gave brownish-red coloration with ferric chloride. (Found : C, 73.0 ; H, 6.5 ; $C_{19}H_{20}O_4$ requires C, 73.1 ; H, 6.4 per cent.) When reduced

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by amalgamated zinc, it gave 7-hydroxy-6-ethyl-trans-octalino-(2' : 3' : 4') coumarin, which was also obtained by condensing 4-ethylresorcinol with *trans*- β -decalone-3-carboxylate (4.4 g.) in presence of concentrated sulphuric acid (15 c.c.). It crystallised from dilute alcohol in needles melting at 308° C. This coumarin forms a sparingly soluble sodium salt when treated with a dilute solution of caustic soda, and gives blue fluorescence. It could not be methylated by alkali and dimethyl sulphate. (Found : C, 76.5; H, 7.3; $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4 per cent.)

The *acetyl derivative* crystallised from dilute alcohol in needles melting at 172° C. (Found : C, 73.9; H, 7.2; $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.2 per cent.)

Summary.

Resacetophenone has been condensed with cyclic- β -ketonic esters such as cyclohexanone-2-carboxylate, alkylcyclohexanone-2-carboxylates and *trans*- β -decalone-3-carboxylate in the presence of phosphorus oxychloride to give the formation of 7-hydroxy-6-acetyl derivatives of cyclohexeno- and octaleno-coumarins.

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