HETEROCYCLIC COMPOUNDS—PART I.

Coumarins from Cyclopentanone-2-Carboxylate and 4-Methylcyclopentanone-2-Carboxylate.

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SOME years ago, one of us (R.D.D.) published a paper on the synthesis of Coumarins from phenols and allylacetoacetic ester.[1] Owing to unavoidable circumstances, the work outlined therein could not be resumed. In the meanwhile, a considerable amount of work on the formation of coumarins and chromones from phenols and open-chain β-Ketonic esters has been published by D. Chakravarti and collaborators, and also by A. Robertson and co-workers.[2] A critical search of the literature revealed the presence of very little work on this type of condensation between phenols and cyclic β-Ketonic esters. Dieckmann[3] had studied the condensation of resorcinol and pyrogallol with 4-methylcyclopentanone-2-carboxylate and of resorcinol with cyclohexanone-2-carboxylate. The latter ester had also been condensed with *m*-cresol and α-naphthol by Sen and Basu[4] who had also studied the interaction of 5-methylcyclohexanone-2-carboxylate with phloroglucinol, orcinol and pyrogallol. This being the only work known, we thought it desirable to study the coumarin and chromone formations from the cyclic-β-Ketonic esters derived from cyclopentanone, alkylcyclopentanones, cyclohexanone, alkylcyclohexanones and *trans*-decalones, and the present paper describes our results of the formation of coumarins from the first two esters.

Phenol, *m*-creso *p*-cresol, resorcinol, 4-ethylresorcinol, 4 : 6-diethylresorcinol, orcinol, pyrogallol, phloroglucinol, α-naphthol, β-naphthol, guaiacol, *p*-nitrophenol, thymol and hydroquinone were condensed with cyclopentanone-2-carboxylate and 4-methylcyclopentanone-2-carboxylate in presence of either concentrated H_2SO_4 or phosphorous oxychloride as condensing agents. Resorcinol, 4-ethyl-resorcinol, α-naphthol and pyrogallol gave good yields of coumarins from both the Ketonic esters in presence of concentrated H_2SO_4 ; while phloroglucinol, orcinol and 4 : 6-diethylresorcinol condensed

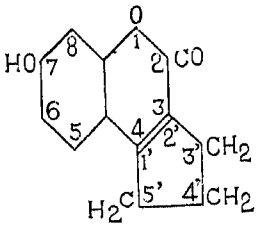
well in the presence of phosphorous oxychloride. The efficiency of this condensing agent in the case of open-chain β-Ketonic esters with polyhydride phenols had already been noted by one of us (Naik, Desai and Trivedi[5]). The yield of coumarins from cresols was not as good as that from the dihydric phenols, while phenol gave the poorest yield. β-Naphthol, guaiacol, *p*-nitrophenol, thymol and hydroquinone did not react in presence of concentrated H_2SO_4.

The coumarin structure was proved by their unusual stability to the hydrolytic action of caustic soda, when the original coumarins were always recovered. If they were the isomeric γ-pyrones, fission to *o*-hydroxy-carboxylic acids or *o*-hydroxy-Ketones should have occurred. The stability of these types of coumarins had also been noticed by Sen and Basu (*loc. cit.*) in the case of cyclohexenocoumarines. These products are also insoluble in hydrochloric acid (1.1), and do not react with benzaldehyde in presence of sodium ethoxide. The isomeric γ-pyrones which we have prepared are soluble in hydrochloric acid, and form styryl derivatives (unpublished work).[6] Therefore, there is no doubt regarding the coumarin structure of the compound described in this communication. The coumarin from orcinol may have its hydroxyl group, either in the 5 or 7 position. Dey[7] has adopted the 5-hydroxy structure of the coumarin formed from orcinol and acetone dicarboxylic acid. As the behaviour of our coumarin from orcinol was similar to that of coumarins from 4 : 6-diethylresorcinol and phloroglucinol (*vide* experimental part), we are inclined to accept the 5-hydroxy structure for it.

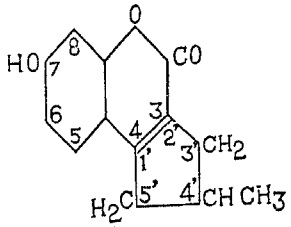
Sen and Chakravarti[8] were successful in mercurating coumarins from open-chain β-Ketonic esters ; while Naik and Patel[9] have studied the effect of substituents in the mercuration of these types of coumarins. As these interesting types of coumarins were in hand, we thought it interesting to mercurate them using the method of Sen and Chakravarti. The coumarins obtained from cyclopentanone-2-carboxylate, and 4-methylcyclopentanone-2-carboxylate with α-naphthol, pyrogallol, resorcinol, orcinol, phloroglucinol and 4-ethylresorcinol were mercurated giving similar types of results showing that the cyclopenteno- and methylcyclopenteno-rings in the 3 : 4-positions exerted similar influence. That some influence is exerted by the rings in 3 : 4-position is shown by the fact that different results are obtained by mercurating 3 : 4-cyclohexeno-coumarins (unpublished work). The coumarins from α-naphthol did not undergo mercuration, the reason being that the coumarin ring could not be opened up, while the coumarin from pyrogallol did not give a pure product. The coumarins from resorcinol, orcinol and phloroglucinol gave diacetoxymercuro-derivatives. The positions occupied

by acetoxymercuro groups are probably 6 and 8, because they are free in all these compounds, and the usual reactivity of coumarins is centred in these positions. The coumarin from 4-ethylresorcinol gave a mixture of mono and diacetoxy-mercuro-derivatives. This coumarin has its 6-position substituted by the ethyl group, and should have given only a mono-acetoxy-mercuro derivative, but our efforts to isolate it in a pure condition were unavailing. We are, however, examining the mercuration of coumarins obtained from 4-ethylresorcinol and open-chain β-Ketonic esters to clear up this point. The anomalous behaviour of coumarins with a negative substituent in 6-position has also been observed by Sen and Chakravarti[8] and Naik and Patel,[9] and our work supports other observations of these previous authors.

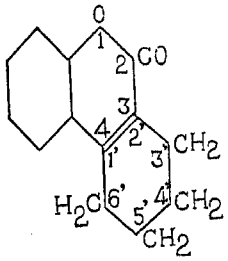
As we have studied the formation of coumarins from cyclic β-Ketonic esters having cyclopentane, cyclohexane and decalin rings, we wish to propose a nomenclature for them, as the one due to Dieckmann (*loc. cit.*) is not satisfactory. This is essentially based upon the nomenclature proposed for naphthacoumarins by Robinson and Rose.[10] These coumarins, as well as those which are to be described in the succeeding papers of this series, contain cyclopentene, cyclohexene and octalin rings fused to the coumarin ring in 3 : 4-positions, therefore, they should be called cyclopenteno-(1': 2': 4 : 3)-coumarin, cyclohexeno-(1': 2': 4 : 3)-coumarin and trans-octalino-(1 : 2 : 3 : 4)-coumarin. The numbering of the substituents in various rings could be illustrated by the following examples :—



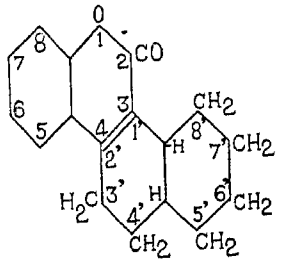
7-Hydroxy-cyclopenteno-(1': 2': 4 : 3)-coumarin



7-hydroxy-4'-methyl-cyclopenteno-(1': 2': 4 : 3) coumarin



Cyclohexeno-(1': 2': 4 : 3)-coumarin



Trans-octalino-(1': 2': 3 : 4)-coumarin

Experimental.

Cyclopentanone-2-carboxylate and 4-methylcyclopentanone-2-carboxylate were prepared by the method of Dieckmann.[3]

Cyclopenteno-(1': 2': 4 : 3)-*coumarin*.—To a mixture of phenol (6 g.) and cyclopentanone-2-carboxylate (9 g.), concentrated sulphuric acid (25 c.c., d. = 1·84) was slowly added with constant shaking and cooling. After allowing the mixture to stand at the room temperature for three days, it was poured on ice water, and the flocculent precipitate that separated out was collected, and crystallised from dilute alcohol (charcoal) when white needles, melting at 129°, were obtained (yield 0·5 g.). The sample dried in a vacuum over $CaCl_2$ was analysed. [Found: C, 74·4 ; H, 5·4 ; $C_{12}H_{10}O_2,\frac{1}{2}H_2O$ requires C = 73·8 ; H, 5·6 per cent.]

6-*Methylcyclopenteno*-(1': 2': 4 : 3)-*coumarin* was similarly prepared from para-cresol (5 g.), the above ester (5 g.) and concentrated H_2SO_4 (20 c.c.). The solid (0·7 g.) crystallised from dilute alcohol in needles melting at 173°–174°. [Found : C, 77·6 ; H, 6·1 ; $C_{13}H_{12}O_2$ requires C, 78·0 ; H, 6·0 per cent.]

7-*Methylcyclopenteno*-(1': 2': 4 : 3)-*coumarin* was similarly prepared from *m*-cresol (5 g.), the above ester (5 g.) and concentrated H_2SO_4 (20 c.c.), and crystallised from dilute alcohol in needles (0·8 g) melting at 105°. [Found: C, 77·9 ; H, 6·3 ; $C_{13}H_{12}O_2$ requires C, 78·0 ; H, 6·0 per cent.] This, as well as the above two coumarins, did not dissolve in boiling caustic soda, and were recovered unchanged.

7-*Hydroxy-cyclopenteno*-(1': 2': 4 : 3)-*coumarin* was prepared from resorcinol (5 g.), the above ester (6 g.) and concentrated H_2SO_4 (20 c.c.), and crystallised from dilute alcohol in needles, m.p. 247° (yield 5·5 g.). [Found : C, 71·3 ; H, 5·1 ; $C_{12}H_{10}O_3$ requires C, 71·3 ; H, 5·0 per cent.] It dissolved in alkali with a blue fluorescence and was recovered unchanged after heating the solution for two hours.

The acetyl derivative prepared by heating the coumarin (0·5 g.) with acetic anhydride (5 c.c.) on a sand-bath for one hour crystallised from alcohol in glistening plates, m.p. 158–159.° [Found: C, 68·5 ; H, 5·1 ; $C_{14}H_{12}O_4$ requires C, 68·8 ; H, 4·9 per cent.]

The benzoyl derivative obtained by treating the pyridine solution of the coumarin (0·5 g.) with benzoyl chloride (1 c.c.) crystallised from dilute alcohol (charcoal) in needles, m.p. 166-167°. [Found: C, 74·5 ; H, 4·6 ; $C_{19}H_{14}O_4$ requires C, 74·8 ; H, 4·6 per cent.].

7-*Hydroxy*-6·8-*bis-acetoxy-mercuro-cyclopenteno*-(1' : 2' : 4 : 3)-*coumarin*.—The hydroxy-coumarin (1 g.) was dissolved in 5 per cent. caustic soda

(8 c.c.) and neutralised with 5 per cent. acetic acid (3·2 c.c.). This solution was then added to a solution of mercuric acetate (4 g. in 100 c.c. of water) gradually with vigorous shaking. The curdy precipitate was filtered off, washed with water under suction, dissolved in 2 per cent. sodium hydroxide solution, filtered, and reprecipitated with dilute acetic acid. The precipitate was again filtered, washed with water, and thoroughly extracted with boiling alcohol. A grey, amorphous powder which did not melt was finally obtained. [Found : Hg, 55·0 ; $C_{16}H_{14}O_7Hg_2$ requires Hg, 55·7 per cent.]

7-*Hydroxy*-6-*ethyl-cyclopenteno*-(1': 2': 4 : 3)-*coumarin* was prepared from 4-ethylresorcinol (6 g.), the ester (6 g.) and concentrated H_2SO_3 (30 c.c.), and crystallised from alcohol (charcoal) in colourless needles, m.p. 266°. [Found : C, 73·0 ; H, 5·8 ; $C_{14}H_{14}O_3$ requires C, 73·0 ; H, 6·1 per cent.] (Yield 3·2 g.)

The acetyl derivative was obtained by boiling the substance (1 g.) with acetic anhydride (10 c.c.) for four hours and crystallised from alcohol in needles, m.p. 168°. [Found : C, 70·5 ; H, 6·3 ; $C_{16}H_{16}O_4$ requires C, 70·6 ; H, 5·9 per cent.] It was mercurated under conditions used for the 7-hydroxy-coumarin, and purified as described before. The dried product gave 46·6 per cent. Hg. An equimolecular mixture of mono- and bis-acetoxymercuro-derivatives, *i.e.*, $\frac{1}{2}$ ($C_{16}H_{16}O_5Hg + C_{18}H_{18}O_7Hg_2$) requires Hg = 47·3 per cent.

5-*Hydroxy*-6 : 8-*diethyl-cyclopenteno*-(1': 2' : 4 : 3)-*coumarin*.—A mixture of the ester (1 g.), 4 : 6-diethylresorcinol (1 g.) and phosphorous oxychloride (4 c.c.) was warmed on a water-bath for about 5 to 10 minutes ; copious fumes of HCl were evolved, and the mixture after cooling was poured into water, warmed, and the precipitate filtered off. On crystallising from dilute alcohol (charcoal) colourless needles, m.p. 195°, were obtained (yield 0·6 g.). [Found : C, 74·4 ; H, 7·1 ; $C_{16}H_{18}O_3$ requires C, 74·4 ; H, 7·0 per cent.] The coumarin dissolved in dilute caustic soda with a yellow solution, which was non-fluorescent.

5-*Hydroxy*-7-*methyl-cyclopenteno*-(1': 2': 4 : 3)-*coumarin* was similarly prepared from the ester (3 g.), orcinol (2 g.) and phosphorous oxychloride (4 c.c.) and purified in an identical manner. When crystallised from methyl alcohol, colourless needles, m.p. 253–254°, were obtained (yield 2 g.). [Found : C, 71·8 ; H, 5·5 ; $C_{13}H_{12}O_3$ requires C, 72·2 ; H, 5·6 per cent.] It dissolved in alkali with a non-fluorescent yellow solution, and was recovered unchanged on acidification. *The acetyl derivative* prepared as usual crystallised from dilute alcohol in colourless needles, m.p. 139–140°. [Found : C, 69·4 ; H, 5·6 ; $C_{15}H_{14}O_4$ requires C, 69·7 ; H, 5·4 per cent.]

5-*Hydroxy-7-methyl*-6 : 8-*bis-acetoxymercuro-cyclopenteno*-(1': 2' : 4 : 3)-*coumarin* was prepared by the method used for the resorcinol analogue and was a grey, amorphous powder that did not melt. [Found : Hg, 53·8; $C_{17}H_{16}O_7Hg_2$ requires Hg, 54·6 per cent.]

5 : 7-*Dihydroxy-cyclopenteno*-(1': 2': 4 : 3)-*coumarin* was obtained from phloroglucinol (1·5 g.), the ester (2 g.) and phosphorous oxychloride (3 c.c.). After the usual purification, it crystallised from dilute alcohol in colourless needles, m.p. 273° (yield 1·5 g.). [Found : C, 63·1 ; H. 4·8 ; $C_{12}H_{10}O_4$, $\frac{1}{2}$ H_2O requires C, 63·4 ; H, 4·7 per cent.] Its alkaline solution was yellow and non-fluorescent.

The diacetyl derivative crystallised from dilute alcohol in colourless needless, m.p. 140°. [Found : C, 63·7 ; H, 4·8 ; $C_{16}H_{14}O_6$ requires C, 63·6 ; H, 4·7 per cent.]

5 : 7-*Dihydroxy*-6 : 8-*bis-acetoxy-mercuro-cyclopenteno*-(1': 2': 4 : 3)-*coumarin* was prepared by the usual method, and was an amorphous, grey powder that did not melt. [Found : Hg, 54·0 ; $C_{16}H_{14}O_8$ Hg_2 requires Hg, 54·5 per cent.]

7 : 8-*Dihydroxy-cyclopenteno*-(1': 2' : 4 : 3)-*coumarin* was prepared from the ester (3 g.), pyrogallol (2·5 g.) and phosphorous oxychloride (10 c.c.), and crystallised from methly alcohol (charcoal) in pinkish needles, m.p. 270° (yield 2 g.). [Found : C, 65·9 ; H, 4·2 ; $C_{12}H_{10}O_4$ requires 66·1 ; H, 4·4 per cent.] Its alkaline solution was reddish-yellow in colour, and did not fluoresce.

The diacetyl derivative crystallised from alcohol in colourless needles, m.p. 194°. [Found : C, 63·4 ; H, 4·7 ; $C_{16}H_{14}O_6$ requires C, 63·6 ; H, 4·7 per cent.]

Cyclopenteno-(1': 2': 4 : 3)-1 : 2-*α-naphthapyrone* was prepared from the ester (3 g.), α-naphthol (3 g.) and concentrated H_2SO_4 (15 c.c.). Crystallisation from alcohol gave pale-yellow needles, m.p. 218° (yield 3·5 g.). [Found : C, 81·1 ; H, 4·9 ; $C_{16}H_{12}O_2$ requires C, 81·3 ; H, 5·1 per cent.] The pyrone did not dissolve in dilute alkali, even on prolonged boiling.

Coumarins from 4-methyl-cyclopentanone-2-carboxylate.—This ester was condensed with the various phenols under conditions which were similar in all details to those adopted in the case of cyclopentanone-2-carboxylate. The yields of coumarins in the case of different phenols were also comparable. Therefore, only the necessary information is given in each case.

7-*Hydroxy*-4'-*methylcyclopenteno*-(1': 2': 4 : 3)-*coumarin* prepared from resorcinol crystallised from alcohol in colourless needles, m.p. 173°.

[Found : C, 72·0 ; H, 5·3 ; calc. for $C_{13}H_{12}O_3$; C, 72·2 ; H, 5·5 per cent.] Dieckmann (*loc. cit.*) gives the m.p. 180°.

The acetyl derivative crystallised from alcohol in white, soft needles, m.p. 143–144° (Dieckmann gives 133–134°). [Found : C, 69·7 ; H, 5·4 ; calc. for $C_{15}H_{14}O_4$: C, 69·8 ; H, 5·4 per cent.]

7-Hydroxy-6 : 8-bis-acetoxymercuro-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-coumarin was a grey amorphous powder with no melting point. [Found : Hg, 53·2 ; $C_{17}H_{16}O_7Hg_2$ requires Hg, 54·6 per cent.]

6-Ethyl-7-hydroxy-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-coumarin obtained from 4-ethyl-resorcinol crystallised from alcohol (charcoal) in colourless needles, m.p. 198°. [Found : C, 73·5 ; H, 6·6 ; $C_{15}H_{16}O_3$ requires C, 73·8 ; H, 6·6 per cent.]

The acetyl derivative crystallised from alcohol in colourless needles, m.p. 116°. [Found : C, 71·0 ; H, 6·2 ; $C_{17}H_{18}O_4$ requires C, 71·3 ; H, 6·3 per cent.]

Its mercuration gave an amorphous powder with no m.p. [Found : Hg, 46·6 ; $\frac{1}{2}(C_{17}H_{18}O_5Hg + C_{19}H_{20}O_7Hg_2)$ requires Hg, 46·3 per cent.]

5-Hydroxy-7-methyl-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-coumarin prepared from orcinol crystallised from alcohol in colourless needles, m.p. 215–216°. [Found : C, 72·9 ; H, 6·3 ; $C_{14}H_{14}O_3$ requires C, 73·1 ; H, 6·1 per cent.] Its solution in dilute sodium hydroxide was deep-yellow and non-fluorescent.

The acetyl derivative crystallised from alcohol in needles, m.p. 107–108°. [Found : C, 70·5 ; H, 6·0 ; $C_{16}H_{16}O_4$ requires C, 70·6 ; H, 5·8 per cent.]

The 6 : 8-bis-acetoxymercuro-derivative was an amorphous powder. [Found] Hg, 52·8 ; $C_{18}H_{18}O_7Hg_2$ requires Hg, 53·6 per cent.].

5-Hydroxy-6 : 8-diethyl-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-coumarin prepared from 4 : 6-diethylresorcinol crystallised from dilute alcohol in needles, m.p. 181°–182°. [Found : C, 74·7 ; H, 7·6 ; $C_{17}H_{20}O_3$ requires C, 75·0 ; H, 7·3 per cent.] Its alkaline solution was deep-yellow and non-fluorescent.

5 : 7-Dihydroxy-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-coumarin prepared from phloroglucinol crystallised from dilute alcohol in needles or plates, m.p. 273°. [Found : C, 64·4 ; H, 5·3 ; $C_{13}H_{12}O_4$, $\frac{1}{2}H_2O$ requires C, 64·7 ; H, 5·4 per cent.]

The diacetyl derivative crystallised from alcohol in needles, m.p. 133–134°. [Found : C, 64·4 ; H, 5·0 ; $C_{17}H_{16}O_6$ requires C, 64·5 ; H, 5·1 per cent.]

The 6 : 8-bis-acetoxymercuro-derivative was a grey, amorphous powder. [Found : Hg, 53·4 ; $C_{17}H_{16}O_8Hg_2$ requires Hg, 53·4 per cent.]

4'-Methylcyclopenteno-(1' : 2' : 4 : 3)-1 : 2-α-naphthapyrone prepared from

α-naphthol crystallised from alcohol in needles, m.p. 167°. [Found: C, 81·8; H, 5·8; $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6 per cent.]

7 : 8-*Dihydroxy-4'-methylcyclopenteno-*(1': 2': 4 : 3)-*coumarin* obtained from pyrogallol crystallised from alcohol in needles, m.p. 240° (sintering at 230°). Dieckmann (*loc. cit.*) gives 207-210°. [Found : C, 67·4; H, 5·1; calc. $C_{13}H_{12}O_4$: C, 67·6; H, 5·3 per cent.]

The diacetyl derivative crystallised from methyl alcohol in needles, m.p. 118–119°. [Found: C, 64·4; H, 5·2; $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1 per cent.]

We have great pleasure in expressing our thanks to Dr. R. F. Hunter for his kind interest in this work, and to Dr. R. C. Shah for his helpful criticism and gift of 4-ethyl and 4 : 6-diethylresorcinols.

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