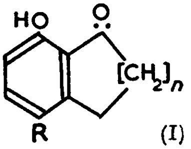
315. peri-*Hydroxy-carbonyl Compounds. Part I. The Synthesis of* peri-*Hydroxy-indanones, -tetralones, and -benzo*cyclo*heptenones.*

By N. F. Hayes and R. H. Thomson.

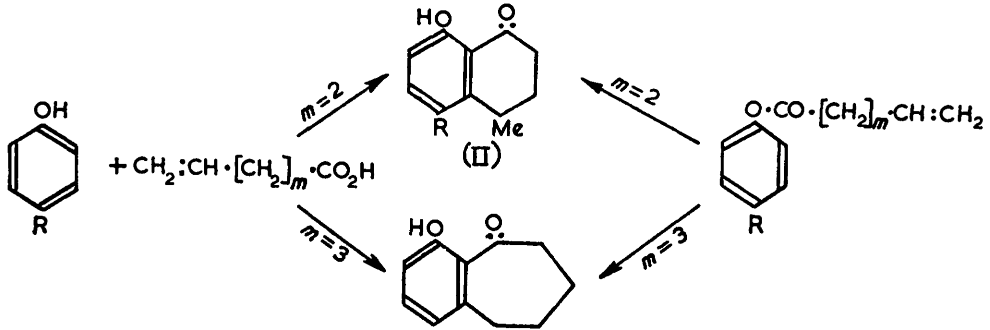
The preparation of compounds of type (I; $n = 2$, 3, and 4) is described.

In hydroxy-ketones of type (I), the size of the alicyclic ring will determine the distance between the two oxygen atoms and this in turn will influence the degree of hydrogen bonding. In order to study this effect a number of ketones of type (I) where $n = 2$, 3, and 4 was required, and the synthetic methods adopted are discussed in this paper. With one exception the ketones were obtained by variations of the Friedel and Crafts procedure, and as the quantities required were small the rapid sodium chloride–aluminium chloride fusion method[1] was used as far as possible.



(I)

Indanones, tetralones, and one benzo*cyclo*heptenone were obtained by Fries rearrangement of aryl esters of appropriate unsaturated acids. This is a recognised method for the preparation of hydroxyindanones, but when it was extended to the synthesis of six- and seven-membered ring ketones we found that the yields fell sharply with increasing ring size. However, alternative syntheses are lengthy and this rapid method is advantageous if only small amounts are needed. The same tetralones and benzo*cyclo*heptenone were also obtained by direct condensation of phenols with unsaturated acids in sodium chloride–aluminium chloride but the yields were very poor, owing, in part, to the volatility of the acids. The examples below illustrate the formation of tetralones by using pent-4-enoic acid, and of the benzo*cyclo*heptenone (III; R = OH) by using hex-5-enoic acid. The structures of the tetralone (II; R = OH) and the benzo*cyclo*heptenone (III; R = OH) were established by conventional methods of synthesis (see Experimental section). The tetralones derived from phenol, *p*-cresol, and *p*-chlorophenol were viscous yellow oils characterised as their 2 : 4-dinitrophenylhydrazones. In view of the low yield of the benzo*cyclo*heptenone (III; R = OH) obtained from quinol, the reaction of hex-5-enoic acid with less reactive phenols was not investigated. The parent benzo*cyclo*heptenone (III; R = OH; H in place of Me) was prepared by standard procedures.



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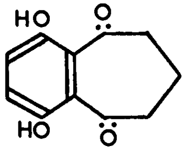
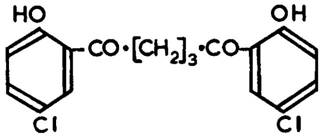
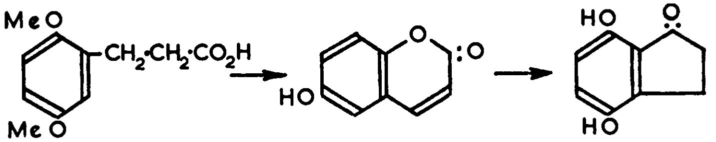
[1] Bruce, Sorrie, and Thomson, *J.*, 1953, 2403.

1 : 5- and 1 : 6-Dihydroxynaphthalene have been reduced to 5- and 6-hydroxytetralone, respectively, by Raney nickel alloy and aqueous sodium hydroxide[2] but we obtained negligible amounts of 8-hydroxy-1-tetralone from 1 : 8-dihydroxynaphthalene by this method. The ketonic material isolated was characterised as its 2 : 4-dinitrophenylhydrazone.

A number of indanones were prepared by reaction of phenols with γ-butyrolactone.[1] Phenol and *p*-cresol afforded two isomers, the 7-hydroxy-derivative predominating in both cases; but only one isomer, 4-chloro-7-hydroxy-3-methylindan-1-one, was isolated on reaction with *p*-chlorophenol, as acylation did not occur *ortho* to the chlorine atom. A parallel was found in the condensation of glutaric anhydride with *p*-chlorophenol; whereas glutaric anhydride and quinol form the cyclic diketone (IV), *p*-chlorophenol under the same conditions yields the bis-condensation product (V). Acylation *ortho* to the chlorine atom in *p*-chlorophenol is known in the condensation with maleic anhydride, which yields 5-chloro-8-hydroxy-1 : 4-naphthaquinone. Two possible explanations were put forward by Baddeley, Makar, and Ivinson[3] and in view of the product we obtained with glutaric anhydride it seems more likely that the cyclisation of the intermediate β-aroylacrylic acid to the quinone depends on its rearrangement to a chelated *cis*-configuration. *p*-Nitrophenol and *p*-hydroxybenzoic acid did not react with γ-butyrolactone when fused in sodium chloride–aluminium chloride at 180°.

(IV) 

 (V)



(VI) (VII) (VIII)

4 : 7-Dihydroxyindanone could not be obtained by a rapid method. Direct condensation of quinol and acrylic acid is not feasible at ordinary pressure and no useful result was obtained from a Fries reaction. Quinol diacrylate was apparently obtained once on a small scale, but this could not be repeated as the crude product polymerised during distillation. A single fusion of the diester gave a very low yield of a yellow phenolic ketone, m. p. 186°, regarded initially as the required product (VIII). This was incorrect and the compound has not been identified. The indanone (VIII) was obtained without difficulty by a conventional route, *i.e.*, cyclisation of β-(2 : 5-dimethoxyphenyl)propionic acid (VI) with phosphoric oxide in boiling benzene followed by demethylation with hydrobromic acid, but an attempt to combine the two steps by rapid fusion of the acid (VI) in sodium chloride–aluminium chloride gave an unexpected product: this compound $C_9H_8O_3$ was not a ketone and yielded only a monoacetate and so must be 3 : 4-dihydro-6-hydroxycoumarin (VII), formed by demethylation and lactonisation of the acid (VI). Dihydrocoumarins are very easily formed by heating β-*o*-hydroxyphenylpropionic acids,[4, 5] and the 6-hydroxy-derivative (VII) was previously obtained by Nebauer and Flatow[6] from a persulphate oxidation of β-*o*-hydroxyphenylpropionic acid and also by reduction of β (2 : 5-dihydroxyphenyl)acrylic acid with sodium amalgam. Loudon and Razdan[7] have

[2] Papa, Schwenk, and Breiger, *J. Org. Chem.*, 1949, **14**, 366.
[3] Baddeley, Makar, and Ivinson, *J.*, 1953, 3969.
[4] Ramart-Lucas and Hoch, *Bull. Soc. chim. France*, 1935, **2**, 327.
[5] Jones, Mackenzie, Robertson, and Whalley, *J.*, 1949, 562.
[6] Nebauer and Flatow, *Z. physiol. Chem.*, 1907, **52**, 392.
[7] Loudon and Razdan, *J.*, 1954, 4299.

recently shown that dihydrocoumarins behave like aliphatic lactones when fused for a relatively long time with aluminium chloride, in forming an acyl cation by ring fission, which by an intramolecular cyclisation produces an isomeric hydroxyindanone. We found, in agreement, that prolonged fusion of the dihydrocoumarin (VII) afforded the dihydroxyindanone (VIII).

EXPERIMENTAL

4-(2 : 5-*Dimethoxyphenyl*)*pent*-3-*enoic Acid*.—To methyl β-(2 : 5-dimethoxybenzoyl)-propionate[8] (15 g.), dissolved in ether (90 ml.) and cooled in ice-water, was added, dropwise with swirling, the Grignard reagent from magnesium (2·1 g.) and methyl iodide (12 g.) in ether (40 ml.). The mixture was kept at 0° during the addition and thereafter for 30 min. It was then allowed to warm to 25° for the next 30 min. and finally refluxed on the steam-bath for 3 hr. On cooling, the complex was decomposed with ice (100 g.) and concentrated hydrochloric acid (200 ml.) and boiled for 1 hr. to hydrolyse the ester. The solution was exhaustively extracted with ether, the latter was shaken with aqueous sodium carbonate (3 × 50 ml.), and the combined alkaline extracts were acidified with dilute hydrochloric acid to give 4 g. only of crude acid. Evaporation of the ether extract left an oil (incomplete hydrolysis). Refluxing this with 30% aqueous sodium hydroxide for 1 hr. followed by acidification gave a further 8 g. of crude *acid*, m. p. 96°. It crystallised from water as needles, m. p. 105° (Found : C, 65·9; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

5 : 8-*Dihydroxy*-4-*methyl*-1-*tetralone*.—(*a*) Quinol (1·65 g.) and allylacetic (pent-4-enoic) acid[9] were condensed in a sodium chloride–aluminium chloride melt in the usual way. The product was isolated with chloroform. Evaporation of the solvent, sublimation of the residue at 150°/0·05 mm., and crystallisation from light petroleum (b. p. 100—120°) gave the *tetralone* as yellow needles, m. p. 186° (0·1 g., 3·5%) (Found : C, 68·9; H, 6·0. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%). It gave a green colour with ferric chloride. The *diacetate* crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 150° (Found : C, 65·0; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·1; H, 5·8%).

(*b*) Pent-4-enoyl chloride (4 g.) and quinol (2 g.) were refluxed together for 10 min. The resultant ester was distilled at 90—95°/ 20 mm. and without further purification was added to a melt of anhydrous aluminium chloride (16 g.) and sodium chloride (4 g.) at 180°, and worked up as before. Yellow needles, m. p. 186° (0·3 g., 20%), of the tetralone were obtained.

(*c*) The above pentenoic acid was hydrogenated over Adams catalyst in chloroform–methanol. The resulting pentanoic acid (b. p. *ca.* 100°/0·05 mm.), when fused in aluminium chloride–sodium chloride as before, gave the tetralone, m. p. and mixed m. p. 186° (60%).

Condensation of Pent-4-enoic Acid with Other Phenols.—The methods used were (*a*) direct condensation of phenol and acid, and (*b*) Fries rearrangement of the requisite pent-4-enoate as described previously.[1]

5-Chloro-8-hydroxy-4-methyl-1-tetralone, obtained by both methods from *p*-chlorophenol, was isolated as a viscous yellow oil, which gave a green ferric chloride colour and formed a 2 : 4-*dinitrophenylhydrazone*, orange needles, m. p. 256° (from acetic acid) (Found : C, 54·4; H, 4·0; N, 14·9; Cl, 9·0. $C_{17}H_{15}O_5N_4Cl$ requires C, 54·6; H, 3·75; N, 15·0; Cl, 9·5%).

8-Hydroxy-4 : 5-dimethyl-1-tetralone obtained from *p*-cresol as a yellow oil, yielded an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 247° (from acetic acid) (Found : C, 58·2; H, 4·85; N, 14·8. $C_{18}H_{18}O_5N_4$ requires C, 58·4; H, 4·85; N, 15·1%).

8-*Hydroxy*-4-*methyl*-1-*tetralone*. Phenol and pent-4-enoic acid similarly gave a yellow liquid, which formed a bright red 2 : 4-*dinitrophenylhydrazone*, m. p. 220° (from acetic acid) (Found : C, 57·25; H, 4·65; N, 15·9. $C_{17}H_{16}O_5N_4$ requires C, 57·3; H, 4·5; N, 15·8%).

1′ : 4′-*Dihydroxy*-7-*methylbenzo*cyclo*hept*-1-*en*-3-*one*.—(*a*) Hex-5-enoyl chloride[10] (4·5 g.) and quinol (1·5 g.) were refluxed together until evolution of hydrogen chloride had ceased (5—10 min.), and the resultant ester was distilled. Without further purificatlon, this was added to a melt of aluminium chloride–sodium chloride at 180°. The black solid obtained was dried and sublimed at 150°/0·05 mm. to give yellow crystals which were finally purified from light petroleum (b. p. 100—120°) and had m. p. 186° (0·2 g., 5%) (Found : C, 69·6; H, 7·75. $C_{12}H_{14}O_3$ requires C, 69·9; H, 7·75%). Direct condensation of quinol (2 g.) with hex-5-enoic acid (2 g.) in the same medium gave yellow needles, m. p. and mixed m. p. 186° (0·1 g., 2%).

(*b*) Methyl γ-(2 : 5-dimethoxybenzoyl)butyrate (10 g.) was treated with methylmagnesium

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[8] Dalal and Nargund, *J. Indian Chem. Soc.*, 1937, **14**, 406.

[9] Conrad and Bischoff, *Annalen*, 1880, **204**, 170.

[10] Helferich and Malkomes, *Ber.*, 1922, **455**, 704

iodide, as in the preparation of the lower homologue; the product was dissolved in methanol and hydrogenated over Adams catalyst. The hexanoic acid (3 g.) was then added to a melt of anhydrous aluminium chloride (20 g.) and sodium chloride (5 g.) at 180° and the ketone sublimed and crystallised from light petroleum (b. p. 100—120°), to give yellow needles, m. p. and mixed m. p. 186° (0·5 g., 20%).

δ-(2 : 5-*Dimethoxyphenyl*)*valeric Acid*.—γ-(2 : 5-Dimethoxybenzoyl)butyric acid (12 g.) (obtained by the method used by Fieser [11] for the corresponding propionic acid, but not by Shah and Nargund's procedure [12]) was reduced by the Clemmensen–Martin procedure during 24 hr. Distillation *in vacuo* gave a colourless liquid, which solidified. The desired *acid* crystallised from light petroleum (b. p. 50—60°) as prisms, m. p. 50° (6 g., 45%) (Found : C, 65·4; H, 7·3. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·5%).

1′ : 4′-*Dihydroxybenzo*cyclo*hept*-1-*en*-3-*one*.—Cyclisation of the dimethoxyphenylvaleric acid in sodium chloride–aluminium chloride yielded the *ketone* as yellow needles, m. p. 121° (from light petroleum, b. p. 100—120°) (30%) (Found : C, 68·6; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%). It gave a transient blue-green colour with ferric chloride. The *diacetate* crystallised from light petroleum (b. p. 100—120°) as colourless rosettes, m. p. 112° (Found : C, 65·3; H, 6·0. $C_{15}H_{16}O_5$ requires C, 65·2; H. 5·8%), and the 2 : 4-*dinitrophenylhydrazone* formed orange crystals, m. p. 206° (from aqueous acetic acid) (Found : C, 54·8; H, 4·5; N, 14·9. $C_{17}H_{16}O_6N_4$ requires C, 54·8; H, 4·3; N, 15·1%). The *dimethyl ether* (methyl sulphate–acetone–potassium carbonate) separated from light petroleum (b. p. 50—60°) as colourless needles, m. p. 60° (Found : C, 70·8; H, 7·55. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). The ether has since been prepared by Anderson *et al.*[13] by cyclisation of the dimethoxyphenylvaleric acid with phosphoric acid.

8-*Hydroxy*-1-*tetralone*.—The procedure adopted was similar to that of Papa *et al.*[2] 1 : 8-Dihydroxynaphthalene (1·4 g.) was dissolved in 10% aqueous sodium hydroxide (100 ml.), the solution warmed to 40—50°, and nickel–aluminium alloy (5 g.) added in portions during 30 min. Then the mixture was refluxed for 1 hr. and filtered into ice and concentrated hydrochloric acid. The product was extracted with ether and distilled *in vacuo*, to give a few drops of a colourless liquid whose 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as red needles, m. p. 253° (Found : C, 56·3; H, 4·15; N, 16·1. $C_{16}H_{14}O_5N_4$ requires C, 56·1; H, 4·1; N, 16·3%). Starting material was recovered together with a small amount of yellow non-ketonic crystals, m. p. 218° (from light petroleum, b. p. 100—120°) (Found : C, 82·8; H, 4·1%).

5-*Chloro*-8-*hydroxy*-7-*methoxy*-1-*tetralone*.—5-Chloro-7 : 8-dimethoxytetralone (0·5 g.) in glacial acetic acid (5 ml.) and concentrated hydrochloric acid (20 ml.) was refluxed for 2 hr. After cooling and dilution with water (50 ml.), the precipitate was collected, washed, dried, and crystallised from light petroleum (b. p. 80—90°) as yellow needles, m. p. 104° (0·3 g., 60%). Ghosh and Robinson [14] obtained this compound as a by-product in the cyclisation of γ-(2-chloro-4 : 5-dimethoxyphenyl)butyric acid. The *acetate* separated from light petroleum (b. p. 100—120°) as colourless rosettes, m. p. 97° (Found : C, 57·9; H, 4·8; Cl, 13·6. $C_{13}H_{13}O_4Cl$ requires C, 58·1; H, 4·8; Cl, 13·2%).

Condensation of γ-Butyrolactone with Various Phenols.—The general procedure of Bruce, Sorrie, and Thomson [1] was used.

(*a*) *p*-Cresol and γ-butyrolactone yielded two products. The major portion, 7-*hydroxy*-3 : 4-*dimethylindan*-1-*one* (57%), was obtained as colourless prisms, m. p. 54° (from light petroleum b. p. 50—60°). This compound was only slightly soluble in aqueous sodium hydroxide and gave an intense violet ferric chloride colour. The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as orange needles, m. p. 262° (Found : C, 57·1; H, 4·5; N, 15·9. $C_{17}H_{16}O_5N_4$ requires C, 57·3; H, 4·5; N, 15·7%). The second product was obtained as a sublimate after distillation of the more volatile isomer. On crystallisation from water 4-*hydroxy*-3 : 7-*dimethylindan*-1-*one* formed colourless needles, m. p. 175° (4%) (Found : C, 74·8; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). This indanone was readily soluble in cold aqueous sodium hydroxide but gave no colour with ferric chloride. The 2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene as dark red needles, m. p. 300° (Found : C, 57·05; H, 4·5; N, 15·3%).

(*b*) Phenol and γ-butyrolactone similarly gave two isomeric indanones. 7-Hydroxy-3-methylindanone distilled as a colourless liquid, b. p. 63°/0·05 mm. (50%) (Found : C, 74·05;

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[11] Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2966.
[12] Shah and Nargund, *J. Univ. Bombay*, 1947, **15**, *A*, 19.
[13] Anderson, Horton, Walker, and Weiler, *J. Amer. Chem. Soc.*, 1955, **77**, 598.
[14] Ghosh and Robinson, *J.*, 1944, 506.

H, 6·3. Calc. for $C_{10}H_{10}O_2$: C, 74·1; H, 6·2%). The *acetate* separated from aqueous acetic acid as colourless needles, m. p. 120° (Found: C, 70·7; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%), and the 2 : 4-*dinitrophenylhydrazone* from acetic acid as orange-red needles, m. p. 256° (Found: C, 57·45; H, 4·05; N, 16·7. $C_{16}H_{14}O_5N_4$ requires C, 57·8; H, 4·2; N, 16·9%). The isomeric ketone, 5-hydroxy-3-methylindanone, formed colourless needles (from water), m. p. 148° (8%) (Found: C, 73·75; H, 6·2%). Its 2 : 4-*dinitrophenylhydrazone* separated from nitrobenzene as red crystals, m. p. 270° (Found: C, 57·75; H, 4·5; N, 16·8%).

(*c*) *p*-Chlorophenol and γ-butyrolactone formed only one product, 4-*chloro*-7-*hydroxy*-3-methylindanone, which crystallised from aqueous alcohol in colourless needles, m. p. 54° (50%) (Found: C, 60·6; H, 4·7; Cl, 17·9. $C_{10}H_9O_2Cl$ requires C, 60·7; H, 4·55; Cl, 18·5%). The *acetate* formed colourless needles, m. p. 118° (from aqueous acetic acid) (Found: C, 60·35; H, 4·25; Cl, 14·9. $C_{12}H_{11}O_3Cl$ requires C, 60·1; H, 4·5; Cl, 15·2%), and the 2 : 4-*dinitrophenylhydrazone* also crystallised from aqueous acetic acid forming orange needles, m. p. 248° (Found: C, 51·1; H, 3·5; N, 14·9; Cl, 9·5. $C_{16}H_{13}O_5N_4Cl$ requires C, 50·9; H, 3·45; N, 14·8; Cl, 9·7%).

7-*Hydroxy*-4-*methylindan*-1-*one*.—*p*-Cresol (1 g.) and acryloyl chloride (1 g.) were refluxed until hydrogen chloride was no longer evolved (5 min.) and the resultant ester distilled (b. p. *ca.* 200°). This liquid (0·7 g.) was added to a melt of anhydrous aluminium (20 g.) and sodium chloride (5 g.) at 180° and after 2 min. at this temperature the mixture was cooled and decomposed with ice and hydrochloric acid. The ketone was purified by sublimation at 60°/0·05 mm. and crystallisation from aqueous alcohol, forming colourless needles, m. p. 110° (0·4 g., 26%). 7-Hydroxyindan-1-one, m. p. 111°, and 4-chloro-7-hydroxyindan-1-one, m. p. 122°, were similarly obtained from phenol and *p*-chlorophenol respectively.

Quinol Diacrylate.—Acryloyl chloride (1·5 g.) and quinol (0·9 g.) were refluxed together for 5 min. The solid deposited on cooling crystallised from aqueous alcohol, to give the *diester* as colourless plates, m. p. 88° (Found: C, 66·0; H, 4·6. $C_{10}H_{10}O_4$ requires C, 66·0; H, 4·6%). Attempts to repeat this experiment failed.

1 : 3-*Di*-(2-*hydroxy*-5-*chlorobenzoyl*)*propane*.—*p*-Chlorophenol (5·7 g.) and glutaric anhydride (5 g.), fused in sodium chloride–aluminium chloride, gave the *diketone* as pale yellow needles (from aqueous alcohol), m. p. 156° (5·8 g.) (Found: C, 57·5; H, 3·8; Cl, 20·5. $C_{17}H_{14}O_4Cl_2$ requires C, 57·8; H, 4·0; Cl, 20·1%). The *bis*-2 : 4-*dinitrophenylhydrazone* separated from *o*-dichlorobenzene as orange crystals, m. p. 258° (Found: C, 48·7; H, 3·2; N, 15·5; Cl, 10·4. $C_{29}H_{22}O_{10}N_8Cl_2$ requires C, 48·8; H, 3·1; N, 15·7; Cl, 10·0%), and the *diacetate* separated from light petroleum (b. p. 100—120°) as colourless rosettes, m. p. 92° (Found: C, 57·4; H, 4·3; Cl, 15·95. $C_{21}H_{18}O_6Cl_2$ requires C, 57·7; H, 4·1; Cl, 16·2%).

3 : 4-*Dihydro*-6-*hydroxycoumarin*.—To a molten mixture of anhydrous aluminium chloride (30 g.) and sodium chloride (7·5 g.) at 180°, was added slowly with stirring, β-(2 : 5-dimethoxyphenyl)propionic acid[8] (2 g.). After 5 min., the mixture was cooled, treated with water (200 ml.) and concentrated hydrochloric acid (100 ml.), and extracted with ether. After being dried ($MgSO_4$), the solvent was removed and the residue, crystallised from water, had m. p. 163° (55%) (Found: C, 65·0; H, 5·1. Calc. for $C_9H_8O_3$: C, 65·2; H, 4·9%). It gave no ferric chloride colour and formed an acetate, m. p. 86°.

4 : 7-*Dihydroxyindan*-1-*one*.*—(*a*) 4 : 7-Dimethoxyindan-1-one[15] (0·2 g.) was dissolved in 48% hydrobromic acid (10 ml.) and refluxed for 2 hr. The solvent was removed *in vacuo* and the residue crystallised from ethyl acetate–light petroleum (b. p. 100—120°) to give colourless needles, m. p. 198° (Found: C, 65·75; H, 4·75. $C_9H_8O_3$ requires C, 65·85; H, 4·9%).

(*b*) 3 : 4-Dihydro-6-hydroxycoumarin (0·1 g.) was added to a melt of anhydrous aluminium chloride (10 g.) and sodium chloride (2·5 g.) at 180° and the temperature was maintained between 180° and 220° for 45 min. After decomposition of the complex in the usual way, ether-extraction yielded a colourless solid, which crystallised from ethyl acetate–light petroleum in needles, m. p. and mixed m. p. 198°.

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THE UNIVERSITY, OLD ABERDEEN, SCOTLAND. [*Received, December 7th*, 1955.]

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* The compound named 4 : 7-dihydroxyindanone in ref. 7, p. 4302, should be 5 : 7-dihydroxyindanone.

[15] Arnold and Zaugg, *J. Amer. Chem. Soc.*, 1941, **63**, 1317.