UNSYMMETRICALLY SUBSTITUTED 3,3′-METHYLENE BRIDGED 2,2′-DIHYDROXYCHROMONES[1,2]

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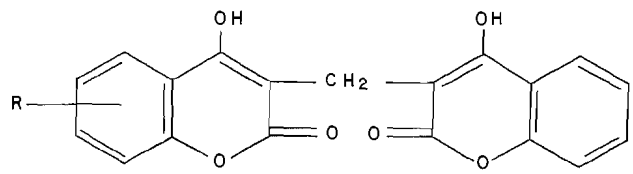
ABSTRACT

Unsymmetrically substituted dicoumarol derivatives* have been synthesized by taking advantage of the fact that 4-hydroxycoumarins will undergo the Mannich reaction at C_3 and also take part in Michael-type addition reactions. In the presence of methyl iodide, 4-hydroxy-3-*N*-piperidinomethylcoumarin and 4-hydroxycoumarin gave dicoumarol. By using monosubstituted 4-hydroxycoumarins a variety of unsymmetrically substituted dicoumarols have been prepared in good yield. The infrared spectra of some of the intermediates and products are reported and discussed.

A large variety of substituted derivatives of the anticoagulant dicoumarol have been prepared with a view to the production of a more active product having less side effects. These compounds fall into two main groups: (i) those bearing a substituent on the bridge methylene group are generally prepared by condensing an aldehyde or ketone with 4-hydroxycoumarin; (ii) symmetrically disubstituted dicoumarols, prepared by condensing a substituted 4-hydroxycoumarin derivative with formaldehyde, as well as combinations of (i) and (ii). Neither of these methods is amenable to the preparation of unsymmetrically substituted derivatives (I) of dicoumarol, which are of a twofold interest: (*a*) as possible physiologically active analogues of dicoumarol; (*b*) a monohydroxylated dicoumarol may be an active metabolic product of the anticoagulant but this hypothesis has never been tested owing to the unavailability of such hydroxydicoumarols. We have now developed a method which appears to be fairly general for the synthesis of this type of compound.



(I)

The methylene group at C_3 in 4-hydroxycoumarin is reactive and will undergo Michael addition with suitably activated double bonds. For instance, addition will take place across the double bond in ethylideneacetone (1). Sullivan *et al.* (2) suggest that formation of dicoumarol itself from formaldehyde and 4-hydroxycoumarin proceeds by this type of addition: the unstable 3-methylene-2,4-diketochroman is first formed; this is very reactive and cannot be isolated but reacts quickly with another molecule of 4-hydroxycoumarin to form dicoumarol, this last step involving a Michael addition.

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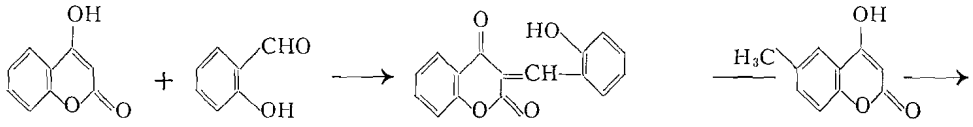
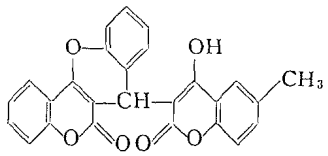
[2]*This article is based on a paper presented at the 41st Annual Conference and Exhibition of the Chemical Institute of Canada, Toronto, May 26–28, 1958.*

**The chemical name for dicoumarol is 3,3′-methylenebis(2-hydroxychromone) (see p. 1506). On this basis the name of ring-monosubstituted derivatives becomes very clumsy, e.g., 2-hydroxy-7-methyl-3-chromonyl-2-hydroxy-3-chromonylmethane. We propose to use the name dicoumarol to represent the ring system of 3,3′-methylenebis(2-hydroxychromone) and this practice will be adhered to throughout this paper.*

They obtained support for this suggestion by condensing 4-hydroxycoumarin (II) with an equimolar quantity of salicylaldehyde to give 3-(*o*-hydroxybenzylidene)-2,4-diketochroman (III), which could be isolated, and which reacted with 4-hydroxy-6-methylcoumarin (IV) to give (V), indicating the stepwise nature of the reaction. Incidentally, (V) was the only example of a derivative of an unsymmetrically substituted



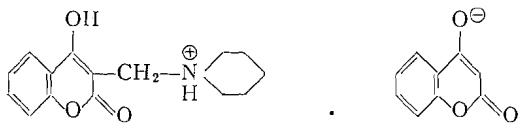
(II) (III) (IV)



(V)

dicoumarol we were able to find in the literature. If 3-methylene-2,4-diketochroman could be generated *in situ* in the presence of a substituted 4-hydroxycoumarin derivative, addition would take place to give the required type of compound. Condensation of 4-hydroxycoumarin with formaldehyde in the presence of a substituted 4-hydroxycoumarin was ruled out, since this would probably give rise to an inseparable mixture of dicoumarol derivatives. On the other hand, formation of the activated double bond *in situ* from a Mannich base was considered particularly suitable, since, by taking advantage of the active methylene at C_3, Robertson and Link (3) and also Prochazka (4) introduced a variety of aminomethyl groups in that position.

Heating together an equimolar mixture of 4-hydroxy-3-*N*-piperidinomethylcoumarin (VI) and 4-hydroxycoumarin (II) gave a highly insoluble 'addition complex' whose molecular composition corresponded to the sum of one mole of (VI) and one of (II). In view of the insolubility and instability of this complex its structure could be that of a salt of the type (VII*a*).



(VII*a*)

It was hoped that the infrared spectrum would shed some light onto its structure, so that it was first necessary to study the spectrum of 4-hydroxycoumarin and that of 4-hydroxy-3-*N*-piperidinomethylcoumarin, and then to see what changes took place when these two combined to form the complex.

Infrared Spectra of 4-Hydroxycoumarins

4-Hydroxycoumarin can exist in a number of tautomeric modifications, but, according to Arndt (5), because of resonance stabilization the two main forms are the 4-hydroxycoumarin (II) and the 2-hydroxychromone (VIII) structures (see also ref. 5*b*).

(II) (VIII)

As to which form predominates seems to depend on the experimental conditions and the nature of the substituents if present. From a study of the reactions of 4-hydroxycoumarin Klosa (6) concluded that the 4-hydroxycoumarin form (II) was favored but that under special conditions of solvent or acidity the chromone form could be favored. On the other hand, from a consideration of the ultraviolet spectra of 4-hydroxycoumarins in ethanol solution, Garden, Hayes, and Thomson (7) suggested that in this solvent 4-hydroxycoumarins could exist in the keto form (whether structures of types (VIII), or the diketonic structure, were meant is not clear).

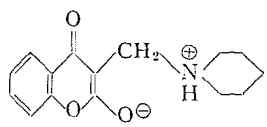
It should be possible to distinguish between structures (II) and (VIII) by infrared spectroscopy: (II) should exhibit a band for an α,β-unsaturated six-membered ring lactone at *ca.* 1710 cm^{-1} (8), whereas (VIII) should have a band at *ca.* 1660 cm^{-1} corresponding to the $\alpha,\beta,\alpha',\beta'$-di-unsaturated ketone (9), and none at 1710 cm^{-1}. An elegant application of this principle is seen in the elucidation of the structures of novobiocin and its degradation products; novobiocin and 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin exist in the 4-hydroxycoumarin form (λ_{max} 5.92 μ) (10), whereas if a free —OH group is present at $C_{(7)}$ as in dihydronovobiocic acid (10) or in 4,7-dihydroxycoumarin (more correctly called 2,7-dihydroxychromone) (11) the chromone structure is the stable form (λ_{max} 6.0 μ). Similarly, the infrared spectra of 4-hydroxycoumarin, 4-methoxycoumarin, and 2-methoxychromone in the carbonyl region were studied by Knobloch and Prochazka (12). In dilute ethylene chloride solution 4-hydroxy- and 4-methoxycoumarin exhibited a single strong band at *ca.* 1710 cm^{-1} (with a medium intensity shoulder at 1700 cm^{-1}) corresponding to the α,β-unsaturated six-membered lactone structure, indicating that in that solvent 4-hydroxycoumarin probably exists exclusively in the 4-hydroxy form. On the other hand, 2-methoxychromone showed a single strong band at *ca.* 1650 cm^{-1} corresponding to the $\alpha,\beta,\alpha',\beta'$-di-unsaturated ketonic stretching motion. Again, Wildi (13) reports a single band at 5.90 μ for 4-hydroxy-3-phenylcoumarin in chloroform solution, together with a weak —OH stretching band at 2.87 μ.

Because of solubility and stability considerations it was only possible to measure the spectrum of the 'addition complex' obtained above as a Nujol mull so that it was desirable to study the spectrum of 4-hydroxycoumarin and 4-hydroxy-3-*N*-piperidinomethylcoumarin under such conditions. The spectrum of 4-hydroxycoumarin in the solid state is much more complex than the solution spectrum. There was no —OH band at *ca.* 2.9 μ but a medium shoulder was present at 3125 cm^{-1} together with two medium peaks at 2730 and 2560 cm^{-1}, indicating that the —OH group is strongly bonded. In the carbonyl region *two* bands were present: at 1700 (s) (with an ill-defined shoulder at 1709) and at 1673 cm^{-1}(s), the latter being the stronger of the two. The spectrum of 4-hydroxy-7-methoxycoumarin is rather similar* with bands at 3125 (sh)(m), 2760 (w), 2620 (w), 1707 (s) (medium shoulder at 1714 cm^{-1}), and 1672 cm^{-1} (ms). It seems rather unlikely

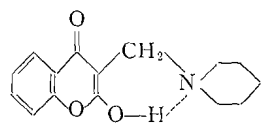
**This spectrum is very similar to that obtained by Dr. R. H. Thomson and co-workers using the* KBr *disk technique. We understand that they have made an infrared study of 4-hydroxycoumarins, which is due to be published soon, but as our limited study was necessary for an interpretation of our results we are including it here. We would like to thank Dr. Thomson for sending us a tracing of the spectrum of 4-hydroxy-7-methoxycoumarin in* KBr.

that the strong band at 1673 cm^{-1} should be due to the conjugated C=C in the 4-hydroxy form; the band for this group is probably merged with the strong broad band at 1618 cm^{-1}. There are two possible interpretations for the presence of the two carbonyl stretching bands at 1700 and 1673 cm^{-1}. One is that in the solid state the compound is a mixture of the two tautomeric modifications, (II) giving rise to the higher and (VIII) to the lower band. Alternatively, the 1673 cm^{-1} band could arise from partial intermolecular hydrogen bonding between the —OH group of one molecule and the lactone carbonyl group of another; the two bands would then be due to a mixture of chelated and unchelated lactone carbonyl groups in the solid state. In dilute ethylene chloride solution, such chelation would not take place and only the band at *ca.* 1710 cm^{-1} would be observed. This would also fit the fact that a chloroform solution of 4-hydroxy-3-phenylcoumarin has a single band at 5.90 μ and a weak —OH band at 2.87 μ (13) (though in this case the steric effect of the phenyl substituent might prevent effective intermolecular chelation). If the first interpretation is accepted one would have to assume that in ethylene chloride solution the 4-hydroxycoumarin form is stabilized with respect to the chromone structure. On the basis of the present evidence it does not seem possible as yet to decide between the two alternatives. The same remarks apply also to 4-hydroxy-7-methoxycoumarin, which again exhibits no peak at 3450 cm^{-1}; in this case the 1672 cm^{-1} peak is somewhat weaker than the 1701 cm^{-1} one and completely resolved from it.

4-Hydroxy-3-*N*-piperidinomethylcoumarin has no hydroxyl band in the 3 μ region (in Nujol mull). There are two bands at 2765 (m) and 2610 cm^{-1} (w), but only a single band is present at 1678 cm^{-1}. The Mannich base, therefore, either exists in the chromone form in the solid state, or is completely intermolecularly chelated, which is less likely. The absence of an —OH band could be due to such a chelation but could also be explained by internal salt formation (VI*a*) or internal hydrogen bonding (VI*b*).



(VI*a*)

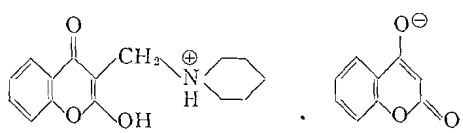


(VI*b*)

In the absence of a band at 2440–2350 cm^{-1} for an R_3NH^+ grouping (14) (VI*b*) seems the more probable structure.

The spectrum of the 'addition complex' in Nujol mull shows bands at 3170 (m) (broad) (bonded —OH), 2750 (m), 2730 (sh)(m), 2570 (m), 2470 (m) (R_3NH^+), 1719 (s) (α,β-unsaturated δ-lactone), and 1672 cm^{-1} (s) ($\alpha,\beta,\alpha',\beta'$-di-unsaturated $\rangle C{=}O$). These fit structure (VII*b*) rather well.*

The chemical evidence was also in accord with this ammonium salt structure for the



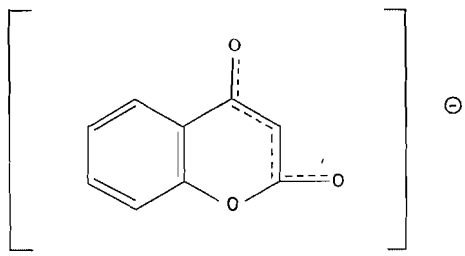
(VII*b*)

**For footnote see* NOTE *on p. 1505.*

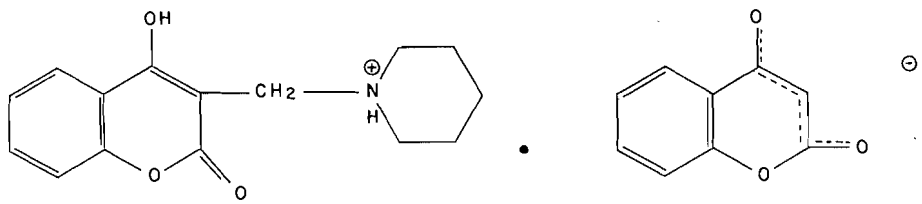
addition complex. Thus, it could not be recrystallized without decomposition; two recrystallizations from nitromethane transformed it completely into dicoumarol, which was also obtained by heating the complex with mineral acid. These properties are in accord with the known reactivity of Mannich bases quaternary salts (15). The structure postulated for the complex led us to the expectation that if 4-hydroxy-3-*N*-piperidinomethylcoumarin was quaternized with methyl iodide before treatment with 4-hydroxycoumarin (II), then the addition complex would not be formed and heating with (II) should lead to dicoumarol readily. This was fully confirmed by experiment, no complex being formed and dicoumarol (I, R = H) being obtained in good yield.

It was now necessary to prove that the reaction had taken place by the addition of the added 4-hydroxycoumarin to the 2,4-diketo-3-methylenechroman formed *in situ* from the Mannich base, and not by a partial reversal of the Mannich condensation followed by addition of the 4-hydroxycoumarin so formed to the chroman (the yield of dicoumarol obtained in the reaction already excludes this possibility). This was readily done by treating 4-hydroxy-3-*N*-piperidinomethylcoumarin methiodide with 4-hydroxy-7-methylcoumarin to give 7-methyldicoumarol (I; R = 7–CH_3–) which could also be obtained from 4-hydroxy-7-methyl-3-*N*-piperidinomethylcoumarin methiodide and 4-hydroxycoumarin. Because of possible ambiguity owing to the closeness of analytical figures

NOTE: *Drs. K. P. Link and S. Preiss have kindly informed us that they have observed a broad band at 1635 cm^{-1} in the spectrum of the sodium salt of 4-hydroxycoumarin, presumably corresponding to the anion*



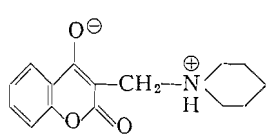
No band at 1719 cm^{-1} was observed. They suggest, therefore, that structure (VIIc) would fit the infrared data also.



(VIIc)

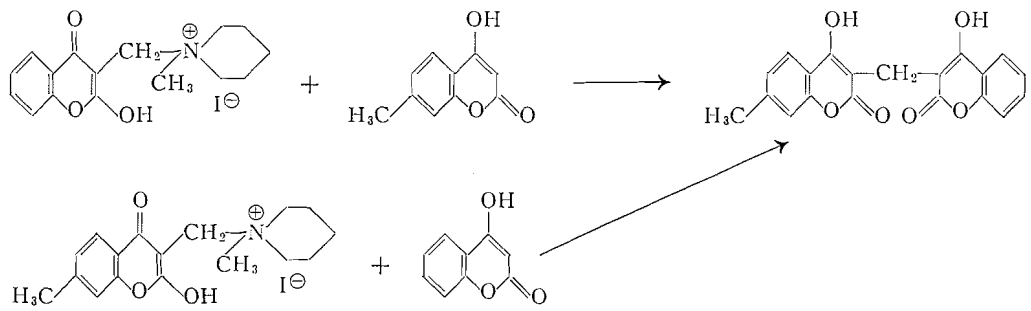
The fact that we observed a sharp band at 1672 cm^{-1} for this compound at a much higher frequency than the broad band for the anion seems to speak against this possibility though it does not rule it out by any means. We would like to thank Drs. Link and Preiss for pointing the possibility out to us.

Structure



for the 3-piperidinomethyl derivative is ruled out by the absence of a band at 2440–2350 cm^{-1}.

7,7′-dimethyldicoumarol was also prepared for comparison and shown to be different from the unsymmetrical dicoumarol obtained above.



Having established the nature of the reaction, a number of unsymmetrically substituted dicoumarols were prepared to examine its scope; 6-methyl-, 6-chloro-, and 7-hydroxydicoumarol were readily obtained in good yields from 4-hydroxy-3-*N*-piperidinomethylcoumarin methiodide and the corresponding substituted 4-hydroxycoumarin. With 4-hydroxy-7-methoxycoumarin a product was readily obtained which consisted mainly of the expected 7-methoxydicoumarol, m.p. 245–248°, as shown by analysis, ultraviolet and infrared spectra, and by demethylation to the 7-hydroxydicoumarol prepared above. A small proportion of the product, however, was a highly insoluble higher melting (290–292°) substance for which good carbon and hydrogen analytical values could not be obtained. That it was a dicoumarol derivative was shown by its infrared spectrum (dicoumarols have a very characteristic type of absorption bands in the 6 μ region) which, apart from the fact that it had one extra band at 1110 cm^{-1} (m), was practically identical with that of 7-methoxydicoumarol. Also its ultraviolet absorption spectrum in dioxan solution was very similar to that of 7-methoxydicoumarol, differing only slightly in the ratios of the intensities of the peaks, indicating that the chromophoric systems were probably the same. The starting 4-hydroxy-7-methoxycoumarin was a pure compound, as shown by a comparison of its melting point and infrared spectrum with that of a specimen kindly supplied by Dr. R. H. Thomson, and also by demethylating it to the known 2,7-dihydroxychromone. The higher melting by-product was not investigated further at this stage. The infrared spectra of the dicoumarols were measured and are reported in the experimental section. They are in accord with the results of Knobloch and Prochazka (12) and will not be discussed here (dicoumarol has been represented by the 4,4′-dihydroxydicoumarin formula throughout this paper for convenience, though the infrared data indicate that the correct structure is that of a 2,2′-dihydroxydichromone with strongly intramolecularly chelated —OH groups (see ref. 12)).

The method described here for the synthesis of unsymmetrically substituted dicoumarols seems to be of general application. It is probable that it can be extended to dicoumarols bearing a substituent at the bridge methylene group by using aldehydes other than formaldehyde in the Mannich reaction.

EXPERIMENTAL

The melting points are uncorrected. Infrared spectra were measured with a Perkin–Elmer Model 21 instrument using sodium chloride optics. Ultraviolet absorption spectra were measured with a Beckmann DK 2 recording spectrophotometer.

*Reaction between 4-Hydroxycoumarin and 4-Hydroxy-3-*N*-piperidinomethylcoumarin*

4-Hydroxy-3-*N*-piperidinomethylcoumarin was best prepared by the method of Robertson and Link (3).

(*i*) *Without Methyl Iodide*

Pure 4-hydroxycoumarin (0.164 g) and 4-hydroxy-3-*N*-piperidinomethylcoumarin (0.26 g) were dissolved in hot absolute ethanol (5 ml) and the solution boiled under reflux for 10 minutes. After 3 minutes a crystalline solid began to separate out. The cooled suspension was filtered, and the addition complex (A) (0.386 g) washed with a little hot alcohol. The product, m.p. 255–257°, could not be recrystallized without decomposition. It was insoluble in ethanol, benzene, chloroform, and carbon tetrachloride but soluble in dioxan, tetrahydrofuran, acetic acid, *cyclo*hexanone, and dimethyl formamide. One recrystallization from nitromethane gave impure product, m.p. 258–260°, and a second recrystallization from the same solvent converted the material into dicoumarol, m.p. 293–295°, undepressed on admixture with an authentic specimen. For analysis purposes, (A) was washed repeatedly with hot alcohol and dried, the melting point remaining unchanged at 255–257°. Found: C, 68.35; H, 5.5. Calc. for $C_{24}H_{23}O_6N$: C, 68.3; H, 5.5%.

Heating the addition complex (0.386 g) in ethanol with concentrated hydrochloric acid (2 drops) for $1\frac{3}{4}$ hours gave dicoumarol (0.129 g, 89.5%), m.p. 290–292°.

Infrared spectrum of the addition complex (Nujol mull) (main peaks only): 3170 (m) (broad), 2750 (m), 2730 (sh) (m), 2570 (m), 2470 (m), 1719 (s), 1672 (s), 1618 (s) (broad), 915 (m), 768 (s), 684 cm^{-1} (w).

(*ii*) *Using Methyl Iodide*

4-Hydroxy-3-*N*-piperidinomethylcoumarin (0.13 g) was dissolved in absolute ethanol (3 ml) and treated with an excess of methyl iodide (1 ml; if molar quantities are used only the addition complex (A) is obtained). 4-Hydroxycoumarin (0.082 g) in hot ethanol (3 ml) was added and the solution boiled under reflux for 4 hours, during which time dicoumarol gradually separated out. The product (0.151 g) was collected and recrystallized from *cyclo*hexanone giving pure dicoumarol, m.p. 289–292°. Found: C, 68.21; H, 3.36. $C_{19}H_{12}O_6$ requires C, 68.0; H, 3.6%.

Infrared spectrum (Nujol mull) (main peaks only): 2770 (w), 2650 (w), 1663 (s), 1640 (s), 1612 (s), 1575 (s), 1555 (m), 1112 (s), 913 (m), 772 (s), 751 (m), 742 cm^{-1} (s).

*4-Hydroxy-7-methyl-3-*N*-piperidinomethylcoumarin*

A solution of piperidine (0.73 ml) and formaldehyde (0.5 ml, 38%) in absolute ethanol (5 ml) was added to a boiling solution of 4-hydroxy-7-methylcoumarin (1.0 g) in absolute ethanol (10 ml) and the mixture kept at 5° in the refrigerator for 3 days. The solid which separated (1.42 g), m.p. 177–179°, was recrystallized by dissolving it in hot ethanol and adding anhydrous ether until a turbidity appeared and then allowing to stand. After three such recrystallizations the pure base, m.p. 173–174°, was obtained. Found: C, 70.27; H, 7.04. Calc. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01%.

7-Methyldicoumarol

(*i*) *From 4-Hydroxy-7-methylcoumarin*

A solution of 4-hydroxy-3-*N*-piperidinomethylcoumarin (0.259 g) in ethanol was treated with methyl iodide (1 ml) and after heating for a few minutes a solution of 4-hydroxy-7-methylcoumarin (0.174 g) in hot ethanol was added and the mixture boiled under reflux for 3 hours. The solid which separated (0.31 g), m.p. 256–259°, was recrystallized from *cyclo*hexanone giving 7-methyldicoumarol, m.p. 261–262°. Found: C,

68.80; H, 3.97. Calc. for $C_{20}H_{14}O_6$: C, 68.5; H, 4.03%. Infrared spectrum (Nujol mull) (main peaks only): 2755 (w), 2620 (w), 1658 (s), 1633 (s), 1613 (s), 1570 (m), 1555 (sh)(m), 1105 (s), 805 (m), 777 (m), 755 (m), 738 cm^{-1} (m).

The product was different from both dicoumarol and 7,7′-dimethyldicoumarol.

In the absence of methyl iodide the corresponding addition complex, m.p. 234–236°, was obtained in 70% yield. It, too, decomposed to give the dicoumarol on attempted recrystallization, and a specimen pure enough for analysis could not be obtained.

(*ii*) *From 4-hydroxy-7-methyl-3-N-piperidinomethylcoumarin*

Methyl iodide (1 ml) was added to a solution of 4-hydroxy-7-methyl-3-*N*-piperidinomethylcoumarin (0.273 g) in absolute ethanol, the solution heated for 5 minutes, and 4-hydroxycoumarin (0.162 g) in hot ethanol added. After boiling under reflux for 5 minutes the product began to separate. The mixture was refluxed for another $2\frac{1}{2}$ hours, cooled, filtered, and the solid (0.245 g), m.p. 255–258°, recrystallized from *cyclo*hexanone to give 7-methyldicoumarol, m.p. 255–257°, undepressed on admixture with the specimen obtained as under (i).

7,7′-Dimethyldicoumarol

Formaldehyde (2 ml, 38%) was added to a boiling solution of 4-hydroxy-7-methyldicoumarol (0.5 g) in 50% ethanol (50 ml) and the solution boiled for 5 minutes giving impure product (0.484 g), m.p. 273–293°. Recrystallization from glacial acetic acid gave 7,7′-dimethyldicoumarol, m.p. 292–294°, depressed to 260–270° on admixture with 7-methyldicoumarol. Found: C, 69.24; H, 4.47. Calc. for $C_{21}H_{16}O_6$: C, 69.2; H, 4.44%. Anschutz (16) gives m.p. 273–275° for this compound.

6-Methyldicoumarol

This was obtained in 89.4% yield from 4-hydroxy-6-methylcoumarin, 4-hydroxy-3-*N*-piperidinomethylcoumarin, and methyl iodide. It had m.p. 250–251° (from *cyclo*hexanone). Found: C, 68.57; H, 4.01. Calc. for $C_{20}H_{14}O_6$: C, 68.57; H, 4,03%.

6-Chlorodicoumarol

This was similarly obtained from 6-chloro-4-hydroxycoumarin, 4-hydroxy-3-*N*-piperidinomethylcoumarin, and methyl iodide. Yield 90.3%. Recrystallization from *cyclo*hexanone gave pure product, m.p. 266–268°. Found: C, 62.2; H, 2.93. Calc. for $C_{19}H_{11}O_6Cl$: C, 61.6; H, 3.00%. Infrared spectrum (Nujol mull) (main peaks only): 2720 (w), 2595 (w), 1657 (s), 1632 (s), 1607 (m), 1576 (m), 1500 (w), 1109 (m), 914 (w), 809 (w), 765 cm^{-1} (m).

7-Methoxydicoumarol

4-Hydroxy-7-methoxycoumarin was prepared from 2-hydroxy-4-methoxyacetophenone, diethyl carbonate, and pulverized sodium by the method of Desai and Sethna (17) and was identical in melting point (mixed melting point undepressed) and infrared spectrum with a specimen kindly supplied by Dr. R. H. Thomson (Aberdeen University, Scotland).

4-Hydroxy-3-*N*-piperidinomethylcoumarin (5.2 g) in absolute ethanol (50 ml) was treated with a large excess of methyl iodide (20 ml). 4-Hydroxy-7-methoxycoumarin (3.84 g) in ethanol (80 ml) was then added and the mixture boiled under reflux for 4 hours. The cooled suspension was filtered and the solid, m.p. 245–260°, extracted three times with boiling glacial acetic acid. On cooling, the combined extracts deposited slightly impure 7-methoxydicoumarol (5.0 g), which on recrystallization from glacial acetic acid gave product (4.9 g), m.p. 245–248°. Further recrystallizations from acetic acid did not raise the melting point. Found: C, 65.41; H, 4.05. Calc. for $C_{20}H_{14}O_7$: C, 65.57;

H, 3.85%. Infrared spectrum (Nujol mull) (main peaks): 1655 (s) (broad), 1620 (s), 1602 (s), 1565 (s), 1512 (m), 1098 (s), 835 (m), 805 (m), 775 (m), 752 (m), 740 cm^{-1} (sh)(m). Ultraviolet spectrum (in dioxan solution): λ_{max} 323 (infl.), 317, 307 (infl.), 289 $m\mu$ 10^{-3} ϵ: 35.99, 29.95, 37.52, 29.95.

The residue (0.5 g) from the acetic acid extraction was recrystallized from *cyclo*hexanone giving colorless crystals, m.p. 290–292°. Good analytical figures could not be obtained for this compound (found: C, 64.17; H, 4. 45%), which differed greatly in solubility from the 7-methoxydicoumarol, m.p. 245–248°, obtained above. The infrared spectrum was identical with that of 7-methoxydicoumarol except for a single weak peak at 1110 cm^{-1} which was absent in the spectrum of the lower melting product. The ultraviolet spectrum measured in dioxan is very similar to that of 7-methoxydicoumarol indicating that no change has occurred in the chromophoric system. λ_{max} 324 (infl.), 317, 307 (infl.), 289 $m\mu$ 10^{-3} ϵ (assuming the same molecular weight as 7-methoxydicoumarol): 35.44, 40.12, 33.70, 20.33.

4,7-Dihydroxycoumarin (2,7-Dihydroxychromone)

A mixture of 4-hydroxy-7-methoxycoumarin (0.8 g) and anhydrous aluminum chloride (4 g) in dry benzene (150 ml) was boiled under reflux for 6 hours. Crushed ice and dilute hydrochloric acid were then added to the cold mixture and the benzene evaporated off giving 4,7-dihydroxycoumarin (0.74 g), m.p. 265–268°, which could be recrystallized from dilute methanol. Bauer and Schoder (18) give m.p. 264° (decomp.) for this compound.

7-Hydroxydicoumarol

(i) 4-Hydroxy-3-*N*-piperidinomethylcoumarin (0.114 g) in absolute ethanol was treated with methyl iodide (2 ml) and then with 4,7-dihydroxycoumarin (0.75 g) and the mixture refluxed for 8 hours. Working up in the usual way gave 7-hydroxydicoumarol (0.115 g), m.p. 300–302°, which on recrystallization from glacial acetic acid had m.p. 300–302°. Found: C, 64.67; H, 3.79. Calc. for $C_{19}H_{12}O_7$: C, 64.77; H, 3.43%. Infrared spectrum (Nujol mull) (main peaks only): 3380 (m) (broad), 2740 (w), 2600 (w), 1655 (sh) (s), 1635 (s), 1608 (s), 1573 (s), 1315 (s), 1113 (s) (broad), 856 (m), 808 (m), 798 (m), 770 (s), 755 (s), 744 cm^{-1} (m).

(ii) 7-Methoxydicoumarol (0.5 g, m.p. 245–248°) and anhydrous aluminum chloride (2.5 g) in dry benzene (100 ml) were boiled under reflux for 8 hours. Cracked ice and dilute hydrochloric acid were added to the cold mixture, the benzene was removed, and the product recrystallized from glacial acetic acid giving 7-hydroxydicoumarol (0.321 g), m.p. 300–302° undepressed in admixture with material obtained as under (i) above. The infrared spectra of the two products were also identical.

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