

Synthesis of *cis*-Disalicylide and of Flavones containing a Chromeno-[4,3-*b*]chromen Nucleus

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Salicylic acid reacts with phosgene and slightly less than 2 mol. equiv. of triethylamine to give 1,3-benzodioxan-2,4-dione in high yield. A trace of triethylamine converts this compound into *cis*-disalicylide(dibenzo[*b.f*][1,5]-dioxocin-6,12-dione) almost quantitatively. With ethyl sodioacetoacetate *cis*-disalicylide readily gives chromeno-[4,3-*b*]chromen-6,7-dione (XIII); with sodioacetylacetone it gives 6-hydroxy-6-methylchromeno[4,3-*b*]chromen-7-one (VIIIb).

In polyketide syntheses by the Hauser-Harris¹ method ethyl benzoate is used to supply a terminal benzoyl group, and extension to a salicylic ester might be expected to yield a phenolic triketone such as (I). Since preliminary results were unsatisfactory and the presence of a free phenolic function seemed responsible, we examined the use of the cyclic ester (II), 1,3-benzodioxan-2,4-dione, in which this function is protected.

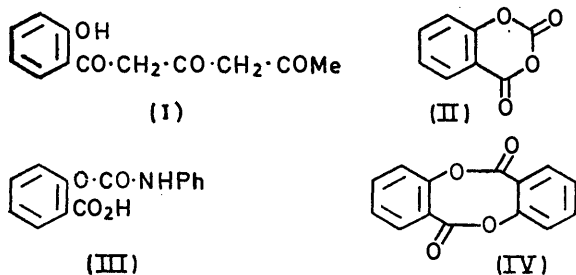
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Again the results were unsatisfactory. We have confirmed the report by Davies² that this cyclic ester differs from related compounds in that its carbonate carbonyl group appears to be the more reactive, giving

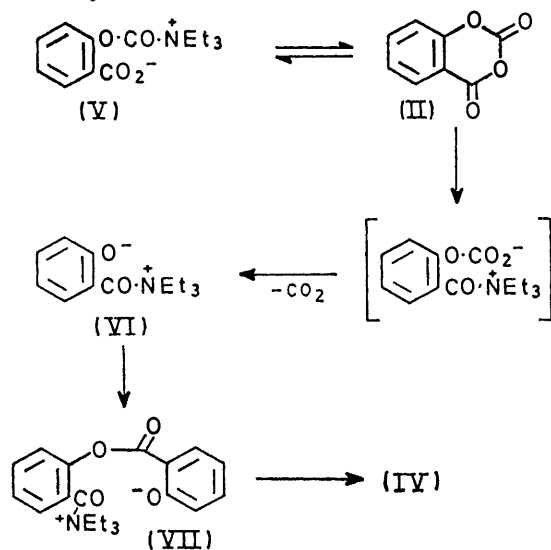
¹ M. I. Miles, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1963, **85**, 3884; *J. Org. Chem.*, 1965, **30**, 1007; H. O. House, *Rec. Chem. Progr.*, 1967, **28**, 99.

² W. H. Davies, *J. Chem. Soc.*, 1951, 1357.

with aniline the carbamate (III). Concluding that this carbonyl group would also react with carbanions we abandoned further work with the cyclic carbonate in favour of studies on *cis*-disalicylide (IV) which has but one type of carbonyl group.



A new synthesis of *cis*-disalicylide was evolved. First, a preparation of the cyclic carbonate (II) was devised which is more convenient than existing methods^{3,4} and gives high yields of almost analytically pure material. It consists of the slow addition of triethylamine to solutions of salicylic acid and phosgene in inert solvents, slightly less than the stoichiometric 2 mol. equiv. of base being used. If this precaution is not observed, salicylic polymers preponderate. When the cyclic carbonate was separately treated with catalytic amounts of triethylamine, however, it rapidly gave *cis*-disalicylide (IV) free from the higher polymers characteristic of synthesis by thermal methods.⁴⁻⁶



SCHEME 1

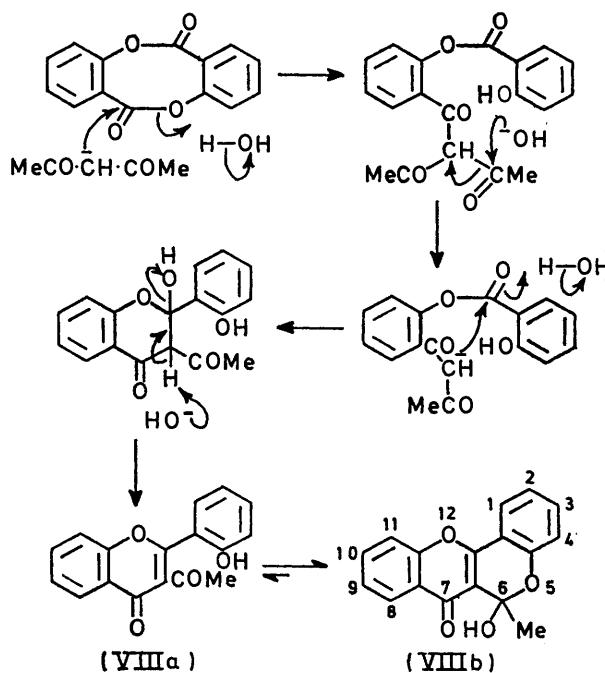
Presumably the carbonate carbonyl group also reacts preferentially with triethylamine giving the zwitterion (V); but this reaction must be readily reversible and therefore does not interfere with the slower reaction leading (with irreversible loss of carbon dioxide) to the zwitterion (VI) and thence to the coupled product (VII).

³ A. Chichibabin, *Compt. rend.*, 1941, **213**, 355; L. A. Dupont, *Fr. Pat.* 771,653/1964.

⁴ H. P. Kaufman, A. Seher, and P. Hagedorn, *Annalen*, 1954, **587**, 226.

Here the stereochemistry and relatively low reaction temperature would favour ring closure to *cis*-disalicylide (IV) rather than coupling with another molecule of (VI) to form trimers and tetramers (Scheme 1).

The reaction between *cis*-disalicylide and the dianion of pentane-2,4-dione was also very complex, but in this case the monoanion afforded a smooth series of reactions ending in the formation in high yield of 6-hydroxy-6-methylchromeno[4,3-*b*]chromen-7-one (VIIIb). Though several variations are possible at almost every stage, the reaction sequence is believed to be essentially as in Scheme 2. At one stage hydroxide ion is introduced



SCHEME 2

to account for removal of one acetyl group; in practice only a trace of any hydroxylic material (as initiator) would be needed since a later step subsequently regenerates it.

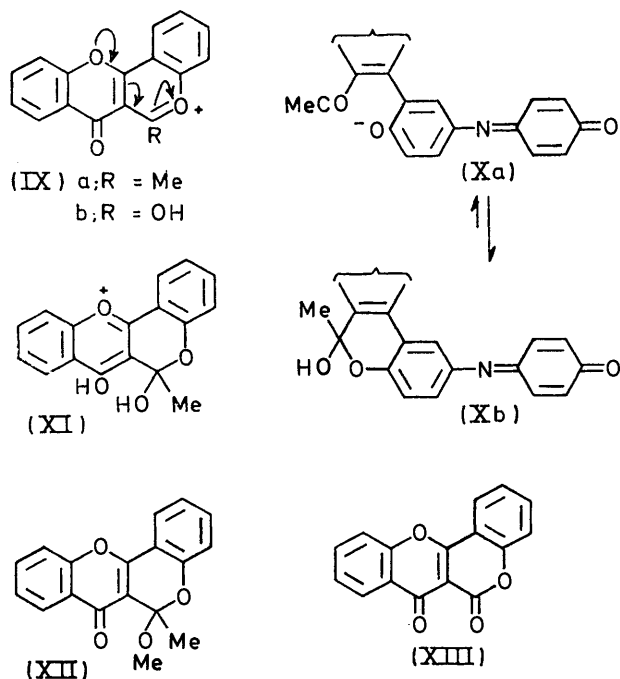
In accordance with structure (VIIIb), the new compound gave a strong signal in the mass spectrum at m/e 280, and others at 265 (loss of Me) and 263 (loss of OH), these losses leaving the stable pyrylium ions (IX). Another important peak at m/e 237 corresponds to the loss of CO as is usual with flavones. The i.r. carbonyl absorption (mulls) occurring at 1624 cm^{-1} is at rather low wavenumber and, since derivatives behave similarly, is not merely a consequence of hydrogen bonding with the hydroxy-group, which itself absorbs at 3365 cm^{-1} . A one-proton multiplet at τ 1.79 (J 8 and 2 Hz) in the n.m.r. spectrum shows that there is but one proton *ortho* to a carbonyl group [position 8 in (VIIIb)]; a similar multiplet at higher field (τ 2.28) can be attributed

⁵ H. K. Hall and A. K. Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6409.

⁶ W. Baker, J. F. W. McOmie, and W. D. Ollis, *J. Chem. Soc.*, 1951, 200; W. Baker, W. D. Ollis, and T. S. Zealley, *ibid.*, p. 201.

to the proton at position 1 in (VIIIb) since this is firmly held in the deshielding plane of the pyrone ring. No other aromatic proton signals could be assigned without ambiguity, but the tertiary methyl group resonated as a sharp singlet at τ 8.01 and the hydroxylic proton as a broad band at 4.37, lost upon deuteration.

The existence of the expected equilibrium between the hemiacetal (VIIIb) and the phenolic ketone (VIIIa) was clearly disclosed only by the u.v. absorption. In neutral solutions, the hemiacetal exhibits a spectrum appropriate to a flavone, but addition of alkali causes a shift in the long-wavelength band from 335 to 347 nm which is annulled by neutralisation and is indicative of a phenolic flavone. Attempts to detect a phenolic grouping by means of Gibbs reagent gave only a most uncharacteristic red colour: it might be that condensation does occur at the free *para*-position in the phenolic residue of (VIIIa) but that the hemiacetal arrangement is so favoured that the characteristic blue colour of the anion (Xa) is masked by the red of the ring-closed species (Xb). Efforts to shift the equilibrium in favour of the blue anion by increasing the alkalinity of the medium led only to decomposition of the pigment.



The hemiacetal (VIIIb) is also sensitive to acids and gives a brilliantly fluorescent solution in chloroacetic acid, probably indicative of the pyrylium ion (IXa) in which the charge can be shared by both ring oxygen atoms as indicated by the arrows. The u.v. spectrum, however, suggests that ionisation is incomplete, whereas material in solution in trifluoroacetic acid appears to be wholly ionised and exhibits a spectrum unlike that of the parent compound. However, flavones are themselves somewhat basic, so it is necessary to ensure that the spectral changes are not due merely to the protonated

species (XI), though here charge sharing by two oxygen atoms can be achieved only if there is loss of benzenoid aromaticity. Treated with methanol and the minimum catalytic amount of acid, the hemiacetal yields an ether (XII) with the appropriate spectroscopic features and a u.v. spectrum not affected by alkali. In benzene, the methoxy-protons resonate at τ 6.82 and the tertiary methyl protons at 7.55. Protonation as in (XI) would be expected to move both these resonances to lower field consonant with deshielding by the aromatic pyrylium system. Formation of ion (IXa), on the other hand, changes the tertiary methyl group into a π -deficient aromatic methyl group, which should therefore register a large downfield shift, and the methoxy-group into methanol which should show no marked shift. Gradual addition of trifluoroacetic acid to the benzene solution produces a progressive diminution in the two original bands, a new, composite band appearing at 6.91 and replacing them. This large downfield shift ($\Delta\tau$ 0.64) in the tertiary methyl band and the small upfield shift ($\Delta\tau$ 0.09) in the methoxy-band thus clearly establish the existence of ion (IXa). As addition of acid continued the salt separated as an oil which, unfortunately, did not crystallise and could not be purified for further study.

cis-Disalicylide (IV) also reacts smoothly with the sodium salt of ethyl acetoacetate; an acetyl group is eliminated as before and the product, formed in high yield, is chromeno[4,3-*b*]chromen-6,7-dione (XIII). This compound contains a coumarin system and shows the intense, broad band typical of a coumarin carbonyl group at 1727 cm^{-1} , the flavone carbonyl absorption appearing at about 1620 with less intense bands at 1648 and 1584 cm^{-1} . The u.v. spectrum is correspondingly complex, the characteristic three main absorption bands of a flavone having shoulders and an additional band, typical of a coumarin, being superimposed on the flavone spectrum at 320 nm. Mass spectral fragmentation of the molecular ion m/e 264 gives two important peaks at 236 and 208 corresponding to the sequential loss of two carbonyl units. A different route to derivations of (XIII) has been described.⁷

EXPERIMENTAL

2-Methoxyethanol was distilled immediately before use. I.r. spectra were obtained from mulls in paraffin and u.v. spectra from 10^{-4} M-solutions in methanol.

1,3-Benzodioxan-2,4-dione (II).—Salicylic acid (4.2 g) in ether (20 ml; dried over lithium aluminium hydride) was added gradually during 5 min to phosgene (3.7 g) in the same solvent (100 ml) at -20° , and the solution was kept at that temperature for 35 min with strict exclusion of moisture. Then it was treated with triethylamine (6.8 g; freshly distilled from lime) in dried ether (60 ml), added dropwise during 3 h with vigorous stirring. The mixture was left overnight to gain room temperature, the precipitated triethylammonium chloride was removed, and the solution concentrated under reduced pressure to about 50 ml. A crystalline powder separated slowly and when

⁷ E. Zieger, K. Meyr, and U. Rossman. *Mvnatsh.* 1961, **92**, 296.

recrystallised from ether supplied the dione as tiny prisms (4.5 g), m.p. 118° (lit.,^{3,4} 114°, 118–120°), ν_{\max} 1834sh, 1812 (carbonate CO), 1756 (benzoate CO), and 1618 and 1595 cm^{-1} (aromatic) (Found: C, 58.8; H, 2.5. Calc. for $\text{C}_8\text{H}_4\text{O}_4$: C, 58.55; H, 2.5%). With water this compound reacted in a few minutes giving carbon dioxide and salicylic acid. When a sample (90 mg) was dissolved in ether (10 ml) and kept with aniline (60 mg) for 18 h the product was 2-carboxyphenyl phenylcarbamate² (III), crystallising from ethanol as needles, m.p. 151° (lit.,² 148–150°), ν_{\max} 3420 (OH), 2690 (NH), 1700–1720br (CO_2H and $\text{CO}_2\cdot\text{NH}$); m/e 257 ($\text{C}_{14}\text{H}_{11}\text{NO}_4$).

cis-Disalicylide (Dibenzo[b,f][1,5]dioxocin-6,12-dione) (IV).—The foregoing dione (100 mg) in ether (10 ml) was treated with triethylamine (1 drop) and kept at 23° for 15 min. The precipitate consisted of practically pure *cis*-disalicylide, m.p. and mixed m.p.⁶ 233°.

6-Hydroxy-6-methylchromeno[4,3-b]chromen-7-one (VIIIb).—Solutions of *cis*-disalicylide (1.2 g) in 2-methoxyethanol (20 ml) and sodioacetylacetone (0.6 g) in the same solvent (25 ml) were stirred together at 45° for 20 min. Then the solvent was removed *in vacuo* and water (35 ml) was added with shaking to produce during a few minutes a pale yellow powder (1.4 g). Crystallised from acetone–cyclohexane (1:1) this provided the *chromenochromenone* as yellow prisms (1.1 g), m.p. 156° (Found: C, 72.5; H, 4.5%; M , 280.07318. $\text{C}_{17}\text{H}_{12}\text{O}_4$ requires C, 72.8; H, 4.3%; M , 28.07355). The u.v. spectrum varied according to the conditions: λ_{\max} (MeOH) 238inf, 257, 291.5, and 339 nm ($\log \epsilon$ 2.15, 4.21, 4.18, and 4.06); λ_{\max} (MeOH–NaOH) 245, 292, 310inf, 347, and 404 nm ($\log \epsilon$ 2.20, 4.10, 4.06, 3.92, and 3.36); λ_{\max} ($\text{F}_3\text{C}\cdot\text{CO}_2\text{H}$) 267, 301inf, 323, and 341inf nm ($\log \epsilon$ 4.47, 4.04, 4.04, and 4.01).

The chromenochromenone (50 mg) was suspended in methanol (3 ml) and methanolic 0.01N-toluene-4-sulphonic acid (20 drops) was added. Addition of more acid is deleterious as it promotes re-ionisation to (IXa). On warming, the yellow colour faded and the cooled solution then deposited a solid. The acid catalyst was neutralised with sodium hydrogen carbonate, and ether and water were then added. Evaporation of the dried (MgSO_4) ethereal solution left 6-methoxy-6-methylchromeno[4,3-b]chromen-7-one (XII), which separated from methanol as needles, m.p. 138°, λ_{\max} 240inf, 254, 288, and 335 nm ($\log \epsilon$ 4.19, 4.24, 4.21, and 4.15), unaffected by addition of a drop of 2N-sodium hydroxide; ν_{\max} 1640, 1625, 1610, 1584, and 1665 (chromone C:O, C:C and aromatic) (Found: C, 73.5; H, 4.8%; M , 294. $\text{C}_{18}\text{H}_{14}\text{O}_4$ requires C, 73.2; H, 4.8%; M , 294).

Chromeno[4,3-b]chromen-6,7-dione (XIII).—Solutions of *cis*-disalicylide (0.6 g) in 2-methoxyethanol (15 ml) and the sodio-derivative (0.4 g) of ethyl acetoacetate in the same solvent (15 ml) were stirred together at 45° for 20 min. The solvent was removed *in vacuo* and water (30 ml) was added to the yellowish residue, giving a colourless solid (0.63 g) that was collected after 5 min and crystallised from acetone–cyclohexane (1:1), thus providing the *chromenochromendione* as thin plates (0.49 g), m.p. 233°, λ_{\max} 231, 262.5, 297.5, and 320 nm ($\log \epsilon$ 4.21, 4.49, 4.11, and 4.00) (all with minor shoulders) (Found: C, 72.6; H, 3.1%; M , 264.04296. $\text{C}_{16}\text{H}_8\text{O}_4$ requires C, 72.7; H, 3.05%; M , 264.04225).

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