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Benzopyrans. Part 30[1]. Synthesis of Substituted Xanthones from 3-Acyl-2-methyl-1-benzopyran-4-ones

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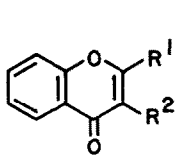
Abstract : The xanthone **8** results from the base catalysed self-condensation of the chromone **1**. The chromone **2** gives the xanthones **9** and **11** with sodium and DMF-$POCl_3$ respectively, phenol **14** with NaOMe, and the pyran **22** with 2-thiomethylchromone **6**. The enamine **16** on Vilsmeier-Haak reaction affords the chloroxanthone **12**. The pyran **15**, isolated as a byproduct from the reaction of ω-acetyl-2-hydroxyacetophenone with $HC(OEt)_3$-Ac_2O, affords the xanthone **13** by refluxing with NaOMe in MeOH.

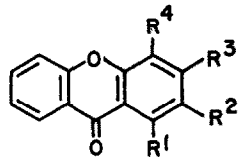
Resurgent interest in xanthone is due to successful synthesis of some xanthone based analogues of the anthracycline antitumour agents[2] and the antibiotic bikaverin[3,4] a fungal metabolite with a benzo[b]xanthone skeleton. Xanthones are mostly synthesised from appropriate benzene derivatives[5], the examples of conversion of 1-benzopyran-4-ones[4,6] and particularly 2-methylchromones[7] being very few. Conversion of the title benzopyranones to a few xanthone derivatives is described herein.

We intended to prepare the xanthone **7** by Knoevenagel condensation of the pyranaldehyde **1**[8,9] with acetylacetone (→**3**) and subsequent cyclisation. Contrary to our expectation, refluxing an equimolar mixture of the chromone **1** and acetylacetone in pyridine containing piperidine produced exclusively 2-salicyloyl-3-methylxanthone (**8**), acetylacetone having no participation in the reaction. Anticipated acylation of the active 2-methyl group[10,11] of 3-acetyl-2-methylchromone (**2**) with ethyl acetate to the triketone **4** apparently cyclisable to 1-hydroxy-3-methyl- or(and) 3-hydroxy-1-methyl-xanthone could not also be achieved; the reaction of the chromone **2** with

ethyl acetate in the presence of molecularised sodium resulted the xanthone **9**. The chromone **2**, unlike its homologue **1**, however, survived heating under reflux in a

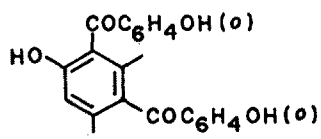


	R^1	R^2
1	Me	CHO
2	Me	Ac
3	Me	$CH{=}CAc_2$
4	CH_2Ac	Ac
5	H	Ac
6	SMe	Ac



	R^1	R^2	R^3	R^4
7	H	Ac	Me	H
8	H	Salicyloyl	Me	H
9	Me	Salicyloyl	Me	H
10	H	Salicyloyl	H	H
11	Cl	CHO	H	H
12	Cl	H	H	CHO
13	OH	H	Het	H

Het = 2-Methyl-4-oxo-4*H*-1-benzopyran-3-yl



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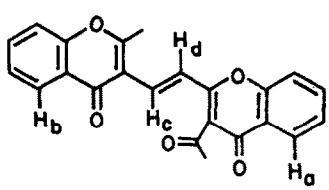

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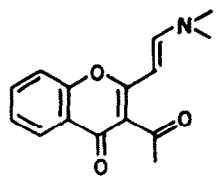
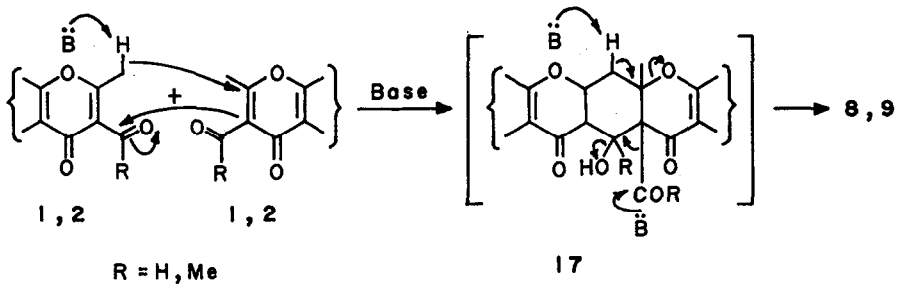


16

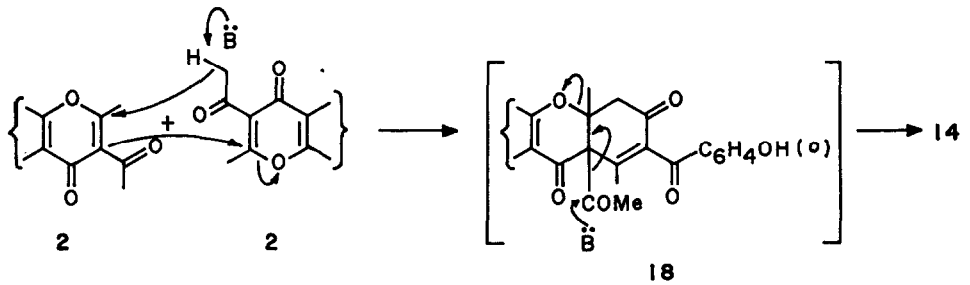
pyridine-piperidine mixture. The xanthones **8** and **9** obviously result from the self-condensation of the chromones **1** and **2**, respectively. 2-Methylchromone (**1** or **2**) undergoes in the presence of a base an intermolecular Michael Initiated Ring Closure (MIRC) to the benzoxanthene intermediate **17** that on base catalysed deacylative hydroxy elimination and pyran ring opening (Scheme 1) (or deacylative pyran ring opening and water elimination) leads to the xanthone (**8** or **9**). This reaction is analogous to the base catalysed formation of the xanthone **10** from either the aldehyde **1** or the corresponding *N*,*N*-dimethylhydrazone and an unsubstituted chromone or chromone having an acyl or alkoxycarbonyl substituent at its 3-position[8].

Surprisingly, the chromone **2** on being heated under reflux in methanol containing

sodium methoxide yielded the 2,4-disalicyloylphenol derivative **14** in complete exclusion of the xanthone **9**. Here the intermolecular MIRC reaction is initiated by the attack of the carbanion generated from the acetyl group of **2** at 2-position of a second molecule of **2**; the resultant intermediate **18** undergoes base catalysed deacylative pyran ring opening leading to **14** (Scheme 2).



Scheme 1

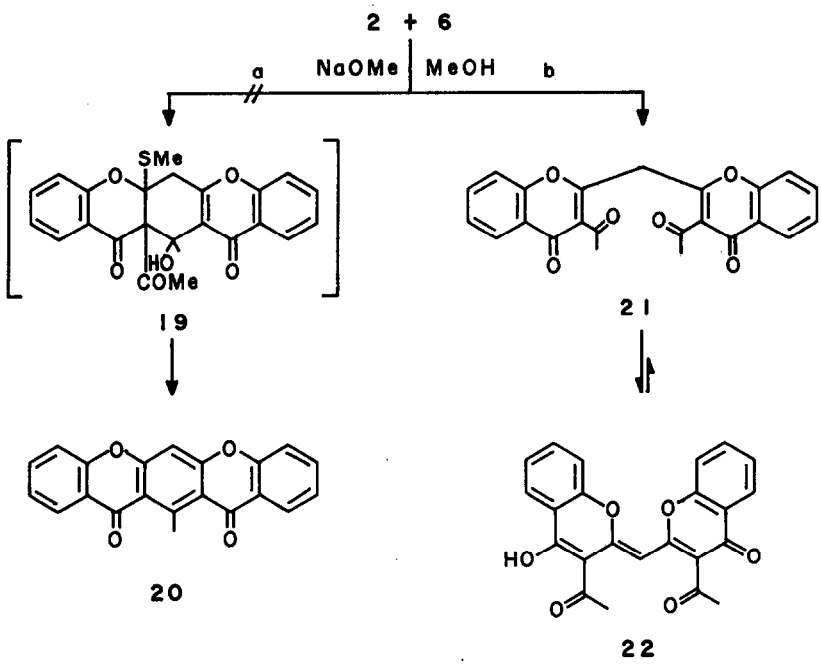


Scheme 2

ω-Acetyl-2-hydroxyacetophenone gives **2** with acetic anhydride[12] but 3-acetylchromone (**5**) with orthoformic ester and acetic anhydride[13]. During preparation of **5** from ω-acetyl-2-hydroxyacetophenone, orthoformic ester and acetic anhydride following the literature procedure[13] we always obtained in 2-4% yield the hitherto unreported byproduct **15** apparently arising from the condensation of **2** with either **5** or **1**. No reaction, however, took place when an equimolar mixture of **1** and **2** or that of **2** and **5** dissolved in either acetic anhydride or a mixture of acetic anhydride and ethyl orthoformate was heated under reflux. Heating an equimolar mixture of **1** and **2** with molecularised sodium suspended in dimethoxyethane afforded a mixture of **8** and **9** in complete exclusion of **15**. So it seems that **15** arises not by any straightforward condensation of **2** with either **1** or **5** but by condensation of the precursors (non-isolable) of **2** and **5** formed in the reaction of ω-acetyl-2-hydroxyacetophenone with orthoformic ester and acetic anhydride. The chromone **15** on refluxing with sodium methoxide in methanol underwent cyclisation and subsequent

aromatisation giving the xanthone **13**.

Base catalysed condensation of acetophenone and several ketomethylene compounds with 3-acetyl-2-thiomethylchromone (**6**)[14] gives substituted xanthones[15]. We anticipated that 2-methylchromone **2** in the presence of a base would similarly give with **6** the xanthone **20** via the MIRC intermediate **19** (Scheme 3 - path a). Contrary to our expectation, **2** in the presence of sodium methoxide underwent simple S_NV reaction with **6** giving **21** that exists exclusively in the tautomeric form **22** at least in chloroform solution (Scheme 3 - path b); the compound **22** was accompanied by a small amount of 3-acetyl-4-hydroxycoumarin formed by base catalysed hydrolysis of the unreacted chromone **6**[14].



Scheme 3

Next we subjected the chromone **2** to Vilsmeier-Haak reaction; the product from its elemental analysis, IR, PMR and mass spectra was found to be xanthone substituted by a chloro and a formyl group. On mechanistic ground it might be assigned the structure **11** or **12**. PMR spectrum is of little help to distinguish between these two isomeric structures (**11** and **12**). In its CMR spectrum, however, appearance of two doublets at δ 117.9 and 117.6 ppm attributable to unsubstituted 4-C and 5-C of xanthone[16] convincingly proves the structure **11** for this product. The other isomer **12** was also obtained by reacting the enamine **16**, derived from **2** and dimethylformamide dimethylacetal[11], with phosphorus oxychloride and dimethylformamide.

Experimental

The recorded melting points are uncorrected. IR spectra were recorded on a Beckman IR-20A and NMR in $CDCl_3$ with $SiMe_4$ as internal reference on a Jeol JNM-FX-100 spectrophotometer. Light petroleum refers to the fraction with b.p. 60–80°.

3-Methyl-2-salicyloylxanthone (**8**) : A mixture of the chromone **1** (1.88 g, 0.01 mol), acetylacetone (1.0 g, 0.01 mol), pyridine (15 ml), and piperidine (2 ml) was heated under reflux for 8 h. After distilling out some amount (~10 ml) of the solvent, the reaction mixture was diluted with water and extracted with chloroform. The organic extract on usual work-up gave a semisolid mass which on crystallisation twice from chloroform - light petroleum yielded the xanthone **8** (0.87 g, 52%), m.p. 144° (Found: C, 76.7; H, 4.0. $C_{21}H_{14}O_4$ requires C, 76.4; H, 4.3%); IR ($CHCl_3$) : 3065 (chelated OH), 1655 (xanthone CO), 1625 (CO chelated with OH), and 1600 (C=C)cm^{-1}; PMR : δ 11.84 (1H, s, exchangeable, OH), 8.72 (1H, d, J = 1 Hz, xanthone 1-H), 8.32 (2H, m, xanthone 8-H + PhH *ortho* to CO), 7.84 - 7.20 (7H, m, other ArH), and 2.06 (3H, s, Me).

1,3-Dimethyl-2-salicyloylxanthone (**9**) : To pulverised sodium (0.90 g, 0.04 mol) taken in a 250 ml round bottomed flask equipped with a reflux condenser and cooled in an ice bath was added a solution of the chromone **2** (4.04 g, 0.02 mol) in ethyl acetate (50 ml). After the addition was over, the reaction mixture was heated on a water bath for 4 h with occasional shaking. It was then cooled and crushed ice added to it. The reaction mixture was then acidified with conc. HCl and extracted with ethyl acetate. The organic extract after usual work-up gave the xanthone **9** (1.90 g, 55%), m.p. 148° (chloroform - light petroleum) (Found : C, 76.5; H, 4.5. $C_{22}H_{16}O_4$ requires C, 76.7; H, 4.7%); IR (KBr) : 3060 (chelated OH), 1650 (xanthone CO), 1625 (CO chelated with OH), and 1600 (C=C)cm^{-1}; PMR : δ 12.02 (1H, s, exchangeable, OH), 8.28 (1H, dd, J = 8, 2 Hz, xanthone 8-H), 7.80 - 6.64 (8H, m, other ArH), 2.72 (3H, s, 1-Me) and 2.24 (3H, s, 3-Me); MS : *m/z* 344 (M^+, 83%), 329 (M - Me, 48), 327 (M - OH, 23), 315 (M - CO - H, 100), 301 (329 - CO, 42), 299 (327 - CO, 52), 224 (M - $C_7H_4O_2$, 49), and 121 (HOC_6H_4CO, 46). Its acetate had m.p. 144°; PMR : δ 8.36 (1H, dd, J = 8, 2 Hz, xanthone 8-H), 7.84 - 7.08 (8H, m, other ArH), 2.76 (3H, s, 1-Me), 2.26 (3H, s, 3-Me), and 2.20 (3H, s, OAc).

1-Chloro-2-formylxanthone (**11**) : To a well cooled (ice-salt bath) and stirred solution of the chromone **2** (2.02 g, 0.01 mol) in dimethylformamide (25 ml) was added phosphorus oxychloride (2.7 ml, ~ 0.03 mol) dropwise so that temperature of the reaction mixture did not rise above -5°. After the addition was over, the reaction mixture was kept at room temperature for 16 h, then poured into an ice-water mixture (80 ml) with constant stirring, the deposited solid filtered off, and crystallised from ethanol to afford the xanthone **11** (1.10 g, 41%). On recrystallisation from

benzene it had m.p. 215° (Found : C, 64.7; H, 3.1. $C_{14}H_7ClO_3$ requires C, 65.0; H, 2.7%); IR (KBr) : 2900, 1690 (CHO), and 1665 (xanthone CO) cm^{-1}; PMR : δ 10.68 (1H, s, CHO), 8.32 (1H, dd, J = 8, 2 Hz, 8-H), 8.22 (1H, d, J = 8 Hz, 3-H), and 7.76 - 7.44 (4H, m, other ArH); CMR : δ 188.6 (CHO), 175.5 (9-C), 161.0 (4a-C), 154.6 (4b-C), 140.0 (1-C), 135.3 (6-C), 134.4 (3-C), 129.8 (2-C), 127.1 (8-C) 125.1 (7-C), 122.1 (8a-C), 118.8 (9a-C), 117.9 (4-C), and 117.6 (5-C); MS : *m/z* 260, 258 (M^+, 100%), 230 (M - CO, 5), 222 (M - HCl, 3), 201 (230 - CHO, 6), 195 (230 - Cl, 4), 166 (M - C_6H_4O, 15), and 138 (M - $C_7H_4O_2$, 24).

1-*Chloro*-4-*formylxanthone* (**12**) : Like the compound **2**, the enaminoketone **16** (300 mg, 1.2 mmol) dissolved in DMF (10 ml) was treated with phosphorus oxychloride (1 ml) as described before. The solid product obtained after usual work-up was dissolved in chloroform and filtered through a column of silica gel; the eluate on concentration gave the xanthone **12** (125 mg, 40%), m.p.214° (benzene) (Found : C, 65.3; H, 2.4. $C_{14}H_7ClO_3$ requires C, 65.0; H 2.7%); PMR : δ 10.78 (1H, s, CHO), 8.32 (1H, dd, J = 8, 2 Hz, 8-H); 8.14 (1H, d, J = 8 Hz, 3-H), and 7.80 - 7.46 (4H, m, other ArH); CMR : δ 186.5 (CHO), 174.8 (9-C), 158.5 (4a-C), 154.3 (4b-C), 141.8 (1-C), 135.4 (6-C), 132.8 (3-C), 127.3 (2-C), 127.2 (8-C), 125.2 (7-C), 123.8 (4-C), 122.5 (8a-C), 119.5(9a-C), and 117.4 (5-C).

3,5-*Dimethyl*-2,4-*disalicyloylphenol* (**14**) : Sodium (30 mg) was dissolved in dry methanol (25 ml) and to it was added the chromone **2** (202 mg, 1 mmol) dissolved in methanol (25 ml), the mixture refluxed for 4 h, concentrated, cooled and acidified. The organic matter was extracted with chloroform, chloroform extract washed thoroughly with water, dried, concentrated and chromatographed over silica gel, the eluant being ethyl acetate - light petroleum (1:6). The eluate fractions 6 - 13 (each fraction measuring 15 ml) were pooled together and concentrated to afford the phenol **14** (75 mg, 41%), m.p. 215° (chloroform - light petroleum) (Found : C, 72.6; H, 4.6. $C_{22}H_{18}O_5$ requires C, 72.9; H, 5.0%); PMR : δ 12.21 (1H, s, OH), 11.98 (1H, s, OH), 7.43 (2H, m, ArH *meta* to OH and *para* to CO), 7.25 (2H, dd, J = 8, 1.5 Hz, Ar-H *ortho* to CO), 7.03 (2H, m, ArH *para* to OH), 6.85 (2H, m, ArH *ortho* to OH), 6.69 (1H, s, *ortho* to Me and OH), 6.48 (1H, brs, OH), 2.15 (3H, s, Me), and 1.95 (3H, s, Me); CMR : δ 205.3, 202.9 (Ar CO Ar), 163.1, 162.9, 154.0 (ArCOH), 138.2, 137.3, 133.5, 133.0, 132.5, 132.1, 123.7, 120.7, 120.5, 119.5, 118.6, 118.5, 115.9 (other ArC), 19.6 and 17.7 (ArMe); MS : *m/z* 362 (M^+, 22%), 347 (M - Me, 19), 269 (M - C_6H_5O, 2), 253 (269 - OH + H, 7), 121 (HOC_6H_4CO, 100).

The triacetate of **14** had m.p. 119° ($CHCl_3$ - light petroleum); PMR : δ 7.77 - 7.12 (8H, m, ArH of Salicyloyl group), 6.94 (1H, s, ArH *ortho* to Me and OAc), 2.22 (3H, s, Ac), 2.19 (3H, s, Ac), 2.17 (3H, s, Ac), 2.06 (3H, s, Me), and 1.94 (3H, s, Me); CMR : δ 206.7, 203.2 (ArCOAr), 169.3, 168.5 (acetate CO), 150.6,

150.1, 147.6 (ArCOH), 137.3, 134.8, 134.3, 133.9, 132.4, 132.2, 130.1, 129.6, 126.5, 126.1, 124.5, 124.0, 122.3 (other ArC), 20.6, 20.5, 20.3 (acetate Me), 19.5 and 16.7 (ArMe); MS : *m/z* 488 (M^+), 446 (M - CH_2CO), 404 (M - $2CH_2CO$), 389 (404 - Me), 362 (M - $3CH_2CO$), 347 (362 - Me), 241 (362 - HOC_6H_4CO), and 121 (HOC_6H_4CO).

2-Methyl-3-[2-(3-acetyl-4-oxo-4H-1-benzopyran-2-yl)vinyl]-1-benzopyran-4-one (**15**) : ω-Acetyl-2-hydroxyacetophenone (15 g, 0.084 mol) was heated under reflux in ethyl orthoformate (45 ml) containing acetic anhydride (6 ml) for 12 h. The solid deposited after cooling the reaction mixture was collected by filtration, washed with hot ethanol and crystallised from chloroform to yield the benzopyranone **15** (1.2 g, 4%), m.p. 253° (Found : C, 74.4; H, 3.9. $C_{23}H_{16}O_5$ requires C, 74.2; H, 4.3%); PMR : δ 8.22 (1H, dd, J = 8, 2 Hz, Ha or Hb), 8.14 (1H, dd, J = 8, 2 Hz, Hb or Ha), 7.96 (1H, d, J = 16 Hz, Hc), 7.80 (1H, d, J = 16 Hz, Hd), 7.78 - 7.26 (6H, m, other ArH), 2.70 (3H, s, pyran 2-Me), and 2.68 (3H, s, Ac); MS : *m/z* 372 (M^+), 357 (M - Me), 329 (M - Ac), 315 (M - 2CO -H), 209 (329 - $C_7H_4O_2$), 185, 174, 160, and 121.

1-Hydroxy-3-(2-methyl-4-oxo-4H-1-benzopyran-3-yl)xanthone (**13**) : The chromone **15** (370 mg, ~1 mmol) was heated under reflux in methanol (100 ml) containing sodium methoxide (~2 mmol) for 8 h. The reaction mixture was concentrated, cooled, and acidified with conc. HCl; the separated semi-solid mass was extracted with chloroform, the organic extract washed with water, dried, charged over a silica gel column and eluted with ethyl acetate - light petroleum (1:6). The fractions 5-10, each fraction measuring 8 ml, contained the xanthone **13** (50 mg, 27%), m.p. 172° ($CHCl_3$ - light petroleum) (Found : C, 75.0; H, 4.2. $C_{23}H_{14}O_5$ requires C, 74.6; H, 3.8%); PMR : δ 12.12 (1H, s, exchangeable, OH), 8.32 (3H, m, xanthone 2,8-H + benzopyran 5-H), 7.92 - 6.80 (7H, m, other ArH), and 2.32 (3H, s, Me). Its acetate had m.p. 176° ($CHCl_3$ - light petroleum); PMR : δ 8.36 (3H, m, xanthone 2, 8-H + benzopyran 5-H), 7.88 - 7.12 (7H, m, other ArH), 2.64 (3H, s, pyran 2-Me), and 2.00 (3H, s, OAc).

Treatment of **2** *with* **6** : To a solution of sodium methoxide prepared from sodium (138 mg, 6 mmol) in dry methanol (25 ml) was added a mixture of **6** (702 mg, 3 mmol) and **2** (606 mg, 3 mmol) dissolved in methanol (50 ml) and the mixture refluxed for 6 h, then concentrated, cooled and acidified with conc. HCl. The precipitated solid was filtered off, dried and fractionally crystallised from chloroform when *3-acetyl-2-(3-acetyl-4-oxo-4H-1-benzopyran-2-yl)methylene-4-hydroxy-2H-1-benzopyran* **22** (464 mg, 40%) first crystallised out. It had m.p. 213° (Found : C, 70.8; H, 3.8. $C_{23}H_{16}O_6$ requires C, 71.1; H, 4.2%); PMR : δ 18.80 (1H, s, exchangeable, OH), 8.00 (3H, m, exocyclic olefinic H + benzopyran 5-H), 7.68 - 6.72 (6H, m, other ArH), 3.24 (3H, s, Ac), and 3.16 (3H, s, Ac).

The mother liquor from the above crystallisation gave on concentration 3-acetyl-4-hydroxycoumarin (55 mg, 9%) m.p. 138° (lit.[14] m.p. 137°).

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