Tetrahedron Vol 37, pp 209 to 217
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0040-4020/81/0101-0209 $02.00/0

RUTACEOUS CONSTITUENTS—13[1]

A BIOMIMETIC SYNTHESIS OF ACRONYCINE[2]

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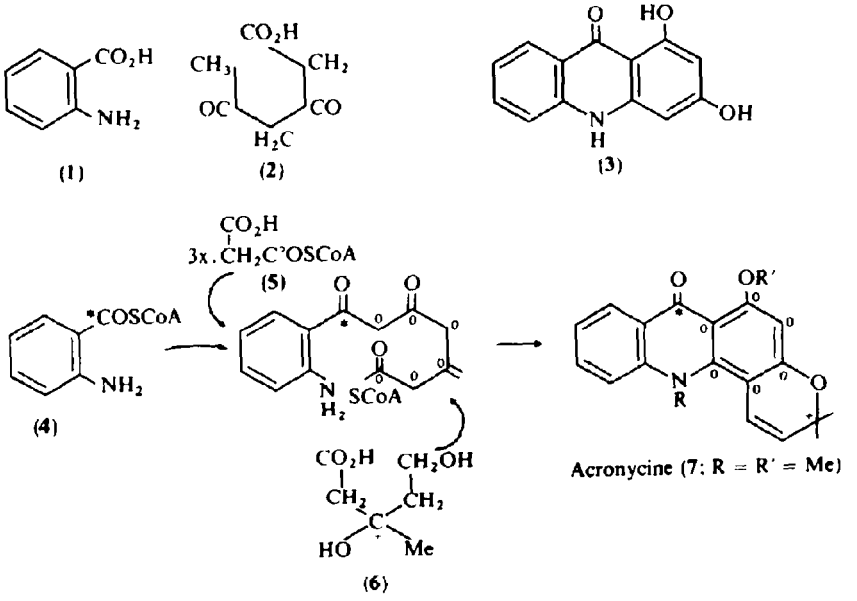
(*Received in U.K. 21 April 1980*)

Abstract—A biomimetic synthesis of the anti-tumor active alkaloid acronycine (7; R=R'=Me) has been obtained by cyclisation of 6-(2-methylaminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (**11**; R=R'=Me); isoacronycine (**20**; R=R'=Me) was also produced. In an analogous manner the aminochromene (**11**; R=H, R'=Me) gave a mixture of des-N-methylacronycine(7; R=H, R'=Me) and des-N-methylisoacronycine (**20**; R=H, R'=Me). The aminochromenes were best synthesised by condensation of lithio-5,7-dimethoxy-2,2-dimethylchromene (**22**; R=Li) with N-methylisatoic anhydride (**26**) or with 2-methyl-3,1-benzoxazin-4-one (**21**).

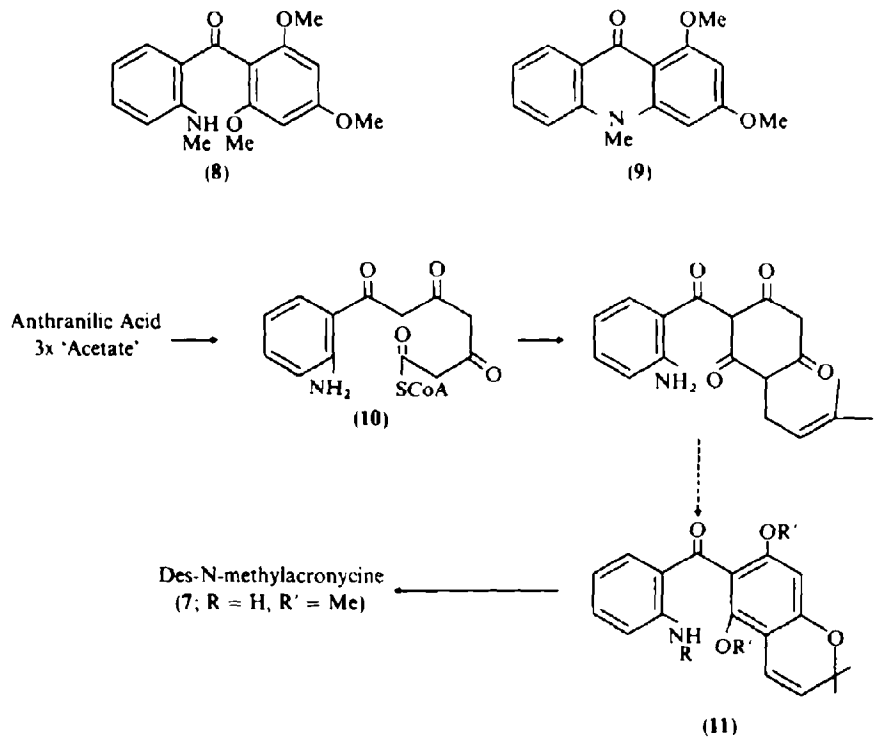
The relevance of this synthetic route to the biogenesis of acridone alkaloids is discussed.

The acridone alkaloids constitute a small group of natural products found exclusively in the Rutaceae family of higher plants.[3,4] A sustained interest in this field has been due to the reported activity of acronycine (**7**), a constituent of *Acronychia baueri* and *Vepris amphody*, as an anti-tumor agent.[5] The first series of syntheses of acronycine involved initially the preparation of 1,3-dihydroxyacridan-9-one[6] with the dimethylpyranyl moiety being introduced at a later stage.[7,8] Recently 5-amino-7-methoxychromene has been used in a synthesis of acronycine and its analogues.[9]

We wish to describe a new synthesis of acronycine based on a route which may have analogy to the biosynthetic pathway of this alkaloid. The early proposals on the biosynthesis of the acridan-9-one nucleus made by Sir Robert Robinson invoked anthranilic acid and acetate,[10] and this suggestion has been experimentally confirmed by the findings of Prager and of Gröger and their collaborators who found that carboxy labelled anthranilic acid (**4**),[11,12] malonate (**5**),[11] and mevalonic acid (**6**)[13] were incorporated into certain acridone alkaloids. Based on this work Gröger has suggested that acronycine (**7**) is elaborated according to the sequence (**4**→**7**) and Lewis has suggested that an intermediate in acridone biosynthesis is an aminobenzophenone[14] and has further shown that the N-methylaminobenzophenone (**8**) is easily and quantitatively converted into 1,3-dimethoxy-10-methylacridan-9-one (**9**).[15,16] The isolation of **8**, called tecleanone, from *Teclea grandifolia*,[17] *Diphasia klaineana*, *Teclea verdoorniana*[18] and *Oricia suaveolens*[19] and of the alkaloid **9** from the latter two plants[19] offered support for the role of aminobenzophenones as biosynthetic intermediates. We now see the biosynthesis of acronycine involving a triketide intermediate



Scheme 1



Scheme 1

followed by introduction of the chromenyl moiety prior to cyclisation and methylation as indicated in Scheme 1.

N-Methylation may occur at a late stage in the sequence since des-N-methylacronycine (**7**; R=H, R'=Me) has been isolated from *Glycosmis pentaphylla*.[20]

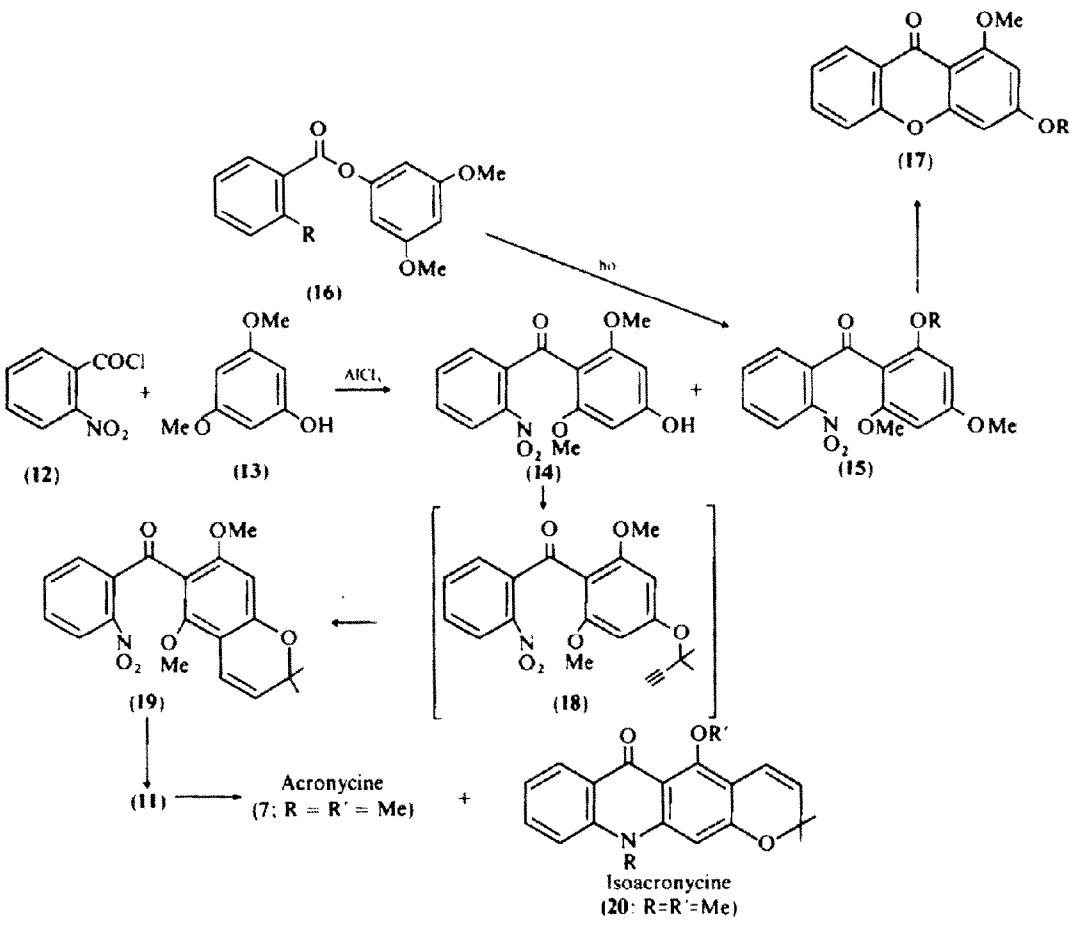
The key intermediates for our synthesis were the aminobenzophenones (**11**; R=H or Me, R'=Me) which in turn can be regarded as the putative precursor to des-N-methylacronycine (**7**; R=H, R'=Me) and acronycine (**7**; R=R'=Me) respectively. Two synthetic routes were considered; formation of a 2-nitrobenzophenone followed by introduction of the dimethylpyranyl group in an analogous manner to that used for the synthesis of acronycine and other chromenyl compounds[7,8] with subsequent reduction to the amino compound or condensation of a benzoxazine or N-methylisatoic anhydride with lithiated 5,7-dimethoxy-2,2-dimethylchromene to give the amines directly.

In the first route Friedel Crafts condensation of 2-nitrobenzoyl chloride (**12**) with 3,5-dimethoxyphenol (**13**) gave two products, 4,6-dimethoxy-2-hydroxy-2'-nitrobenzophenone (**15**; R=H) and as the minor component 2,6-dimethoxy-4-hydroxy-2'-nitrobenzophenone (**14**). Structural assignments for these two isomers were unambiguously made by examination of their NMR spectra; in **14** the two OMe groups at C_2 and C_6 resonated at τ6.42 ppm while those in **15** (R=H) at C_2 and C_4 resonated at τ6.06 and 5.43 ppm respectively.

Due to the poor yield of the desired isomer by direct Friedel-Crafts reaction it was considered that Fries rearrangement of 3,5-dimethoxyphenyl-2'-nitrobenzoate (**16**; R=NO_2) should give the required benzophenone (**14**) since the normal migration associated with the Fries rearrangement gives the *para*-orientated product.[21] A rapid photochemical rearrangement took place but the sole product was the "ortho" isomer (**15**; R=H) similarly photo Fries rearrangement of the amino-ester (**16**; R=NH_2) only provided the "*ortho*" aminobenzophenone.

Several reports in the literature concerning selective demethylation prompted us to investigate non acidic demethylation procedures on the nitrotrimethoxybenzophenone (**15**; R=Me) since it has been well documented that acidic reagents cause selective demethylation of methoxy groups *peri* to CO groups in xanthones, benzophenones and acridones. The use of ethanethiol in DMF[22] gave a complex mixture with negligible quantities of the required phenol and sodium in liquid ammonia gave little demethylation starting material being mostly recoverable. When the nitrobenzophenone was treated with boiling piperidine[23] cyclisation occurred to give 1,3-dimethoxyxanthone (**17**; R=Me) and 3-hydroxy-1-methoxyxanthone (**17**; R=H) both xanthones being produced presumably by prior demethylation followed by elimination of nitrous acid.

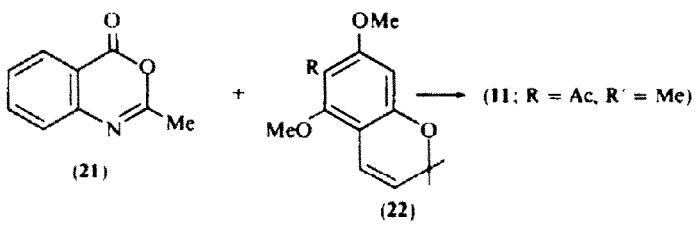
The failure of all but the Friedel Crafts reaction to produce the necessary phenol necessitated a re examination of this condensation and the best yield for the required product was obtained at 0-14 (5%). The phenolic benzophenone (**14**) was now to be converted into the nitrochromene (**19**). A number of methods are available for the introduction of the dimethylpyran ring.[24] It was decided to use the route involving 3-chloro-3-methylbutyne which gives firstly a propargyl ether (e.g. **18**) which can subsequently be cyclised to the pyran (e.g. **19**). Hlubucek *et al.*[25] had used a similar sequence for the synthesis of acronycine where the



Scheme 2

pyran ring was introduced after formation of the acridone ring system.[8] That condensation of 3-chloro-3-methylbutyne with the nitrobenzophenone (**14**) followed by cyclisation had taken place was confirmed from the spectral properties of the product **19** and by its reduction with zinc dust in ethanol to give the 2-aminobenzophenone (**11**; R=H, R′=Me). Both compounds showed typical chemical shift values for two C-methyl groups at $\tau \sim 8.5$ and two coupled vinyl protons at τ about 4.50 and 3.50 ($J = 10$Hz) corresponding to the presence of a dimethyl chromene ring.[26] The amine (**11**; R=H, R′=Me) also showed the characteristic NH_2 stretching vibrations as a doublet at 3470 and 3340 cm^{-1}. Treatment of this amine with NaH in DMSO gave two products, des-N-methylacronycine (**7**; R=H, R′=Me) having the angular structure corresponding to loss of the C-5 methoxy group during cyclisation and des-N-methylisoacronycine (**20**; R=H, R′=Me) having the linear structure, the ratio of the two isomers being ~1:2. The assignment of structure to these acridones was accomplished by comparison of the chemical shift value for the phloroglucinol ring proton in **7** (R=H, R′=Me) at $\tau = 3.80$ with that observed for noracronycine (**7**; R=Me, R′=H) at τ 3.86 and acronycine (**7**; R=R′=Me) at 3.72[26] while the iso-compound **20** (R=H, R′=Me) showed a chemical shift value of $\tau = 3.60$ which conforms with the lower chemical shift values found for linear isomers. Norisoacronycine (**20**; R′=H, R=Me) has its ring proton at $\tau = 3.82$ compared with noracronycine at τ 3.86.[25] Methylation of **7** (R=H, R′=Me) with methyl iodide in acetone in the presence of anhydrous potassium carbonate gave acronycine (**7**; R=R′=Me).

An alternative route to the benzophenone **11** (R=H, R′=Me) was based on the observation that 2-methyl-3,1-benzoxazin-4-one (**21**) reacted with Grignard reagents to give 2-acetylaminobenzophenones.[27,15,16]



From a study of the lithiation of 1,3-dimethoxy benzene whence the 6-lithio-derivative was produced[28] it was considered that lithiation of 5,7-dimethoxy-2,2-dimethyl chromene (**22**; R=H) would proceed in a similar orientation to give **22** (R=Li).

This was realised when the lithiated product from **22** (R=H) was reacted with the benzoxazin-4-one (**21**) and from the reaction product 6-(2-acetylaminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (**11**; R=Ac, R'=Me) was isolated. The spectral properties of this amide showed typical CO absorption at 1695 cm^{-1} corresponding to the aryl amide function and at 1660 cm^{-1} corresponding to the benzophenone CO group. Chemical shift values at τ 8.53 were assigned to the gem dimethyl groups and two pairs of doublets at τ 3.52 and τ 4.45 for the vinyl protons of the chromenyl ring. Hydrolysis of the amide gave the amine **11** (R=H, R'=Me) which was identical with the compound prepared from the nitrochromene (**19**).

Treatment of the acetylaminobenzophenone (**11**; R=Ac, R'=Me) with NaH in DMSO caused cyclisation and loss of the acetyl group to give a mixture of des-N-methylacronycine (**7**; R=H, R'=Me) and des-N-methylisoacronycine (**20**; R=H, R'=Me) in 43% and 46% yield respectively. The cyclisation of N-acetylaminobenzophenones to acridan-9-ones has been reported to proceed via the N-acetylacridan-9-one followed by its rapid hydrolysis to the acridan-9-one.[16] Hydrolysis of **11** (R=Ac, R'=Me) with 5% KOH/MeOH produced the amine **11** (R=H, R'=Me) in excellent yield. The amine **11** (R=H, R'=Me) cyclised under similar conditions to give the angular and linear acridones in 27% and 39% yield respectively.

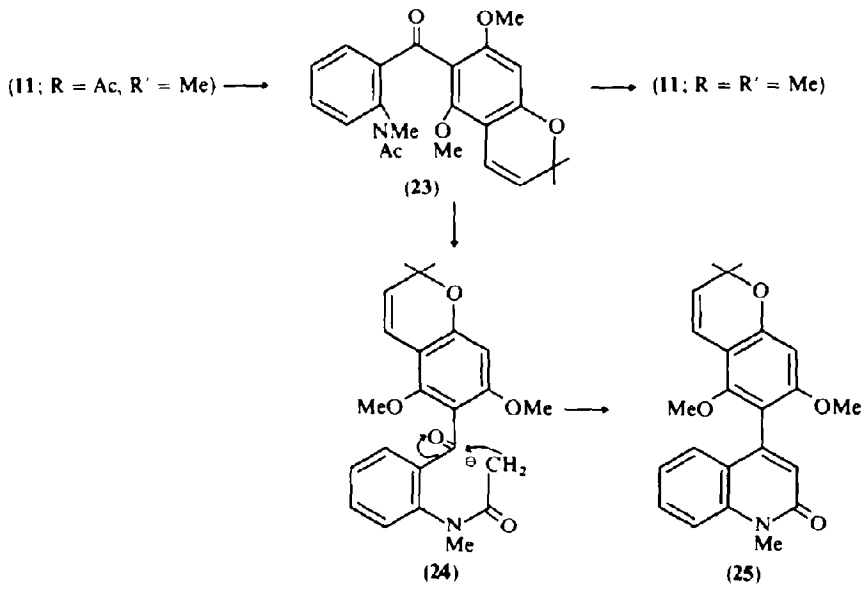
During the early studies on the biogenesis of acridone alkaloids it had been established that N-methylanthranilic acid (as well as anthranilic acid) was a precursor[12] and it was relevant to study the mode of cyclisation of the N-methylaminochromenylbenzophenone (**11**; R=R'=Me) since this amine would be the direct precursor of acronycine. Methylation of the N-acetylchromene (**11**; R=Ac, R'=Me) gave the N-acetyl-N-methyl derivative which upon mild alkaline hydrolysis gave, in poor yield, the required N-methylamine (**11**; R=R'=Me). Accompanying this amine, as the major product, was the quinolone (**25**), formed by intramolecular aldol condensation (**23** → **25**) utilising the acetyl group in the cyclisation.

This type of cyclisation of N-acetyl-N-methylaminobenzophenones had previously been observed when *ortho* methoxy N-acetyl-N-methylaminobenzophenones were treated with NaH/DMSO or when N-acetylaminobenzophenones lacking an *ortho* methoxy group were similarly treated.[16]

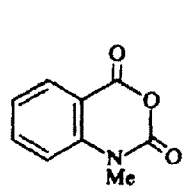
A more efficient synthesis of N-methylaminobenzophenones was considered feasible through the use of N-methylisatoic anhydride (**26**). Previously reported reactions of isatoic and N-methylisatoic anhydride with nucleophiles[29] suggested that the anhydride would react with the lithiated chromene (**22**; R=Li) to give the desired N-methylaminobenzophenone (**11**; R=R'=Me). The condensation produced three compounds two of which being similar in character were only separated by repeated chromatography and identified as the required N-methylamine (**11**; R=R'=Me) and its isomer 8-(2-methylaminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (**27**). The chemical shifts for the proton at C-6 occurred at τ 3.95 and at C-8 at τ 3.78 identifying each compound unambiguously.

The third compound obtained from the condensation had M.W. 541 and showed in its NMR spectrum the presence of three OMe, one N-Me and four gem diMe groups. These data could be interpreted by having the lithiated chromene condensing with N-methylisatoic anhydride to give firstly N-methylaminochromenylbenzophenone (**27**) which was subsequently attacked by a second lithiated chromene moiety to give the tertiary alcohol (**28**) which subsequently cyclised to the acridinol (**29**). Proton NMR signals with chemical shift values at τ 3.55 and τ 4.05 were assigned to position C-4 in the acridine ring and to C-6 in the chromene ring respectively.

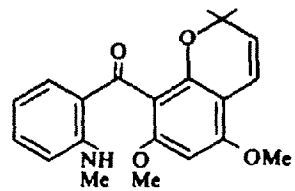
Treatment of N-methylaminochromenylbenzophenone (**11**; R=R'=Me) with NaH in DMSO gave



Scheme 3



(26)



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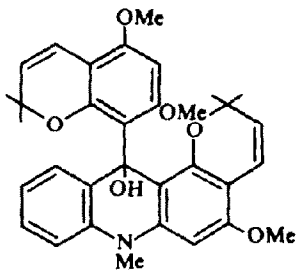

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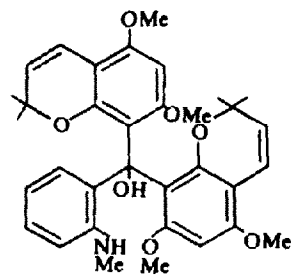

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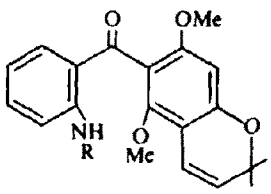
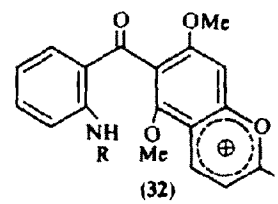
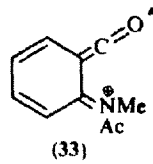


(23), (11) and
(19; NHR = NO_2)



(32)
from (19), (23), (11; R = H, Ac, Me)



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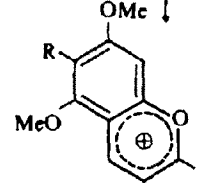

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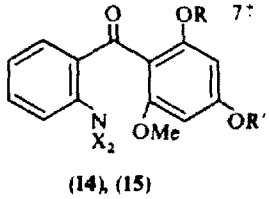
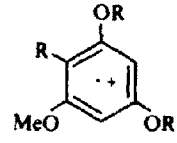


(14), (15)



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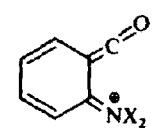
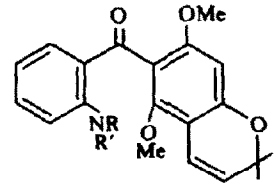


(31)

Scheme 4

Table 1. Cyclisation of aminobenzophenones



R	R'	% angular acridone	linear acridone
—			
H	H	29	42
H	Ac	43	46
Me	H	38	38

acronycine (**7**; R=R'=Me) and isoacronycine (**20**; R=R'=Me) in equal amounts. Table 1 summarises the results obtained for the cyclisation of the amino-chromenylbenzophenones described.

The mass spectral fragmentation of substituted benzophenones has been found to occur mainly through cleavage α to the carbonyl group. *Ortho* substituents influence this cleavage and Ballantine has discussed the various types of splitting that can occur.[30] With our simple nitrobenzophenones (**14**, **15**; R=Me or H; X=H or O) α cleavage occurred with production of ions (**30**; R=Me or H) and **31** (X=H or O_2) with or without hydrogen transfer,[30] to give the base peak; loss of carbon monoxide followed.

With the dimethylchromenylbenzophenones the main breakdown was loss of a methyl or methylene group followed by, in some cases, α-cleavage and hydrogen transfer to give ions such as **32**, **33** and **34**. The loss of a single Me group from dimethylchromenes has been reported to be, often, the only major fragmentation observed.[31]

Both methylaminochromenylbenzophenones (**11**; R=R'=Me) and **27** showed no useful antitumor activity†.

EXPERIMENTAL

UV spectra were recorded on a Perkin Elmer 402 spectrometer, IR spectra on a P.E. 177 instrument, NMR on a Varian HA 100 spectrometer in $CDCl_3$ unless otherwise stated. Mass spectra were measured on an AEI 30 instrument at 70 eV.

Friedel-Crafts condensation between 2-nitrobenzoyl chloride (**12**) *and 3,5-dimethoxyphenol* (**13**). 2-Nitrobenzoyl chloride (12 g) and $AlCl_3$ (anhyd., 13 g) were dissolved in dry ether (50 ml) and this mixture added to a sóln of 3,5-dimethoxyphenol (5 g) in dry ether (50 ml) at 0° and the final mixture stirred at 0° for 3 h, brought to 20° and stirred for a further 3 h. Dil HCl and ice were added and the product extracted with EtOAc (50 ml, 3x), this extract was washed with $NaHCO_3$ aq, water, dried ($MgSO_4$) filtered and evaporated under reduced pressure to yield a dark red oil. This oil was treated with NaOH aq (100 ml, 2M) for 1 h, acidified with dil HCl and re-extracted with EtOAc which gave, after a similar work up, a paled red oil (5.0 g). Tlc showed three components one of which was the phenol **13**. Column chromatography (150 g, silica gel) and elution with benzene:petrol ether, 40–60° (1:1) followed by increasing polarity of solvents (benzene through chloroform to chloroform:ether 4:1) gave 59 fractions. Fractions 1–12 were combined to give a solid which crystallised from benzene to give *4,6-dimethoxy-2-hydroxy-2'-nitrobenzophenone* (**15**; R=H; 1.51 g), m.p. 198–199°, λ_{max} (MeOH) 215 (log ε 4.51), 224 (4.51), 302 nm (4.33); ν_{max} (KBr) 3400–3200 (OH), 1625 cm^{-1} (bonded C=O); τ ($CDCl_3$/CD_3OD) 6.06 (3H, s, OMe), 5.43 (3H, s, OMe), 3.08 (1H, d, J 4 Hz, 3 or 5-H), 2.65 (1H, d, J 4 Hz, 3 or 5-H), 1.40–0.60 (3H, complex, Ar-H), 0.21 (1H, d J 12 Hz, 3'-H), −2.83 (1H, s, OH). Found: C, 59.6; H, 4.4. $C_{15}H_{13}NO_6$ requires: C, 59.4; H, 4.3%; *m/e* 303 (6%), 271 (2), 257 (4), 256 (8), 255 (3), 228 (3), 227 (6), 226 (3), 181 (10), 171 (10), 170 (100), 141 (25), 104 (13).

Fractions 13–21 were discarded. Fractions 22–42 were combined (0.3 g), crystallised from benzene and the product added to that obtained from fractions 43–59 which crystallised from benzene to give *2,6-dimethoxy-7-hydroxy-2'-nitrobenzophenone* (**14**; 0.5 g) m.p. 175–177°, λ_{max} (MeOH 213 (log ε 4.39), 291 nm (3.98)); ν_{max} (KBr) 3400–3200 (OH) 1640 cm^{-1} (CO); τ ($CDCl_3$/CD_3OD) 6.42 (6H, s, 2 and 6-OMe), 3.97 (2H, s, 3,5-H), 2.2–2.6 (3H, complex, Ar-H), 2.08 (1H, dd, J 8 and 2 Hz, 3'-H). Found: C, 59.4; H, 4.1. $C_{15}H_{13}NO_6$ requires: C, 59.4; H, 4.3%; accurate mass 303.0742 required 303.0742; *m/e* 303 (2%), 182 (10), 171 (3), 170 (100), 166 (3), 142 (18), 104 (6).

3,5-Dimethoxyphenyl-2'-nitrobenzoate (**16**; $R=NO_2$). 2-Nitrobenzoylchloride (4 g) and 3,5-dimethoxyphenol (6.8 g) were dissolved in dry acetone (100 ml) containing anhyd K_2CO_3 and the mixture refluxed for 1.5 h. After cooling, filtering and evaporating the acetone under reduced pressure the residual oil was dissolved in EtOAc (100 ml) and worked up in the usual way to give an oil which solidified (6.2 g). The *ester* **16**, ($R=NO_2$) crystallised from EtOH as needles, m.p. 104–105° (5.4 g); λ_{max} (MeOH) 213 (log ε 4.38), 260sh nm (3.78); ν_{max} (KBr) 1738 (ester, CO), 1620 cm^{-1} (bonded C=O); τ 6.20 (6H, s, 2xOMe), 3.58 (3H, s, 2,4,6H), 2.40–1.9 (4H, complex, Ar-H). Found: C, 59.2; H, 4.1. $C_{15}H_{13}NO_6$ requires: C, 59.4; H, 4.3%; *m/e* 303 (9%), 256 (2), 213 (1), 159 (3), 144 (13), 141 (5), 140 (100), 137 (3), 125 (40), 119 (5).

Fries rearrangement of 3,5-dimethoxyphenyl-2'-nitrobenzoate (**16**; $R=NO_2$). The ester (4.5 g) was dissolved in ANALAR benzene (500 ml) and photolysed in a quartz reactor with a medium pressure U.V. lamp for 1.5 h. The soln was evaporated to dryness under reduced pressure and the product (4.5 g) crystallised from benzene as **15** (R=H) m.p. and m. m.p. 195–198°.

3,5-Dimethoxyphenyl-2'-aminobenzoate (**16**; $R=NH_2$). The nitrobenzoate (3.0 g) was dissolved in AcOH (9 ml) containing water (6 ml) and Zn moss (10 g) added slowly over 15 min at r.t. Stirring was continued for a further 0.5 h when the reaction was diluted with water and worked up in the usual way to give an oil (1.69 g) which crystallised from MeOH as the *amine* **16** ($R=NH_2$), m.p. 70–71°, λ_{max} (MeOH 206 (log ε 4.54), 221 (4.56), 249 (3.96), 276 (3.30), 345 nm (3.77)) ν_{max} (KBr) 3495, 3380(NH_2), 1695 (ester CO), 1615 cm^{-1} (bonded CO); τ 6.43 (6H, s, 3 and 5-OMe), 4.24 (2H, broad s NH_2), 3.64 (3H, s, 2,4,6-H), 2.50–3.50 (3H, complex, ArH), 2.63 (1H, dd, J 2 and 8 Hz, 3'-H), 1.95 (1H, dd, J 2 and 8 Hz, 6'-H); Found: Accurate mass 273.1001. $C_{15}H_{15}NO_4$ requires 273.1001).

2'-Amino-4,6-dimethoxy-2-hydroxybenzophenone. The nitrobenzophenone (0.4 g) was dissolved in EtOH (30 ml) containing water (5 ml) and NH_4Cl (1 g) and Zn moss (1.5 g) added as described earlier. The mixture was worked up in the usual way to give an oil (0.38 g) which crystallised from MeOH-benzene, m.p. 71–75° for *2'-amino-4,6-dimethoxy-2-hydroxybenzophenone* (0.22 g). λ_{max} (MeOH) 213 (log ε 4.36), 230 (4.25), 259 (3.93), 265sh (3.90), 376 nm (3.60); ν_{max} (KBr) 3470, 3350 (NH_2), 1610 cm^{-1} (C=O), τ 6.48 (3 H, s, 4-OMe), 6.18 (3 H, s, 6-OMe), 4.63 (2H, broad s, NH_2), 4.04 (1H, d, 2 Hz, 3 or 5H), 3.84 (1H, d, J 2 Hz, 3 or 5H), 2.60–3.56 (4H complex, ArH). Found: Accurate mass 273.1004. $C_{15}H_{15}NO_4$ requires: 273.1001. *m/e* 273 (22%), 272 (2), 257 (11), 256 (3), 24 (4), 181 (18), 180 (6), 154 (13), 121 (4), 120 (100), 119 (8).

Fries rearrangement of aminobenzoate (**16**; $R=NH_2$). The aminoester (0.49 g) was dissolved in Analar benzene (250 ml) and irradiated with a medium pressure UV lamp in a quartz reactor for 12.5 h. The soln was extracted repeatedly with NaOH aq (50 ml, 4M) and the alkaline extracts acidified and extracted with EtOAc (50 ml, 3x) which, after the usual work up, yielded a solid (0.22 g) which crystallised from MeOH benzene as 2'-amino-4,6-dimethoxy-2-hydroxybenzophenone, was not detected in the original reaction mixture nor in the mother liquors obtained.

2'-Nitro-2,4,6-trimethoxybenzophenone (**15**; R=Me). N-[(2-Nitrophenyl)-(2,4,6-trimethoxyphenyl)methylene] aniline (1.0 g) was refluxed in conc HCl (50 ml) and MeOH (20 ml) for 5 days. The mixture was then poured into water and neutralised with $NaHCO_3$ before extraction with EtOAc. Work up of the organic layer in the usual way gave a yell

†Both methylaminobenzenophenones (11, R=R'=Me) and (27) were tested against X5563 myeloma and C1498 myelogenous leukemia (dosage 28 mg/kg) and showed less than 25% tumor inhibition. We thank Eli Lilly Laboratories for these measurements.

solid which crystallised from methanol as *2'-nitro-2,4,6-trimethoxybenzophenone* (**15**; R=Me, 391 mg), m.p. 148–149 ; λ_{max} (MeOH) 213 (log ε 4.47), 233sh (4.20), 289 nm (3.98). ν_{max} (KBr) 1675 cm^{-1} (non-bonded aryl C=O). τ 2.1–2.6 (4H, complex, ArH), 3.94 (2H, s, 3 and 5-H), 6.18 (3H, s, 4-OMe), 6.37 (6H, s, 2 and 6-OMe). Found: C, 60.8; H, 4.5. $C_{16}H_{15}NO_6$ requires: C, 60.6; H, 4.8%. *m/e* 317 (4), 195 (13), 184 (8), 183 (100), 155 (13), 152 (2), 140 (2), 137 (4), 134 (2), 125 (2), 123 (2), 104 (5). *Attempted selective demethylation of* **15** (*R=Me*).

Attempted selective demethylation of **15** (*R=Me*)

(i) *Ethanethiol.* Compound **15** (R=Me, 0.5 g) was dissolved in dried DMF (10 ml) and ethane thiol (0.6 g) dissolved in DMF (10 ml) containing NaH (0.5 g, 60%) added and the mixture refluxed for 3 h. The mixture was poured into water, acidified with dil HCl and extracted with EtOAc, from the organic layer a phenolic fraction was obtained by repeated extraction with 10% NaOH aq but this extract, after acidification, showed that none of the desired phenol was present. The neutral fraction was also shown to be a mixture (tlc) with some starting material present but no phenol.

(ii) *Piperidine.* The benzophenone **15** (R=Me, 1.56 g) was refluxed in piperidine (20 ml) and water (15.5 ml) for 65 h. Tlc indicated two blue fluorescent substances to be present and the product was taken up in EtOAc and the organic layer was washed with dil HCl, 10% NaOH aq, water, dried and evaporated to give a neutral fraction (166 mg) which crystallised from MeOH, m.p. 165–168°, it showed similar spectral properties to those obtained from **17** (R=Me), m.p. 168–169°.[33] The phenolic fraction isolated from the alkaline extract (189 mg) crystallised from acetone, m.p. 293–296° and it showed similar spectral properties to those obtained from **17** (R=H) m.p. and m. m.p. 318°.[34]

Condensation of 3-chloro-3-methylbutyne with benzophenone (**14**). A soln of the benzophenone (**14**; 2 g) and excess 3-chloro-3-methylbutyne[8] (4.5 g) in dry DMF (60 ml) containing anhyd K_2CO_3 (4 g) and dry KI (2 g) was stirred and heated at 65° for 14 h (under N_2). The mixture was cooled, diluted with water, acidified, extracted with chloroform (50 ml 3x) and the extract was worked up in the usual way (including a NaOH wash) to give an oil which was redissolved in DMF (20 ml) and heated at 130°, under N_2 for 7 h whence most of the starting material had disappeared. The solvent was removed under reduced pressure to give a product (0.62 g) which was purified by preparative layer chromatography on silica gel to give *6-(2-nitrobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene* (**19**; 0.22 g) which crystallised from EtOH, m.p. 92–93°; λ_{max} (MeOH) 213 (log ε 4.27), 234 (4.38), 263 (4.24), 298sh (3.90), 342 nm (3.74); ν_{max} (KBr) 1660 (CO), 1630 cm^{-1}; τ 8.50 (6H, s, $C(Me)_2$), 6.30 (6H, s, 2xOMe), 4.50 (1H, d, J 10 Hz, 3-H, 3.72 (1H, s, 8-H), 3.50 (1H, d, J 10 Hz, 4-H), 3.25–3.50 (2H, complex, Ar–H), 2.02–2.80 (2H, complex, ArH). Found: Accurate mass 369.1211. $C_{20}H_{19}NO_6$ requires: 369.1212. *m/e* 369 (6%), 355 (10), 354 (100), 277 (4), 235 (2), 149 (2).

6-(2-Aminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (**11**; R=H, R'=Me). Compound **19** (0.2 g) was dissolved in EtOH (30 ml) containing water (5 ml) and ammonium chloride (1 g) and Zn moss (1.5 g) was added in portions and the mixture stirred at r.t. for 5 days. The soln was filtered, evaporated to dryness under reduced pressure and the residue dissolved in EtOAc (25 ml) and worked up in the usual way to give a solid (0.19 g). Compound **11** (R=H, R'=Me; 0.18 g) crystallised from EtOH with m.p. 123–126°, λ_{max} (MeOH) 218 (log ε 4.51), 230 (4.51), 237sh (4.45), 266 (4.00), 283sh (3.84), 300 (3.65), 372 nm (3.68); ν_{max} (KBr) 3470, 3340 (NH_2) 1632 cm^{-1} (CO bonded); τ 8.56 (6H, s, $C(Me_2)$), 6.35 (6H, s, 2xOMe), 4.48 (1H, d, J 10 Hz, vinyl CH), 3.76 (1H, s, 8-H), 3.50 (1H, d, J 10 Hz, vinyl CH), 3.26–3.45 (2H, complex, Ar-H), 2.56–2.86 (2H, complex, Ar H). Found: Accurate mass 339.1475. $C_{20}H_{21}NO_4$ requires: 339.1470. *m/e* 339 (18%), 325 (13), 324 (100), 308 (1), 292 (2), 278 (5), 205 (5), 162 (3), 120 (6).

Cyclisation of the aminodimethylchromenylbenzophenone (**11**; R=H, R'=Me). Compound **11** (R=H, R'=Me, 0.12 g) was dissolved in DMSO (8 ml) and NaH (0.06 g) added, the mixture was stirred for 6 days at r.t. A further addition of NaH (0.06 g) was made and the soln heated to 50° for 0.5 h whence it was poured into water, extracted with EtOAc and worked up in the usual way to give a crude mixture (0.11 g; 3 components). Separation of this mixture on plc (silica gel, benzene:EtOAc, 10:4) gave *Band* 1 (R_f 0.45; 38 mg) identified as starting material, m.p. and m.m.p. 120–123°.

Band 2 (R_f 0.32; 42 mg; 43%) which crystallised from ethyl acetate as *des-N-methylisoacronycine* (**20**; R=H, R'=Me) m.p. 293–295°; λ_{max} (MeOH) 218 (log ε 3.10), 343sh (3.06), 264sh (3.36), 276 (3.55), 286 (3.62), 298 (3.58), 324 (2.64), 384 (2.76), 400 nm (2.76); ν_{max} (KBr) 3420 (NH), 1630 cm^{-1} (CO); τ 8.52 (6H, s, $C(Me)_2$), 6.06 (3H, s, OMe), 4.34 (1H, d, J 10 Hz, -CH=), 3.57 (1H, s, 4-H), 3.21 (1H, d, J 10 Hz, -CH=), 2.30–3.00 (4H, complex, Ar–H), 1.75 (2H, broad s, NH). Found: C, 74.3; H, 5.8. $C_{19}H_{17}NO_3$ requires C, 74.25; H, 5.6%; accurate mass 307.1207. $C_{19}H_{17}NO_3$ requires 307.1208. *m/e* 307 (63%), 293 (11), 292 (100), 289 (5), 278 (4), 274 (6), 264 (8), 263 (11), 262 (9), 167 (16), 150 (6), 149 (84).

Band 3 (R_f 0.10; 29 mg, 29%) crystallised from ethyl acetate as *des-N-methylacronycine* (7; R=H, R'=Me), m.p. 237–240 d; λ_{max} (MeOH) 210 (log ε 3.31), 220sh (3.25), 250sh (3.42), 258 (3.53), 266 (3.59), 281 (3.37), 292 (3.39), 318 (2.79), 378 (2.76), 396 nm (2.76); ν_{max} (KBr) 3430 (NH), 1630 cm^{-1} (CO); τ 8.54 (6H, s, $C(Me)_2$), 6.12 (3H, s, OMe), 4.48 (1H, d J 10 Hz, -CH=), 3.82 (1H, s, 2-H), 3.24 (1H, d, J 10 Hz, -CH=), 2.40–2.90 (4H, complex, Ar H), 1.60 (1H, d, J 8 Hz, NH). Found: accurate mass 307.1207. $C_{19}H_{17}NO_3$ requires: 307.1208. *m/e* 307 (45%), 293 (11), 292 (100), 278 (8), 277 (5), 263 (8), 262 (10), 249 (3), 248 (3), 220 (2), 146 (5).

Acronycine (7; R=R'=Me). Compound 7 (R=H, R'=Me; 14 mg) was dissolved in dry acetone (10 ml), anhyd K_2CO_3 (1 g), and MeI (2 ml) added and the mixture refluxed for 11 h. The soln was filtered, and the solvents evaporated, the residue EtOAc and worked to give a solid (12 mg), which after purification on tlc, gave acronycine which crystallised from aqueous MeOH, m.p. 171–173°, m.m.p. 169–173° (our sample of authentic acronycine had m.p. 165–168° lit. m.p. 175–176°[6]). This product showed identical U.V. and R_f characterisation when compared with acronycine and had an accurate mass measurement of 321.1368. $C_{20}H_{19}NO_3$ required: 321.1364.

5,7-Dimethoxy-2,2-dimethylchromene (**22**; R=H). A mixture of 3,5-dimethoxyphenol (0.03 m) and 3-chloro-3-methylbutyne (0.06 m) dried K_2CO_3 (5 g) and KI (8 g) in dry acetone (50 ml) was stirred and refluxed for 20 h. The product was isolated as described by Hlubucek *et al.*[25] to give **22**; (R=H; 2.11 g) b.p. 88–89°/0.2 mm.

Condensation of benzoxazine-3-one (**21**) *with the lithio derivative of dimethylchromene* (**22**; R=Li): *6-(2N-acetylaminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene* (**11**; R=Ac, R'=Me)

(a) *Lithiochromene* (**22**; R=Li). Li (240 mg, 0.03 m) was suspended in dry ether (30 ml) and n-bromobutane (3.22 g, 0.025 m) in dry ether (30 ml) added and the mixture was stirred under N_2 until the reaction was complete (2.5 h). The chromene **22** (R=H; 2.2 g; 0.01 m) dissolved in ether (30 ml) was added and the mixture refluxed for 20 h benzoxazine-3-one (**21**; 1.62 g; 0.01 m) dissolved in ether (20 ml) was added and the reflux continued for a further 3 h when it was cooled and treated with iced dil HCl. The organic layer was washed with water, 2N NaOH, water, dried, filtered and evaporated to give an oil (3.64 g). Separation of this mixture by preparative layer chromatography using silica and development with benzene:EtOAc (10:4) gave a mixture of two compounds (827 mg; R_f 0.65) which were further separated on tlc (under similar conditions of development) into two bands, the faster running band on isolation yielded *6-(2-N-acetylaminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene* (**11**; R=Ac, R'=Me; 455 mg) which crystallised from aqueous acetone, m.p. 160–161°; λ_{max} (MeOH) 213sh (log ε 3.80), 233 (4.60), 265 (4.27), 271 (4.29), 310 (4.07), 335 nm (3.80); ν_{max}

3240 (NH), 1695 ($CONH_2$), 1630 cm^{-1} (ArCO); τ 8.53 (6H, s, $C(Me)_2$), 7.72 (3H, s, COAc), 6.35 (6H, s, 2xOMe), 4.45 (1H, d, J 10 Hz, 3-H), 3.76 (1H, s, 8-H), 3.52 (1H, d, J 10 Hz, 4-H), 2.2–3.2 (3H, complex, ArH), 1.25 (1H, dd, J 9 and 2 Hz, 6′-H), −1.74 (1H, broad s, NH). Found: C, 69.0: H, 6.0. $C_{22}H_{23}NO_5$ requires: C, 69.3; H, 6.1%. *m/e* 381 (11), 367 (10), 366 (100), 292 (3), 176 (3), 172 (3), 120 (3%).

Cyclisation of N-*acetylaminobenzophenone* (**11**; R=Ac, R′=Me). The benzophenone **11** (R=Ac, R′=Me; 126 mg) was dissolved in DMSO (25 ml), NaH (200 mg, 60%) added and the mixture stirred at r.t. for 20 h. After pouring into water the products were isolated by extraction with EtOAc and separated on tlc (as described for the cyclisation of the aminobenzophenone) to give at *Band* 2 (46 mg, 46%) des-N-methylisoacronycine m.p. 306–308 (from aqueous acetone), m.m.p. 293–308°. *Band* 3 (43 mg, 43%) des-N-methylacronycine, m.p. 253–255 d (from aqueous acetone) m.m.p. 240–255.

Hydrolysis of N-*acetylaminobenzophenone* (**11**; R=Ac, R′=Me). Compound **11** (R=Ac, R′=Me; 19 mg) was refluxed with methanolic KOH (10 ml, 5M) for 1 h. On pouring the mixture into iced dil HCl and working up in the usual way a yellow oil was obtained which upon tlc purification gave **11** (R=H, R′=Me; 15 mg; 94%), m.p. 136–138 identical with the amine produced previously.

6-(2-N,N-*Acetylmethylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**23**). Compound **11** (R=Ac, R′=Me; 1.54 g) was dissolved in DMSO (30 ml) and stirred with iodomethane (10 ml) and NaH (275 mg, 60%) at r.t. for 20 h. After working up the mixture in the usual way the residue (1.61 g) was purified on plc (R_f 0.15, silica, benzene: EtOAc

6-*Acetylmethylaminobenzoyl*)-5,6-*dimethoxy*-2,2-*dimethylchromene* (**23**; 958 mg) which crystalised from aqueous acetone, m.p. 136–138° λ_{max} (MeOH) 220 (log ε 4.46), 235 (4.51), 251 (4.45), 272 (4.14), 313 nm (3.63); ν_{max} 1670 (COAc), 1655 cm^{-1} (ArCO); τ 8.56 (6H, s, $C(Me)_2$), 8.21 (3H, s, COAc), 7.00 (3H, s, NMe), 6.37 (6H, s, 2xOMe), 4.49 (1H, d, J 10 Hz, 3-H), 3.78 (1H, s, 8-H), 3.57 (1H, d, J 10 Hz, 4-H), 2.2–2.9 (4H, complex, ArH). Found: C, 69.5; H, 6.4. $C_{23}H_{25}NO_6$ requires: C, 69.8; H, 6.4%. *m/e* 395 (14%), 381 (11), 380 (100), 362 (4), 336 (3), 205 (5), 176 (10), 170 (2), 149 (18), 134 (14), 132 (7).

Hydrolysis of 6-(2-N,N-*acetylmethylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**23**); 1-*methyl*-4-(5,7-*dimethoxy*-2,2-*dimethylchromenyl*)-*quinol*-2-*one* (**25**) and 6-(2-*methylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**11**; R=R′=Me). Compound **23** (322 mg) was refluxed with methanolic KOH (30 ml, 5M) for 1 h, and the mixture poured into iced dil HCl and worked up to give a brown oil (317 mg). Plc separation (silica, benzene: EtOAc 10:4) gave two products:

Band 1. (R_f 0.33) yielded, on work up, a white solid (150 mg) which crystallised from aqueous MeOH as 1-*methyl*-4-(5,7-*dimethoxy*-2,2-*dimethylchromenyl*)-*quinol*-2-*one* (**25**), m.p. 187–190°; λ_{max} (MeOH) 213sh (log ε 3.61), 235 (4.69), 279 (4.18), 317 (3.97), 331 (3.91), 349sh nm (3.69); ν_{max} 1645 cm^{-1} (CO); τ 8.53 (3H, s, CMe), 8.50 (3H, s, CMe), 6.53 (3H, s, NMe), 6.38 (3H, s, OMe), 6.23 (3H, s, OMe), 4.47 (1H, d, J 10 Hz, 3′-H), 3.70 (1H, s, 8′-H), 3.49 (1H, d, J 10 Hz, 4′-H), 3.31 (1H, s, 3-H), 2.3–3.0 (4H, complex, Ar H). Found: C, 72.6; H, 6.1. $C_{23}H_{23}NO_4$ requires: C, 73.2; H, 6.1%. *m/e* 377 (22), 364 (4), 363 (45), 362 (100), 361 (3), 346 (2), 332 (2), 319 (2), 304 (2), 288 (2), 276 (5), 181 (28), 152 (3%).

Band 2 (R_f 0.8) yielded a yellow product (23 mg) which was subsequently identified as the 6-(2-N-*methylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**11**; R=R′=Me), m.p. 136–137 (ex aqueous MeOH); λ_{max} (MeOH) 213 (log ε 3.71), 233 (4.62), 270 (4.22), 285sh (4.00), 300sh (3.79), 396 nm (3.96). ν_{max} 3300 (NH) 1640 cm^{-1} (ArCO); τ 8.54 (6H, s, $C(Me)_2$), 7.03 (3H, d, J 5 Hz, N-Me), 6.34 (6H, s, 2xOMe), 4.50 (1H, d, J 10 Hz, 3-H), 3.78 (1H, s, 8-H), 3.51 (1H, d, J 10 Hz, 4-H), 2.5–4.45 (4H, complex, Ar-H), 1.06 (1H, broad q, J 5 Hz, NH). Found: C, 71.2; H, 6.6. $C_{21}H_{23}NO_4$ requires: C, 71.35; H 6.6%. *m/e* 353 (32), 339 (14), 338 (100), 332 (13), 306 (3), 292 (6), 277 (6), 204 (40), 169 (7), 149 (45%).

Alternative hydrolyses were attempted using methanolic aq 2M Na_2CO_3 and with methanolic KOH aq (5%) but with minimal success.

N-*Methylisatoic anhydride* (**26**). N-Methyl anthranilic acid (20 g, prepared most conveniently from anthranilic acid and dimethylsulphate[35]) in water (60 ml) containing K_2CO_3 (9.14 g) was treated with ethyl chloroformate (17.2 g) and the mixture heated on a steam bath for 10 min. The mixture deposited a solid on cooling which on crystallisation from water gave N-carbethoxy-N-methylanthranilic acid (22.7 g), m.p. 115–116 (lit. m.p. 118°). The acid (22.7 g) was heated in an oil bath at 220° for 0.5 h and cooled to give crude **26** which crystallised from EtOH (8.5 g), m.p. 178–179° (lit. m.p. 177°).

Condensation of N-*methylisatoic anhydride* (**26**) *with lithiochromene* (**22**; R=Li): 6-(2-*methylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**11**; R=R′=Me) Compound **22** (R=Li, 0.01 m) was prepared as described earlier and **26** (1.8 g, 0.01 m) dissolved in dry dioxan (60 ml) and powdered NaOH (0.1 g) were added and the mixture refluxed for 2 h (the temp rose gradually to 100° as the diethyl ether was expelled). The mixture was poured into iced 5% NaOH aq and extracted with EtOAc, after drying and evaporation a brown oil remained (2.99 g) which contained three major components (tlc). Separation of this mixture on plc (silica, benzene: EtOAc 10:1) gave:

Band 1 (R_f 0.66) yielded a pale yellow solid (660 mg) which crystallised from aqueous MeOH as the N-*methylaminobenzophenone* (**11**; R=R′=Me), m.p. and m.m.p. 136–137°.

Band 2 (R_f 0.65) yielded a yellow solid (187 mg), the *acridinol* (**29**) crystallised from aqueous MeOH to give m.p. 210–212°; λ_{max} 213 (log ε 4.01), 223 (4.71), 238 (4.72), 269 (4.36), 309 (4.06), 398 nm (3.95); ν_{max} 3305 cm^{-1} (OH); τ 8.65 (3H, s, C-Me), 8.63 (3H, s, CMe), 8.60 (3H, s, CMe), 8.53 (3H, s, C-Me) 7.22 (3H, d, J 5 Hz, N-Me), 6.77 (3H, s, OMe), 6.49 (3H, s, OMe), 6.34 (3H, s, OMe), 4.60 (2H, d, J 10 Hz, 2xCH=C), 4.11 (1H, s, 3′-H), 4.03 (1H, d, J 10 Hz, CH=), 3.56 (1H, s, 4-H), 3.59 (1H, d, J 10 Hz, CH=), 2.4–3.0 and 3.60–3.80 (4H, complex, Ar-H), 1.60 (1H, broad q, OH). Found: C, 73.1; H, 6.5. $C_{33}H_{35}NO_6$ requires: C, 73.2; H, 6.5%. Accurate mass 541.2464. $C_{33}H_{35}NO_6$ 541.2468; *m/e* 541 (25), 529 (3), 528 (32), 527 (100), 511 (3), 510 (8), 480 (2), 392 (2), 256 (9), 134 (6), 132 (5%).

Band 3 (R_f 0.56) yielded a white solid (227 mg) which crystallised from aqueous acetone as 8-(2-N-*methylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**27**) m.p. 172–173°, λ_{max} (MeOH) 214 (log ε 3.66), 236 (4.52), 269 (4.17), 280sh (4.10), 398 nm (3.99); ν_{max} 3315 (NH) 1640 cm^{-1} (ArCO); τ 8.76 (6H, s, C(Me)), 7.03 (3H, s, NMe), 6.39 (3H, s, OMe), 6.14 (3H, s, OMe), 4.59 (1H, d, J 10 Hz, 3-H), 3.95 (1H, s, 6-H), 3.55 (1H, d, J 10 Hz, 4-H), 2.40–3.70 (4H, complex, Ar H), 1.10 (1H, broad s, NH). Found: C, 71.35; C, 6.6. $C_{21}H_{23}NO_4$ requires: C, 71.35; H, 6.6%. *m/e* 353 (35), 339 (9), 338 (56), 321 (14), 222 (16), 205 (16), 169 (7), 134 (71).

Cyclisation of 6-(2-N-*methylaminobenzoyl*)-5,7-*dimethoxy*-2,2-*dimethylchromene* (**11**; R=R′=Me) *to acronycine* (**7**; R=R′=Me) *and isoacronycine* (**20**; R=R′=Me). The N-methylaminobenzophenone (100 mg) was treated in dry DMSO (20 ml with NaH (20 mg, 60%) and the mixture stirred at r.t for 20 h whence the mixture was poured into dil iced HCl and extracted with EtOAc. Isolation of the product and chromatographic separation on plc (silica: benzene: EtOAc 10:4) gave three components:

Band 1 (R_f 0.8) produced starting material (**11**; R=R′=Me, 25 mg) which crystallised from aqueous MeOH, m.p. and m.m.p. 136–137°.

Band 2 (R_f 0.4) produced **20** (R=R′=Me, 33 mg, 38%) which crystallised from aqueous MeOH, m.p. 306–308° dec. its spectral properties were similar to those reported by Oh *et al.*[26]

Band 3 (R_f 0.17) produced (**7** (R=R′=Me, 33 mg, 38%) which crystallised from aqueous MeOH, m.p. and m.m.p. 169–173°.

Acknowledgements -The authors wish to thank the Cancer Research Campaign for a grant which initiated this research.

It is deeply regretted that Dr. Padma Gupta passed away during the preparation of this manuscript. Her contribution to this research was invaluable and this paper is dedicated to her memory.

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