Bridged Xanthenes. I. An Intermolecular Cycloaddition Route

PETER YATES AND D. J. BICHAN

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario M5S 1A1

Received January 22, 1975

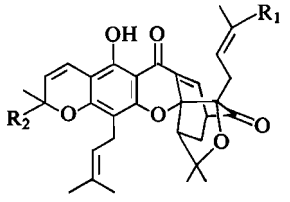
PETER YATES and D. J. BICHAN. Can. J. Chem. **53**, 2045 (1975).

Condensation of *o*-hydroxybenzyl alcohol (**4**) with 1,3-cyclohexanedione (**7**) in hexamethylphosphoramide gives 3,4-dihydro-1(2*H*)-xanthenone (**9**). Treatment of the tosylhydrazone of **9** with methyllithium gives 3,4-dihydroxanthene (**12**), which undergoes Diels–Alder reactions with dimethyl acetylenedicarboxylate and propiolonitrile to give the bridged xanthenes **15** and **17**, respectively. Condensation of *o*-hydroxybenzyl alcohol (**4**) with 4-carboxamido-1,3-cyclohexanedione (**29**) and 4-carbomethoxy-1,3-cyclohexanedione (**38**) gives 2-carboxamido- (**30**) and 2-carbomethoxy-3,4-dihydro-1(2*H*)-xanthenone (**39**), respectively.

PETER YATES et D. J. BICHAN. Can. J. Chem. **53**, 2045 (1975).

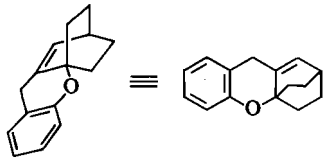
La condensation de l'alcool *o*-hydroxybenzylique (**4**) avec la cyclohexanedione-1,3 (**7**) dans l'hexaméthylphosphoramide conduit à la dihydro-3,4 (2*H*)-xanthènone-1 (**9**). Une réaction entre la tosylhydrazone de **9** et le méthyllithium fournit le dihydro-3,4 xanthène (**12**) qui peut subir des réactions de Diels–Alder avec l'acétylènedicarboxylate de méthyle et le propiolonitrile pour conduire respectivement aux xanthènes pontés **15** et **17**. La condensation de l'alcool *o*-hydroxybenzylique (**4**) avec la carboxamido-4 cyclohexanedione-1,3 (**29**) et la carbométhoxy-4 cyclohexanedione-1,3 (**38**) conduit respectivement aux carboxamido-2 (**30**) et carbométhoxy-2 dihydro-3,4 (2*H*)-xanthènone-1. [Traduit par le journal]

The naturally occurring coloring matters morellin (**1**) (1) and gambogic acid (**2**) (2) and their congeners have a nucleus consisting of the 2,4a-ethano-2,3,4,4a-tetrahydroxanthene system (**3**). In this and the following paper (3) we



1 $R_1 = CHO; R_2 = CH_3$
2 $R_1 = CO_2H; R_2 = CH_2CH_2CH{=}C(CH_3)_2$

discuss two methods that we have developed for the synthesis of this bridged xanthene system.[1] While this work was in progress Quillinan and Scheinmann (5) reported a third route to this system.



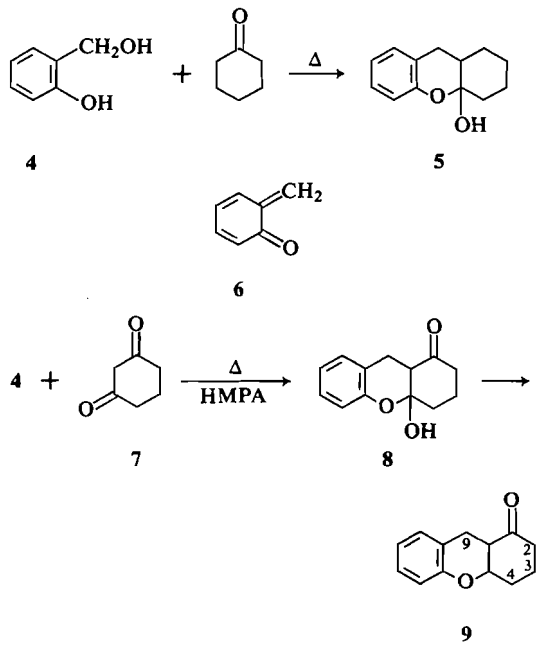
3

[1]For preliminary accounts of this work, see ref. 4.

The approach to be described here is based on the synthesis of the bicyclo[2.2.2]octene system of **3** via a Diels–Alder reaction of the corresponding 1,3-diene with an external dienophile; our other approach (3) involves an intramolecular cycloaddition reaction. The 1,3-dienes required for the intermolecular cycloadditions are 3,4-dihydroxanthenes, a class of compounds that had not been described hitherto. We therefore first addressed ourselves to developing a method for the synthesis of such compounds.

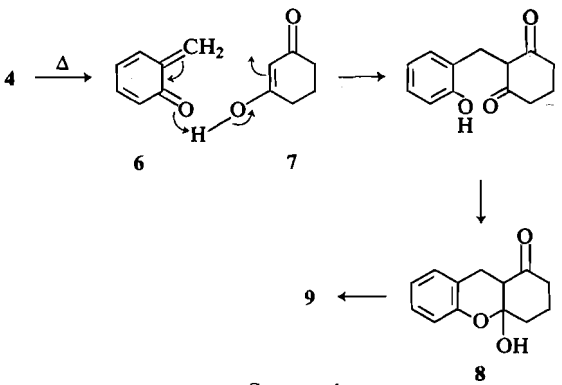
Quagliaro *et al.* (6) have shown that when *o*-hydroxybenzyl alcohol (**4**) and cyclohexanone are heated together to 200° the alcohol **5** is formed; the yield is increased by amine catalysis and *o*-quinonemethide (**6**) is considered to be an intermediate (*cf.* ref. 7). This suggested to us that the reaction of **4** with 1,3-cyclohexanedione (**7**) might provide a ready route to 3,4-dihydro-1(2*H*)-xanthenone (**9**) via dehydration of an intermediate of type **8**, analogous to **5**.

In the event, when **4** was heated with **7** in hexamethylphosphoramide (HMPA) at 195°, a crystalline product was obtained in 43% yield whose elemental composition and spectral characteristics are in accord with its formulation as **9**. Bands at 6.00 (shoulder) and 6.05 μ in its i.r. spectrum and maxima at 221 nm (ε 11 100) and 286 nm (ε 6100) in its u.v. spectrum



4 5 6 7 8 9

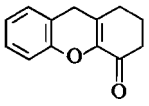
are in good accord with the presence of a β-aryloxy-α,β-enone chromophore. A broad two-proton singlet in its p.m.r. spectrum at δ 3.50 can be assigned to the methylene protons at C.9; multiplets at δ 2.03 (2 H), 2.45 (4 H), and 7.14 (4 H) are attributable to the C.3 protons, the C.2 and C.4 protons, and the aromatic protons, respectively. These data do not rigorously exclude the alternative formulation **10** for this product; however, structure **7** is much more likely on mechanistic grounds (Scheme 1) and was confirmed by subsequent transformations.[2]



6 7 8 9

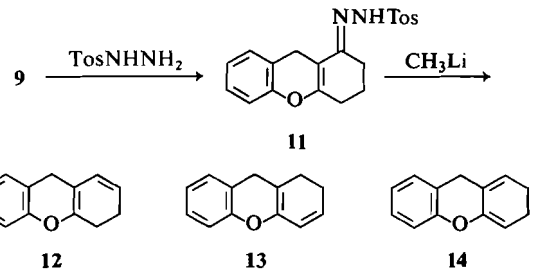
SCHEME 1

[2]For another route to 3,4-dihydro-1(2*H*)-xanthenones, see ref. 8.



10

Compound **9** was converted via its tosylhydrazone **11** to 3,4-dihydroxanthene (**12**) by the method of Dauben *et al.* (9). The diene **12** was obtained in 76% overall yield from **9**; its elemental composition and spectral characteristics are in accord with the structural assignment but do not distinguish it from **13**, the product that would be anticipated from **10**.[3] Bands at 5.92 (m) and 6.03 (w) μ in its i.r. spectrum and maxima in its u.v. spectrum at 290 (ε 6400), 298 (sh, ε 6000), and 314 nm (sh, ε 3700) are in accord with the presence of an aryloxy-1,3-cyclohexadiene chromophore. Two one-proton signals in its p.m.r spectrum at δ 5.56 (m) and 5.68 (d, J = 9 Hz) can be assigned to the vinylic protons at C.2 and C.1, respec-



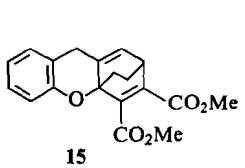
11 12 13 14

tively; a two-proton singlet at δ 3.29 and a four-proton multiplet centered at δ 6.96 are attributable to the C.9 methylene protons and the aromatic protons, respectively; the remaining protons at C.3 and C.4 give rise to a "deceptively simple" doublet at δ 2.29.

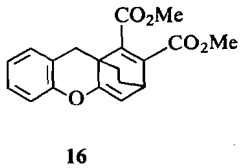
Treatment of **12** with dimethyl acetylenedicarboxylate at room temperature gave a 1:1 adduct in 95% yield. This is assigned the bridged xanthene structure **15**. Its i.r. spectrum shows the presence of two nonequivalent ester groups with carbonyl-stretching bands at 5.70 and 5.78 μ as does its p.m.r. spectrum with two three-proton singlets at δ 3.69 and 3.73. The latter spectrum shows a two-proton broad

[3]Another possible structure, **14**, may be considered to be unlikely, since diene formation from the tosylhydrazones of α,β-enones has previously been observed to occur exclusively via removal of the α′- rather than the δ-hydrogen (9).

singlet at δ 3.48 assigned to the benzylic allylic protons, broadened by slight nonequivalence and by allylic coupling with the olefinic proton. This gives rise to a doublet of triplets at δ 6.11 (1 H), owing to vicinal coupling with the bridgehead proton (J = 6 Hz) in addition to allylic coupling with the two benzylic allylic protons (J = 2 Hz). The doubly allylic bridgehead proton gives a signal at δ 4.17 (1 H), which is a doublet of triplets, attributable to coupling with the vinyl proton (J = 6 Hz) and with each of the methylene protons adjacent to it (J = 3 Hz). Examination of a molecular model indicated that the dihedral angles in this latter situation are each *ca* 60°, in accord with the magnitude of the coupling observed. The u.v. spectrum of the adduct shows absorption comparable with that of chroman (*cf.* ref. 10).



15



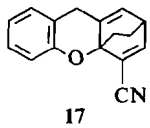
16

The formation of the adduct **15** not only confirms the presence of the 1,3-diene system in **12** but also provides evidence against the alternative diene structure **13**. The adduct of the latter with dimethyl acetylenedicarboxylate would have structure **16**, which is contraindicated by the splitting pattern of the vinylic proton signal in the p.m.r. spectrum of the adduct.[4]

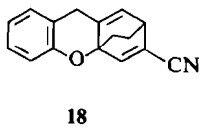
A second bridged xanthene, **17**, was obtained in 93% yield by treating **12** with boiling propiolonitrile (b.p. 42.5°). A choice of structure **17** rather than its regioisomer **18** can be made on the basis of p.m.r. spectroscopy. A one-proton complex multiplet at δ 3.71 is assigned to the bridgehead proton; when double irradiation was carried out at the frequency corresponding to the signal of the adjacent methylene protons, the bridgehead proton signal collapsed to a triplet (J = 6 Hz). This is in accord with equal coupling between the bridgehead proton and the two vicinal vinylic protons of **17**; such equal coupling would not be possible in **18**, where one of the vinyl protons is vicinal and the other allylic with respect to the bridgehead proton.

[4]This spectrum excludes structure **14** for the diene.

In contrast to the case of **15**, the benzylic allylic methylene protons of **17** show a distinct difference in chemical shift, giving rise to a pair of one-proton doublets of doublets at δ 3.40



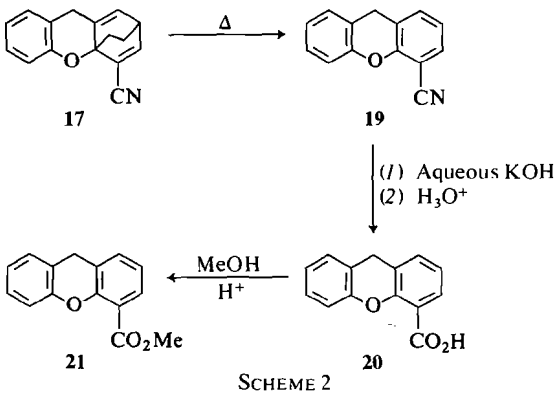
17



18

and 3.51. The coupling constants are 17 and 2 Hz; the former is attributable to geminal coupling between the methylene protons and the latter to coupling of each with the allylic proton. The presence of an α,β-unsaturated nitrile group in **17** was confirmed by a band at 4.54 μ in its i.r. spectrum; its u.v. spectrum resembles that of chroman (10).

Full confirmation of the foregoing assignments was accomplished by a simple degradation of **17**. When **17** was treated at 163° for 5 min, a retro-Diels–Alder reaction occurred with elimination of ethylene to give 4-cyanoxanthene (**19**). The structure of the latter was established by its hydrolysis to 4-xanthenecarboxylic acid (**20**) and the esterification of this to methyl 4-xanthenecarboxylate (**21**) (Scheme 2). The

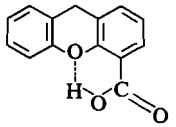


17 19 21 20

SCHEME 2

methylene proton signal in the p.m.r. spectrum of **19** occurs at δ 4.04 (*cf.* xanthene, δ 4.01) but the seven aromatic protons were not differentiable and thus the position of attachment of the nitrile group was not immediately apparent, although its presence was demonstrated by a band at 4.49 μ in the i.r. spectrum of the pyrolysis product. However, the carboxylic acid **20** is a known compound (11) and is reported to have a similar m.p. and u.v. spectrum

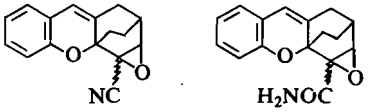
to that of the hydrolysis product obtained here (see Experimental). Furthermore, the carbonyl-stretching band in the i.r. spectrum of this product occurs at 5.76 μ; this is at unusually low wavelength for an aromatic carboxylic acid but is explicable in terms of strong intramolecular hydrogen bonding in the 4-xanthenecarboxylic acid (*cf.* **22**), which disrupts the dimeric structure normally assumed by carboxylic acids in solution. Related phenomena have been thoroughly documented in the i.r. spectra of other *o*-phenoxybenzoic acids (12). Finally, in accord with these structural assignments, the p.m.r. spectrum of the methyl ester **21** shows a one-proton signal at *ca* 0.6 p.p.m. downfield from the signals of the other six aromatic protons; this signal is a doublet of doublets (J = 7 and 2 Hz) and can be assigned to the C.3 proton of **21**.



22

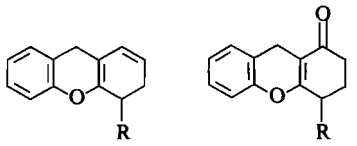
The determination of **19** as the structure of the pyrolysis product from **17** not only establishes the structure of the latter, but also establishes the structure of the diene **12** and, in turn, of the ketone **9**.

Some preliminary experiments were carried out on the further transformation of **17** to a compound with functionality more closely related to **1** and **2**. Epoxidation with *t*-butyl hydroperoxide and potassium *t*-butoxide in dimethyl sulfoxide (*cf.* ref. 13) gave a mixture of products that are considered to be the epimers **23** (see Experimental). These products could not be separated and were not fully characterized; treatment with aqueous alkali gave a mixture considered to consist of the epimeric amides **24**.



23 **24**

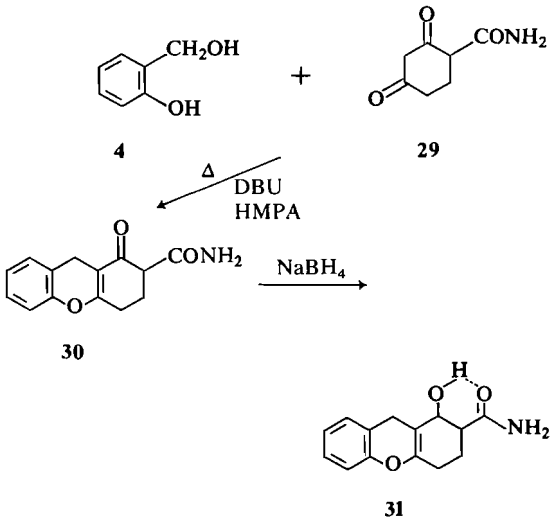
Since any closer approach to **1** and **2** via compounds of type **17** would require the presence of a functional group on the ethano bridge, modifications of the route to **17** were



25 R = $CONH_2$ **27** R = $CONH_2$
26 R = CO_2Me **28** R = CO_2Me

undertaken in attempts to prepare compounds **25** and **26**. This required the preparation of the ketones **27** and **28**. When *o*-hydroxybenzyl alcohol (**4**) and 4-carboxamido-1,3-cyclohexanedione (**29**) (14) were heated at 185° in a mixture of HMPA and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), one major product was formed in 67% yield. The elemental composition and spectra of this product were in accord with its formulation as either **27** or **30**, as was the fact that on treatment with boiling hydrochloric acid it gave compound **9**.

Evidence suggesting that this product is **30** rather than **27** was obtained by its reduction with sodium borohydride, which gave a dihydro compound arising from reduction of the ketonic



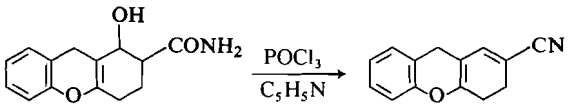
4 **29**

30

31

group. The position of the amide carbonyl-stretching band in the i.r. spectrum of this product at 6.02 μ indicates that the amide carbonyl group is hydrogen bonded with the hydroxyl group as in **31** and that the original product is **30**. This conclusion is buttressed by the observation that bisdehydration of the dihydro compound with phosphorus oxychloride and pyridine gave a product whose spectra

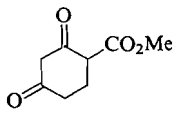
are in accord with its formulation as 2-cyano-3,4-dihydroxanthene (**32**). Thus its i.r. spectrum shows a band at 4.55 μ attributable to an extensively conjugated nitrile group; a high intensity maximum at 336 nm (ε 12 100) also suggests extensive conjugation. Its p.m.r. spectrum shows a single vinyl proton signal at δ 6.53 that appears as a slightly broadened singlet. These data exclude structures **33** and **34** for this product, one or both of which would have been expected to have arisen from the keto amide had it had structure **27**.



31 **32**

33 **34**

Full confirmation of these conclusions was obtained by dehydrogenation of **32** with 5% palladium-on-carbon, which afforded 2-cyanoxanthene (**35**); this in turn was hydrolyzed to the corresponding carboxylic acid **36**, which was esterified to give the methyl ester **37** (Scheme 3). Although **35** and **36** were not fully characterized, it was demonstrated that their i.r. spectra were different from those of the corresponding 4-substituted xanthenes, **19** and **20**, respectively. The ester **37** was fully characterized and shown to be different from methyl 4-xanthenecarboxylate (**21**). Furthermore, as expected in terms of the earlier considerations relating to the 4-substituted xanthene series, the carbonyl-stretching band in the i.r. spectrum of **36** occurs at 5.91 μ and the p.m.r. spectrum of **37** shows the presence of two low field aromatic proton signals. Thus structure **27** can be excluded for the keto amide and structure **30** must be assigned to it.

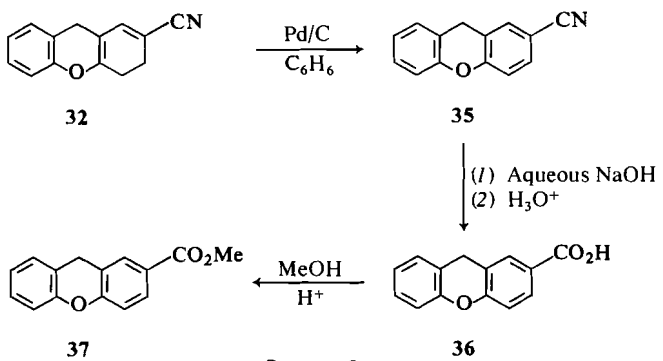


38

Attention was next turned to the case of an ester rather than an amide substituent. When *o*-hydroxybenzyl alcohol (**4**) and 4-carbomethoxy-1,3-cyclohexanedione (**38**) were heated together at 100° without solvent under reduced pressure (15 mm), one major product was formed in 51% yield. The elemental composition and spectra of this product were in accord with its formulation as either the 4-carbomethoxy derivative **28** or the 2-carbomethoxy compound **39**. Reduction, dehydration, and dehydrogenation of this product gave via **40** and **41** a compound that was identical with the ester **37** obtained from **30**; again the undesired regioisomer had been formed and the original keto ester must be **39** (Scheme 4).

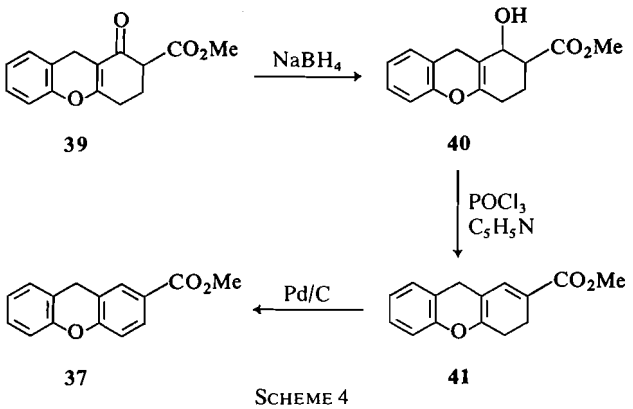
Thus, although the generality of the method for the synthesis of 3,4-dihydro-1(2*H*)-xanthenones has been demonstrated[5] and the conversion of the parent compound to bridged xanthenes has been effected, a close approach to the more ramified systems of compounds **1** and **2** by this route has encountered obstacles.

[5]For other examples, see ref. 4*a*.



32 **35** **37** **36**

SCHEME 3



39 40 41 37

SCHEME 4

Although these may well not be insuperable, the successful outcome of an alternative approach that leads to a bridged xanthene incorporating several of the additional features of **1** and **2** (3) led us to place the present approach in abeyance.

Experimental

Melting points were determined with a Thomas Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded in chloroform solution, ultraviolet spectra in methanol solution, and proton magnetic resonance spectra in deuteriochloroform, unless otherwise indicated. Solutions in organic solvents were dried over anhydrous magnesium sulfate.

3,4-Dihydro-1(2H)-xanthenone (9)

o-Hydroxybenzyl alcohol (**4**) (12.40 g, 100 mmol), 1,3-cyclohexanedione (7) (11.20 g, 100 mmol), and hexamethylphosphoramide (15 ml) were heated together to 195° for 30 min. The cooled solution was taken up in benzene (500 ml) and washed with 5% hydrochloric acid (2 × 400 ml), aqueous 10% sodium hydroxide (3 × 300 ml), and water (400 ml), dried, and evaporated to yield 8.52 g (43%) of **9**, m.p. 79–89°, which after two recrystallizations from methanol had m.p. 90.3–91.3°; $\lambda_{max}(CCl_4)$ 6.00 (sh), 6.05, 7.22 μ; λ_{max}(EtOH) (ε) 221 (11 100), 286 (6100) nm; δ 2.03 (m, 2 H), 2.45 (m, 4 H), 3.50 (br s, 2 H), 7.14 (m, 4 H); *m/e* 200.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.96; H, 6.21.

3,4-Dihydro-1(2H)-xanthenone Tosylhydrazone (11)

3,4-Dihydro-1(2*H*)-xanthenone (**9**) (4.42 g, 22.1 mmol) and *p*-toluenesulfonylhydrazine (4.11 g, 22.1 mmol) were dissolved in 95% ethanol (125 ml) and the solution was stirred for 17 h at room temperature in the presence of 10% hydrochloric acid (10 drops). Filtration yielded 6.59 g (82%) of **11**, m.p. 215–216° (dec.). The filtrate was evaporated to 25 ml and allowed to crystallize to yield a further 670 mg (8%) of **11**, m.p. 212–215° (dec.). Three recrystallizations of the first crop from acetone gave material with m.p. 219–220° (dec.); λ_{max} 3.08 (w), 3.17 (w), 6.00 μ; λ_{max} (ε) 288 (16 400) nm; δ 1.86 (m, 2 H), 2.34 (m, 4 H), 2.40 (s, 3 H), 3.45 (br s, 2 H), 7.18 (m, 6 H), 7.97 (d, J = 8 Hz, 2 H); *m/e* 368.

Anal. Calcd. for $C_{20}H_{20}N_2O_3S$: C, 65.23; H, 5.45; N, 7.61; S, 8.70. Found: C, 65.14; H, 5.46; N, 7.63; S, 8.63.

3,4-Dihydroxanthene (12)

A slurry of 3,4-dihydro-1(2*H*)-xanthenone tosylhydrazone (**11**) (1.73 g, 4.70 mmol) in anhydrous ether (15 ml) was stirred in an ice bath. Ethereal 2.43 *M* methyllithium (10 ml, 24.3 mmol) was added dropwise over 20 min. Stirring was continued for 1 h until gas evolution ceased. The mixture was poured into pentane (200 ml) and water was very carefully added dropwise with stirring until two clear layers separated. The pentane layer was decanted and the aqueous layer was extracted again with pentane (150 ml). The combined extracts were dried and evaporated to yield 800 mg (93%) of **12** as an oil that after sublimation (65°, 0.1 mm) had m.p. 33–35°; $\lambda_{max}(CCl_4)$ 5.92 (m), 6.03 (w) μ; λ_{max} (ε) 290 (6400), 298 (sh, 6000), 314 (sh, 3700) nm; δ 2.29 (d, J = 2 Hz, 4 H), 3.29 (s, 2 H), 5.56 (m, 1 H), 5.68 (d, J = 9 Hz, 1 H), 6.96 (m, 4 H); *m/e* 184.

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.54; H, 6.78.

Reaction of 12 with Dimethyl Acetylenedicarboxylate: Diester 15

3,4-Dihydroxanthene (**12**) (122 mg, 0.66 mmol) and dimethyl acetylenedicarboxylate (94 mg, 0.85 mmol) were mixed and the mixture was allowed to stand at room temperature for 16 h. Deuteriochloroform (0.5 ml) was added and the solution was allowed to stand at room temperature for 33 h. The deuteriochloroform was evaporated and the residue was placed under vacuum (0.03 mm) for 19 h to yield 205 mg (95%) of **15** as a gum that solidified at −20°. Three recrystallizations from methanol gave material with m.p. 92–96°; $\lambda_{max}(CCl_4)$ 5.70, 5.78, 5.97 (w), 6.09 (w) μ; λ_{max} (ε) 269 (2100), 278 (1700), 305 (650) nm; δ 1.70 (m, 4 H), 3.48 (br s, 2 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 4.17 (dt, J = 6, 3 Hz, 1 H), 6.11 (dt, J = 6, 2 Hz, 1 H), 7.04 (m, 4 H); *m/e* 326.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 70.10; H, 5.58.

Reaction of 12 with Propiolonitrile: Nitrile 17

3,4-Dihydroxanthene (**12**) (500 mg, 2.72 mmol) was dissolved in propiolonitrile (1.0 g, 20 mmol) and the solution was boiled under reflux for 10 h. The excess propiolonitrile was distilled and the residue was taken

up in benzene and placed on a column of silica gel (12 g). Elution with benzene yielded 600 mg (93%) of **17** as an oil. Crystallization and recrystallization from methanol yielded material with m.p. 75–78°; $\lambda_{max}(CCl_4)$ 4.54 (m) μ; λ_{max} (ε) 270 (1600), 276 (1400) nm; δ 1.62 (m, 4 H), 3.40 (dd, J = 17, 2 Hz, 1 H), 3.51 (dd, J = 17, 2 Hz, 1 H), 3.71 (m, 1 H), 5.95 (dt, J = 6, 2 Hz, 1 H), 7.14 (m, 5 H); *m/e* 235.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.82; H, 5.54; N, 6.00.

4-Cyanoxanthene (19)

Nitrile **17** (282 mg, 1.20 mmol) was heated to 163° for 5 min while a colorless gas was evolved. The residue solidified on cooling to give 248 mg (100%) of **19**. Two recrystallizations from ethanol–acetone gave material with m.p. 91–93°; $\lambda_{max}(CCl_4)$ 4.49 (w) μ; λ_{max} (ε) 252 (7000), 279 (2100), 307 (4200) nm; δ 4.04 (s, 2 H), 7.29 (m, 7 H); *m/e* 207.

Anal. Calcd. for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.24; H, 4.40; N, 6.76.

Xanthene-4-carboxylic Acid (20)

4-Cyanoxanthene (**19**) (30 mg, 0.15 mmol) and aqueous 10% potassium hydroxide (5 ml) were heated together under reflux for 1 h. The resulting solution was cooled, diluted with water (95 ml), and acidified to p*H* 2 with concentrated hydrochloric acid (~1.5 ml). The resulting precipitate was collected and dried to give 33 mg (100%) of **20**. One recrystallization from boiling benzene–acetone gave material with m.p. 185–186° (dec.); λ_{max} 3.04 (m), 5.76, 5.86 (sh) μ; λ_{max} (ε) 248 (8200), 279 (2400), 303 (2800) nm; *m/e* 226.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.10; H, 4.36.

Methyl Xanthene-4-carboxylate (21)

Xanthene-4-carboxylic acid (**20**) (189 mg, 0.84 mmol) was dissolved in methanol (25 ml). Concentrated sulfuric acid (1 ml) was added with stirring and stirring was continued at room temperature for 21 h; the solution was poured into ether (150 ml). The ethereal solution was washed with water (2 × 100 ml) and saturated aqueous sodium bicarbonate (100 ml), dried, and evaporated to yield 176 mg (87%) of **21**, which was purified by elution with benzene from a column of silica gel (8 g) followed by crystallization from ethanol to give material with m.p. 48–49°; λ_{max} 5.82 μ; λ_{max} (ε) 248 (8200), 278 (2300), 305 (3200) nm; δ 3.94 (s, 3 H), 3.99 (s, 2 H), 7.11 (m, 6 H), 7.72 (dd, J = 7, 2 Hz, 1 H); *m/e* 240.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.71; H, 5.11.

Epoxidation of 17: Cyano Epoxides 23

Nitrile **17** (472 mg, 2.01 mmol) and *t*-butyl hydroperoxide (dried by azeotropic distillation of water with benzene followed by distillation; 181 mg, 2.01 mmol) were dissolved in anhydrous dimethyl sulfoxide (5 ml). Potassium *t*-butoxide (20 mg, 0.18 mmol) was added; the solution was swirled, allowed to stand at room temperature for 5 min, and poured into ether (300 ml). The ethereal solution was washed with water (5 × 50 ml), dried, and evaporated to yield 471 mg (93%) of **23** as a gum. Partial separation of the two diastereomers was achieved by elution from a silica gel column with carbon tetrachloride – 25% methylene chloride. The mixture had $\lambda_{max}(CCl_4)$ 4.45 (w) μ; δ 1.3–2.6 (m, 7 H), 3.88 (d, J = 4 Hz, 1 H), 6.08 (t, J = 1.5 Hz, 1/2 H), 6.25 (t, J = 1.5 Hz, 1/2 H), 6.89 (m, 4 H); *m/e* 251.

Base Hydrolysis of 23: Epoxy Amides 24

Cyano epoxides **23** (91 mg, 0.36 mmol) and sodium hydroxide (92 mg, 2.30 mmol) were dissolved in aqueous 60% methanol (5 ml) and the solution was stirred at room temperature for 19 h and poured into ether (100 ml). The ethereal solution was washed with water (2 × 75 ml), dried, and evaporated to yield 45 mg (46%) of **24** as a gum, λ_{max} 2.94 (m), 3.04 (m), 5.90 μ; δ 3.88 (d, J = 4 Hz).

2-Carboxamido-3,4-dihydro-1(2H)-xanthenone (30)

o-Hydroxybenzyl alcohol (**4**) (1.24 g, 10 mmol), 4-carboxamido-1,3-cyclohexanedione (**29**) (**14**) (1.55 g, 10 mmol), 1,5-diazabicyclo[5.4.0]undec-5-ene (1.5 ml), and hexamethylphosphoramide (3 ml) were heated together in an oil bath at 190° under reflux under a vacuum of 100 mm for 30 min. The mixture was cooled briefly and poured into water (300 ml) with vigorous stirring. The solution was acidified to p*H* 2 with concentrated hydrochloric acid and stirred for 17 h at room temperature. The precipitate was collected and dried to yield 1.62 g (67%) of **30**, which after three recrystallizations from methanol had m.p. 217–218°; λ_{max} 2.96 (m), 3.05 (m), 5.91, 6.12, 7.20 μ; λ_{max} (ε) 221 (12 100), 291 (6800) nm; δ 2.42 (m, 4 H), 3.25 (m, 1 H), 3.52 (br s, 2 H), 5.42 (v br s, 1 H), 7.16 (m, 4 H); *m/e* 243.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.98; H, 5.46; N, 5.72.

Conversion of 30 to 9

2-Carboxamido-3,4-dihydro-1(2*H*)-xanthenone (**30**) (349 mg, 1.44 mmol) and concentrated hydrochloric acid (15 ml) were heated under reflux for 20 h. The mixture was cooled, diluted with water to 200 ml, and extracted with ether (200 ml); the extract was dried and evaporated to yield 139 mg (48%) of a solid, which was recrystallized from methanol and shown (by i.r., m.p., and mixture m.p.) to be identical with **9** prepared from 1,3-cyclohexanedione.

Reduction of 30: Hydroxy Amide 31

A slurry of 2-carboxamido-3,4-dihydro-1(2*H*)-xanthenone (**30**) (538 mg, 2.21 mmol) in 2-propanol (75 ml) was stirred at room temperature. Sodium borohydride (252 mg, 6.63 mmol) was added in three equal portions at t = 0, 45, and 300 min. Ethanol (10 ml) was added after 120 min. After 9 h the solution was poured into water (250 ml) and extracted with chloroform (2 × 250 ml) and ether (2 × 200 ml). The combined extracts were dried and evaporated to yield 511 mg (94%) of **31** which after three recrystallizations from acetone–ethanol had m.p. 188–192°; λ_{max}(KBr) 6.02, 6.08 (m) μ; λ_{max} (ε) 248 (3700), 279 (1900) nm; *m/e* 245.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.52; H, 6.21; N, 5.61.

2-Cyano-3,4-dihydroxanthene (32)

Hydroxy amide **31** (441 mg, 1.80 mmol) was dissolved in anhydrous pyridine (10 ml) and phosphorus oxychloride (225 mg, 1.47 mmol) was added with stirring, which was continued for 4 h at room temperature. The solution was poured into ether (150 ml) and the

ethereal extract was washed with 4% hydrochloric acid (2 × 75 ml) and water (75 ml), dried, and evaporated to yield 210 mg of a gum, which was placed on a silica gel t.l.c. plate (20 × 20 × 0.05 cm) in chloroform. Elution with ether yielded 79 mg (21%) of **32** ($R_f \simeq 0.85$), which after one recrystallization from methanol had m.p. 112–114°; λ_{max} 4.55 (m), 5.97 (m), 6.38 μ; λ_{max} (ε) 232 (4730), 245 (sh, 3500), 279 (sh, 3500), 289 (2700), 336 (12 100) nm; δ 2.52 (br s, 4 H), 3.43 (br s, 2 H), 6.53 (br s, 1 H), 7.02 (m, 4 H); *m/e* 209.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.25; H, 5.30; N, 6.52.

Methyl Xanthene-2-carboxylate (37) (from 32)

2-Cyano-3,4-dihydroxanthene (**32**) (197 mg, 0.94 mmol) was dissolved in benzene (25 ml) and 5% palladium-on-carbon (201 mg) was added. The mixture was stirred and boiled under reflux for 16 h, cooled, filtered, and evaporated to yield 2-cyanoxanthene (**35**) ($\lambda_{max}(CHCl_3)$ 4.48 (w) μ), which was dissolved in methanol (3 ml). Water (2 ml) and sodium hydroxide (185 mg, 4.63 mmol) were added and the solution was boiled under reflux for 21 h, diluted to a volume of 50 ml with water, acidified to p*H* 2 with 4% hydrochloric acid, and extracted with ether (2 × 100 ml). The combined extracts were dried and evaporated to yield xanthene-2-carboxylic acid (**36**) (λ_{max} 3–4 (m), 5.91 μ), which was dissolved in methanol (25 ml). Concentrated sulfuric acid (951 mg) was added and the solution was stirred for 19 h at room temperature, poured into ether (125 ml), and washed with water (2 × 75 ml) and saturated aqueous sodium bicarbonate (75 ml). The organic layer was dried and evaporated to yield 43 mg (19%, from **32**) of **37**, which after crystallization from methanol had m.p. 129–130° and was shown (by i.r. and mixture m.p.) to be identical with **37** prepared from **39**.

4-Carbomethoxy-1,3-cyclohexanedione (38)[6]

Sodium hydroxide (60 g, 1.5 mol) was dissolved in water (600 ml) in a 2-l beaker. The solution was heated to 90° and the heat source was turned off. Nickel–aluminum alloy (1:1, 20 g) was added in small amounts with stirring at a rate sufficient to maintain a temperature of 90–95°. Stirring was continued for a further 30 min at 90° and during subsequent cooling to room temperature. The aqueous layer was decanted and aqueous 10% sodium hydroxide (400 ml) was added; the mixture was stirred for 10 min and the aqueous layer was decanted. This procedure was repeated three times with water. The slurry was transferred to a 500-ml roundbottomed flask (*Caution*: Raney nickel of this activity spontaneously bursts into flame in the presence of oxygen if allowed to become dry), the aqueous layer was decanted, and benzene (250 ml) was added. Azeotropic distillation of the residual water was carried out to completion. Most of the benzene was decanted and dry methanol was added. The mixture was swirled several times, the nickel was allowed to settle, and most of the methanol–benzene solution was decanted. More methanol was used to transfer the nickel to a 500 ml hydrogenation bottle where it was allowed to settle and most of the methanol was decanted. Methyl 2,4-dihydroxybenzoate (32.5 g, 193 mmol) and methanolic sodium methoxide prepared by the reaction of sodium (4.89 g, 213 mmol) with methanol (300 ml) were added to the hydrogenation bottle which was subjected to a pressure of 80 p.s.i. of hydrogen at 55° with shaking for 5 days. The mixture was cooled and filtered and the methanol was evaporated. Water (200 ml) was added followed by concentrated hydrochloric acid to p*H* 8. Saturated aqueous sodium bicarbonate (200 ml) was added and the solution was extracted with ether (400 ml) and chloroform (400 ml). The aqueous layer was acidified with concentrated hydrochloric acid to p*H* 2 and extracted with ether (400 ml) and chloroform (400 ml). The latter extracts were combined, dried, and evaporated to yield 11.5 g (35%) of **38** which after crystallization and recrystallization from boiling benzene had m.p. 81–82°; λ_{max} 2.7–4.3 (m), 5.77, 5.82, 6.21 μ; λ_{max} (ε) 257 (14 500), 286 (sh, 5730) nm; δ 2.55 (m), 3.17 (s), 2.39 (m), 3.74 (s), 3.81 (s), 5.54 (s), 8.47 (br s); *m/e* 170.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 57.00; H, 5.92.

2-Carbomethoxy-3,4-dihydro-1(2H)-xanthenone (39)

o-Hydroxybenzyl alcohol (**4**) (2.17 g, 17.5 mmol) and 4-carbomethoxy-1,3-cyclohexanedione (**38**) (2.94 g, 17.5 mmol) were heated together to 100° at 15 mm for 42 h. The mixture was dissolved in hot methanol (30 ml), cooled, and poured into ether (150 ml). The ethereal solution was washed with aqueous 1% sodium hydroxide (2 × 100 ml), dried, and evaporated to yield 2.30 g (51%) of **39**, which after elution from silica gel (95 g) in benzene – 1% ether and two recrystallizations from methanol had m.p. 126–127.5°; λ_{max} 5.77, 6.00 (sh), 6.10, 7.22 μ; λ_{max} (ε) 222 (13 400), 291 (8200) nm; δ 2.35 (m, 2 H), 2.64 (m, 2 H), 3.48 (m, 1 H), 3.55 (br s, 2 H), 3.79 (s, 3 H), 7.19 (m, 4 H); *m/e* 258.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.72; H, 5.55.

Methyl Xanthene-2-carboxylate (37) (from 39)

4-Carbomethoxy-3,4-dihydro-1(2*H*)-xanthenone (**39**) (463 mg, 1.80 mmol) was dissolved in methanol and cooled to 0° with stirring. Sodium borohydride (284 mg, 7.5 mmol) was added in four equal portions at 30 min intervals. Stirring was continued for 1 h after the last addition and the solution was poured into ether (125 ml). The ethereal solution was washed with water (2 × 75 ml), dried, and evaporated to yield 460 mg of a gum, which was placed on four silica gel t.l.c. plates (20 × 20 × 0.05 cm). Elution with benzene – 50% ether yielded 308 mg (66%) of the hydroxy ester **40** ($R_f \simeq 0.4$); $\lambda_{max}(CHCl_3)$ 2.87–3.20 (m), 5.78, 5.89 (sh) μ.

Hydroxy ester **40** (75 mg, 0.29 mmol) was dissolved in anhydrous pyridine (3 ml) and phosphorus oxychloride (44 mg, 0.29 mmol) was added with swirling. The solution was allowed to stand at room temperature for 19 h under a drying tube and then poured into ether (125 ml). The ethereal solution was washed with 4% hydrochloric acid (75 ml) and water (2 × 75 ml), dried, and evaporated to yield 39 mg (56%) of the diene ester **41**; λ_{max} 5.88, 6.00 (m) μ. This was dissolved in methanol (15 ml) and 5% palladium-on-carbon (103 mg) was added. The mixture was boiled under reflux for 19 h, cooled, filtered, and evaporated to yield 25 mg of a gum, which was placed on a silica gel t.l.c. plate (20 × 5 × 0.05 cm) in

[6]This procedure is a modification of that of Tomino (14).

chloroform. Elution with benzene afforded 10 mg (26%) of **37** ($R_f \simeq 0.4$); λ_{max} 5.82 μ; λ_{max} (ε) 275 (11 800), 300 (sh, 4600) nm; δ 3.98 (s, 3 H), 4.13 (s, 2 H), 7.22 (m, 5 H), 7.98 (m, 2 H); *m/e* 240.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.60; H, 5.03.

We thank the National Research Council of Canada for support of this work.

1. G. KARTHA, G. N. RAMACHANDRAN, H. B. BHAT, P. M. NAIR, V. K. V. RAGHAVAN, and K. VENKATARAMAN. Tetrahedron Lett. 459 (1963); P. M. NAIR and K. VENKATARAMAN. Indian J. Chem. **2**, 402 (1964); H. B. BHAT, P. M. NAIR, and K. VENKATARAMAN. Indian. J. Chem. **2**, 405 (1964); C. G. KARANJGAONKAR, P. M. NAIR, and K. VENKATARAMAN. Tetrahedron Lett. 687 (1966).
2. P. YATES, S. S. KARMARKAR, D. ROSENTHAL, G. H. STOUT, and V. F. STOUT. Tetrahedron Lett. 1623 (1963); W. D. OLLIS, M. V. J. RAMSAY, I. O. SUTHERLAND, and S. MONGKOLSUK. Tetrahedron, **21**, 1453 (1965); S. A. AHMAD, W. RIGBY, and R. B. TAYLOR. J. Chem. Soc. C, 772 (1966); M. AMOROSA and G. GIOVANNINETTI. Ann. Chim. (Rome), **56**, 232 (1966); G. CARDILLO and L. MERLINI. Tetrahedron Lett. 2529 (1967).
3. D. J. BICHAN and P. YATES. Can. J. Chem. This issue.
4. (*a*) P. YATES, D. J. BICHAN, and J. E. MCCLOSKEY. Chem. Commun. 839 (1972); (*b*) D. J. BICHAN and P. YATES. J. Am. Chem. Soc. **94**, 4773 (1972).
5. A. J. QUILLINAN and F. SCHEINMANN. Chem. Commun. 966 (1971).
6. R. QUAGLIARO, M. MOREAU, and J. DREUX. C. R. **257**, 2843 (1963); *cf.* D. MOLHO. Bull. Soc. Chim. Fr. 1417 (1961).
7. W. R. SCHLEIGH. Eastmen Org. Chem. Bull. **43** (1), 1 (1971).
8. L. JURD. J. Org. Chem. **31**, 1639 (1966); T. RIOS. Bol. Inst. Quim. Univ. Nac. Auton. Mexico, **18**, 78 (1966); Chem. Abstr. **67**, 82037 (1967).
9. W. G. DAUBEN, M. E. LORBER, N. D. VIETMEYER, R. H. SHAPIRO, J. H. DUNCAN, and K. TOMER. J. Am. Chem. Soc. **90**, 4762 (1968).
10. G. CHATELUS. Ann. Chim. (Paris) (12), **4**, 541 (1949); BADDELEY and N. H. P. SMITH. J. Chem. Soc. 2516 (1961); J. GRIPENBERG and T. HASE. Acta Chem. Scand. **20**, 1561 (1966).
11. S. AKAGI and T. IWASHIGE. J. Pharm. Soc. Jap. **74**, 608 (1954).
12. M. ŌKI and M. HIROTA. Bull. Chem. Soc. Jap. **37**, 209 (1964).
13. G. B. PAYNE. J. Org. Chem. **26**, 663 (1961).
14. K. TOMINO. Yakugaku Zasshi, **80**, 275 (1960); Chem. Abstr. **54**, 18385 (1960).