Tetrahedron Vol. 39, No. 8, pp. 1265 to 1271, 1983
Printed in Great Britain.

0040-4020/83/081265-07$03.00/0

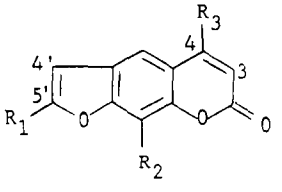
THE DESIGN AND SYNTHESIS OF MONOFUNCTIONAL PSORALENS STRUCTURALLY RELATED TO METHOXSALEN AND TRIOXSALEN

PAT N. CONFALONE† and DIANNE L. CONFALONE
Chemical Research Department, Hoffman-La Roche Inc., Nutley, NJ 07110, U.S.A.

(*Received in U.S.A.* 24 *August* 1982)

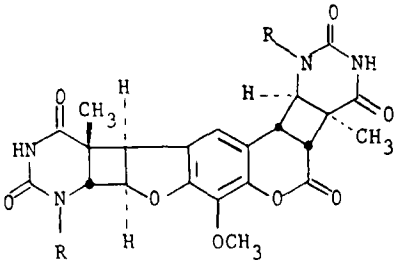
Abstract—The synthesis of novel psoralens structurally related to methoxsalen (**1**) and trioxsalen (**2**) are described. The targeted derivatives were chosen as deactivated substrates which are expected to form only monofunctional photoadducts *in vivo*, avoiding the potentially mutagenic DNA cross-link exemplified in structure **3**. A nine-step preparation of 3, 4-benzomethoxsalen **4** from resorcinol (**5**) is outlined and involves a Claisen rearrangement of the tricyclic O-allyl coumarin **12** followed by an oxidative cleavage to the hydroxydihydrofurocoumarin **14** and dehydration to **4**. The syntheses of trioxsalen analogs from the tricyclic **16** is described and requires preparation of the ketones **19** and **20**, which are ultimately converted to the coumarinyl *O*-acetic acids **23** and **24**. Cyclization of these species provides the C(4′) substituted psoralens **30** and **31**. The final target structure **29** is prepared *via* the dibromide **28** which cyclizes directly to the cyclohexanotrioxsalen **29**.

The biological activities of the linear class of furocoumarins commonly known as the psoralens has been known for more than 3000 years.[1] The Indian sacred book "Atharva Veda[2]" and the old Buddhist Bower manuscript[3] both mention the treatment of leukoderma using material from the plant *Psoralea corylifolia*. Today, 8-methoxypsoralen (methoxsalen) (**1**), a naturally occurring furocoumarin isolated from the extracts of *Ammi majus* Linn, and the trimethyl analog trioxsalen (**2**) are effective photochemotherapeutic agents for the treatment of psoriasis.[4]



1 $R_1 = R_3 = H$ $R_2 = OCH_3$
2 $R_1 = R_2 = R_3 = CH_3$

The mechanism of action of these medicinals involves an initial intercalation into the DNA helix, forming a reversible molecular complex facilitated by the planar nature of the furocoumarin system.[5] Upon irradiation a photoreaction occurs, yielding the covalently bonded structure **3** (shown as the photoadduct of methoxsalen (**1**) with two thymine residues)—a result of [2 + 2] cycloadditions of the thymine olefinic moiety with the Δ^3 and $\Delta^{4'}$ double bonds of the psoralen nucleus. This photobinding, which occurs only with the pyrimidine-type nucleotides, effects cross-linking between opposite strands of DNA when the reaction occurs with bases situated on complementary strands.[6] However, psoralens that react in this so-called *bifunctional* mode have been shown to be mutagenic in procaryotic and eucaryotic systems.[7]

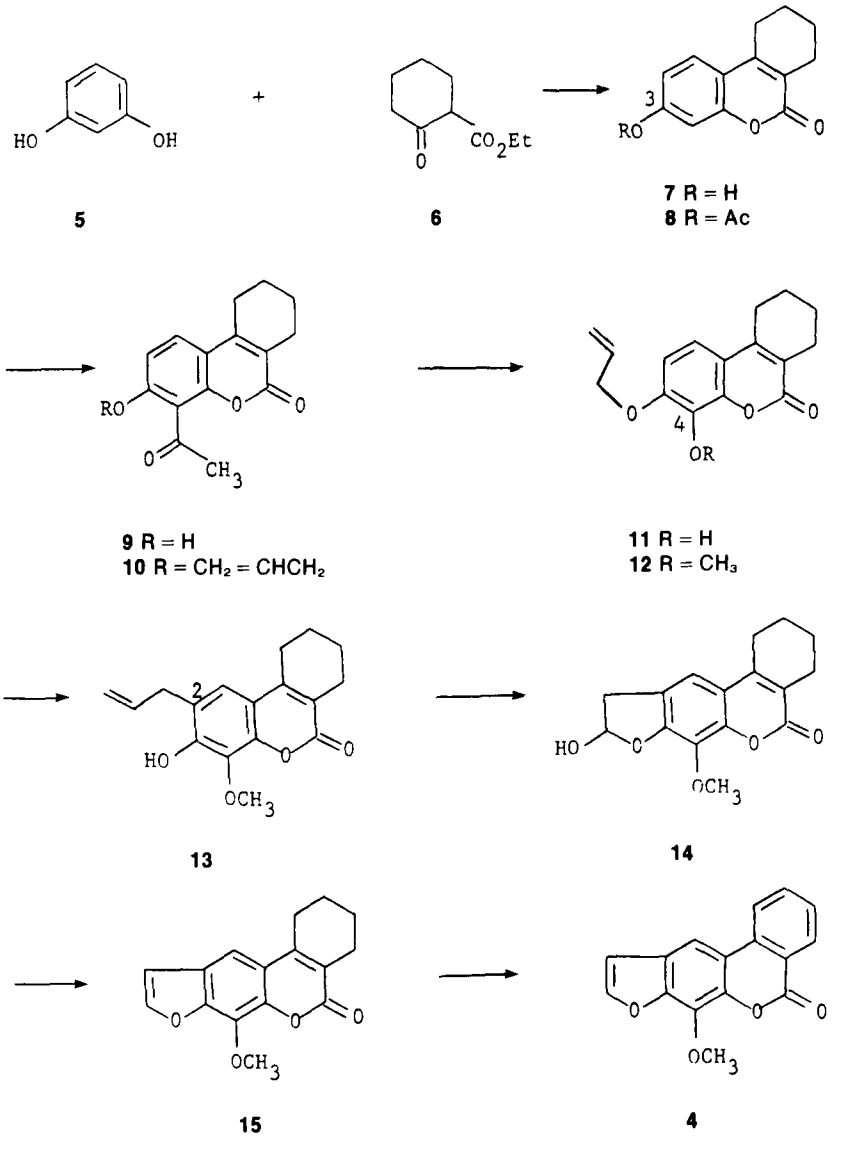


3

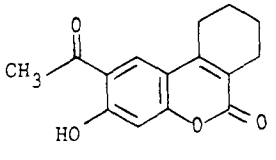
In order to avoid this liability, we decided to deactivate the Δ^3 double bond of methoxsalen (**1**) to an extent that the photoreaction would be precluded.[8] In addition, since intercalation is a requisite first step, the planarity of the system should also be maintained. These considerations suggested 3, 4-benzomethoxsalen (**4**), a furocoumarin that should be capable of reaction in only a *monofunctional* sense, as a target structure meeting these two requirements. The synthesis of this potential monofunctional methoxsalen analog **4** is presented in Scheme 1.

A Peckmann condensation[9] of resorcinol (**5**) with α-carbethoxycyclohexanone (**6**), carried out in conc sulfuric acid at 0°, yielded the tricyclic coumarin **7**.[10] Acetylation of the C(3)–OH with acetic anhydride/pyridine, 1:2, yielded the acetate **8** which underwnt a smooth Fries rearrangement[11] to generate the methyl ketone **9**. Minor amounts of the isomeric product **9a** were readily removed by one recrystallization from ethanol. The selective formation of the desired ketone **9** is in agreement with the enhanced reactivity of the C(8) position vs C(6) in 7-hydroxycoumarin (**9b**) toward Friedel–Crafts reagents.[12]

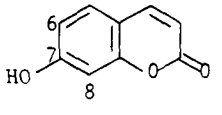
†Present address: E. I. du Pont de Nemours, Inc. Central Research Dept., Wilmington, DE 19898, U.S.A.



Scheme 1.



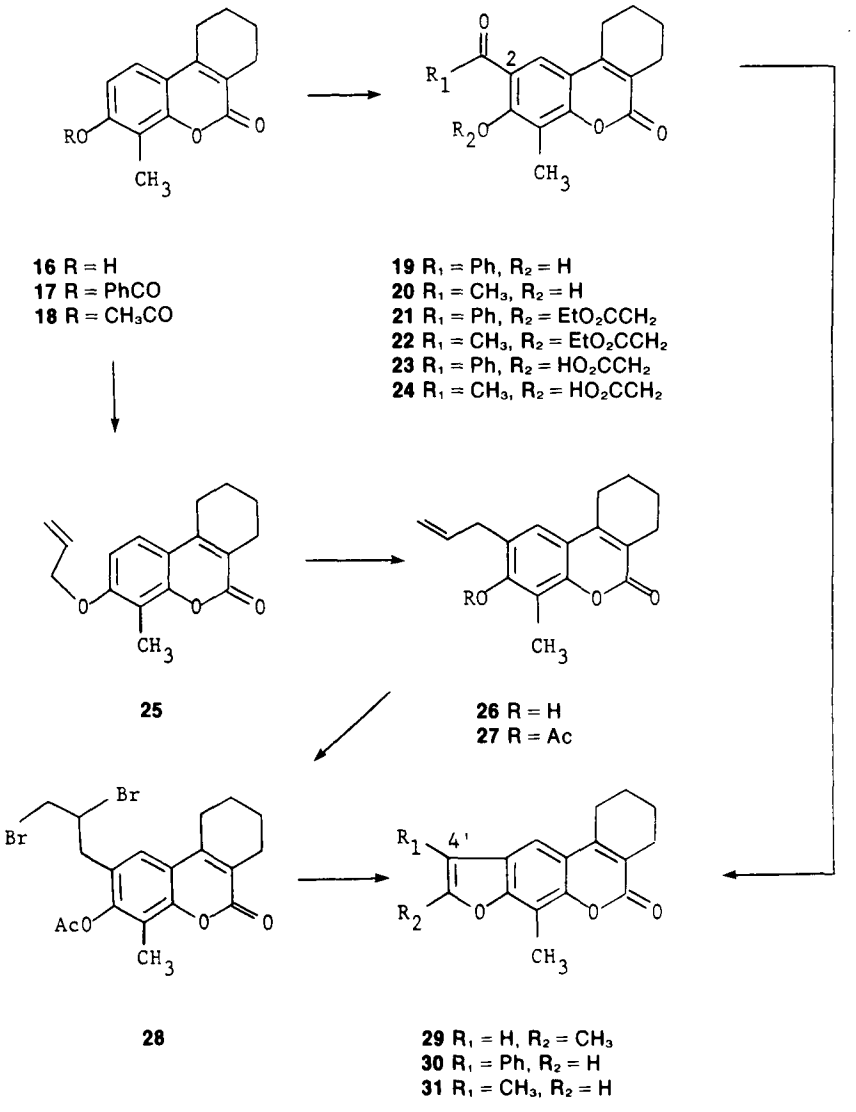
9a



9b

The acetyl function present in **9** is a masked phenolic group at this point, allowing a selective allylation of the free C(3)–OH, affording the O-allyl coumarin **10**. The required C(4)C–O bond was generated next by treatment of **10** with basic hydrogen peroxide.[12] The resulting phenol **11** was methylated with dimethylsulfate/potassium carbonate in refluxing acetone to produce the anisole derivative **12**. Introduction of the C(2)-side chain substituent was carried out by a Claisen rearrangement[13] of **12** in refluxing dimethylaniline, yielding the allyl phenol **13**.[14] Oxidative cleavage of the allyl substituent was achieved with osmium tetroxide (cat)/potassium metaperiodate in a tertiary solvent system of methanol/water/ethyl acetate, 3:2:1, at 25°. This afforded the hydroxylated dihydrofurocoumarin **14**[15] which lost the elements of water upon heating in neat formic acid yielding 3, 4-cyclohexanomethoxsalen (**15**). Finally, dehydrogenation of **15** with Pd/C in diphenyl ether at 260° was employed to complete the synthesis of the target structure—3, 4-benzomethoxsalen (**4**).

Our attention was next directed toward the preparation of potential monofunctional derivatives of trioxsalen (**2**). Fusion of a benzene ring to the methoxsalen molecule in a target such as **4** certainly sequestered the Δ^3 double bond of the psoralen nucleus. However, such a marked perturbation of the UV chromophore might have untoward consequences with respect to the photobiology of the system. Therefore, we decided in this case to employ substituents on the trioxsalen system which would not seriously alter the furocoumarin chromophore but might rather exert their deactivation of the [2 + 2]



Scheme 2.

cycloaddition reactions through steric effects. Notably, annelation of a cyclohexane ring to the Δ^3 double bond of the psoralen nucleus, as was done in the 3,4-benzomethoxsalen precursor **15**, in fact accomplishes this goal. Adaptation of this concept to the trioxsalen system targets the key structure **29**. The synthesis of this substance and two of its derivatives **30** and **31** (substituted alternatively at the 4′ carbon) are depicted in Scheme 2.

The Pechmann reaction product of α-carbethoxycyclohexane and 2-methyl resorcinol,[16] the tricyclic phenol **16**, was acylated with benzoyl chloride or acetic anhydride to yield the corresponding esters **17** and **18**, respectively. A Fries rearrangement[17] afforded the C(2) substituted ketones **19** and **20** which were alkylated with ethyl bromoacetate/potassium carbonate in refluxing acetone to yield the desired ethyl esters **21** and **22**. Saponification afforded the corresponding acids **23** and **24** which underwent a facile benzofuran synthesis, cyclizing to the corresponding target psoralens **30** and **31** in the presence of sodium acetate in refluxing acetic anhydride[18].

Directly allylating the tricyclic **16** yielded the O-allyl derivative **25** which underwent a Claisen rearrangement to afford the allyl coumarin **26**. Bromination of the corresponding acetate **27** yielded crystalline dibromide **28** which cyclized directly to the cyclohexanotrioxsalen derivative **29** upon treatment with ethanolic potassium hydroxide.[19]

In summary, we have prepared several novel derivatives of the photochemotherapeutic agents methoxsalen (**1**) and trioxsalen (**2**) which may offer less mutagenic liabilities owing to the expected deactivating effects of the chosen nuclear substituents upon DNA cross-linking. Further collaborative investigations into the photobiology of the target structures as well as studies related to mutagenicity are currently underway.

EXPERIMENTAL

M.ps were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. IR spectra were obtained by using a Beckmann IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. NMR spectra were

determined with Varian T-60 and HA-100 spectrometers using TMS as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. TLC was carried out by using Merck F-254 silica gel plates.

7,8,9,10-*Tetrahydro*-3-*hydroxyl*-6H-*dibenzo*[b, d]*pyran*-6-*one*(**7**). To a mixture of 110.0 g (1.0 mol) of **5** and 164.4 g (1.17 mols) of **6** at 0° was added 0.5 L of conc H_2SO_4 dropwise over 1 hr with mechanical stirring. The reaction was stirred at 0° for 2.5 hr, diluted rapidly with 3L ice/water and stirred an additional 2 hr. The tricyclic **7** was filtered off and dried to afford 95.0 g (44%) crude product used directly in the next step. For analysis, the compound was recrystallized from abs. EtOH to give a white solid: m.p. 185° dec (lit.[10] m.p. 201–2°); IR (KBr) 3495 (OH), 1683 (CO), 1620 cm^{-1}; UV max (CH_3OH 321 (15,200) nm; NMR (DMSO) δ 7.38 (d, 1H, Ar–H), 6.70 (m, 2H, Ar–H), 2.71 (bm, 2H, CH_2), 2.39 (bm, 2H, CH_2), 1.75 (m, 4H, CH_2CH_2); mass spectrum *m/e* 216 (M^+, base), 201, 188, 160; Anal. ($C_{13}H_{12}O_3$; 216.24) C, H.

3-*Acetoxy*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b, d]*pyran*-6-*one* (**8**). A soln of 267.0 g (1.24 mols) of **7** in 950 mL warm pyridine was treated with 465 mL Ac_2O in one portion. The reaction was allowed to proceed at ambient temp. during which time the product separated. The mixture was concentrated on a rotary evaporator attached to a vacuum pump. The residue was triturated with EtOAc pentane, 1:1, and the product was filtered off, washed well with pentane, and dried to afford 293.6 g (92%) of **8**. For analysis, a sample was recrystallized from abs. EtOH to yield a white solid: m.p. 186–187° (lit.[16] m.p. 186°); IR (KBr) 1768 (Ac), 1718 (CO), 1205 cm^{-1}; UV max (CH_3OH) 272 (10,500), 282 (10,500), 310 (11,300) nm; NMR ($CDCl_3$) δ 7.6–6.9 (m, 3H, Ar–H), 2.8–2.6 (m, 4H, 2 × CH_2), 2.32 (s, 3H, Ac), 1.83 (m, 4H, CH_2CH_2); mass spectrum *m/e* 258 (M^+), 216 (M^+–CH_2CO, base), 201, 188; Anal. ($C_{15}H_{14}O_0$, 258.27) C, H.

4-*Acetyl*-7,8,9,10-*tetrahydro*-3-*hydroxy*-6H-*dibenzo*[b, d]*pyran*-6-*one* (**9**). An intimate mixture of 50.0 g (0.194 mol) of **8** and 125.0 g $AlCl_3$, anhy. was heated at 150° for 1 hr. The reaction evolved copious amounts of HCl. To the hot mixture was added rapidly sufficient ice/water to simultaneously hydrolyze the unreacted $AlCl_3$ and its complexes and cool the accompanying reaction. By this work-up, **9** separated as a fine light yellow powder which was filtered off, washed with water, and dried to afford 49.0 g (98%) of crude **9**. The product was recrystallized from 2L of abs EtOH to yield 40.0 g of pure **9** as a white solid: m.p. 170–171° (lit.[16] m.p. 171°); IR (KBr) 1723 (CO), 1630 (CH_3CO) cm^{-1}; UV max (CH_3CH) 208 (25,800), 271 (10,020), 275 (10,080), 305 (10,000), 336 (7400) nm; NMR ($CDCl_3$) δ 7.60, 6.84 (q, 2H, Ar–H), 2.95 (s, 3H, CH_3), 2.9–2.6 (m, 4H, 2 × CH_2), 1.8 (m, 4H, CH_2CH_2): mass spectrum *m/e* 258 (M^+, base), 243, 230, 216. (M^+–CH_2CO); Anal. ($C_{15}H_{14}O_4$, 258.27) C, H.

4-*Acetyl*-3-(*allyloxy*)-7, 8, 9, 10-*tetrahydro*-6H-*dibenzo*-[b, d]*pyran*-6-*one* (**10**). A soln of 3.53 g (13.68 mmols) of **9** in 75 mL acetone was treated with 1.31 mL (15.05 mmols) allyl bromide and 2.27 g (16.42 mmol) K_2CO_3, anhy. and heated under reflux for 24 hr. The reaction was cooled and the solid was filtered off and washed with acetone. The filtrate plus washings were combined and evaporated to yield 3.99 g (98%) of **10** of sufficient purity for use in the next step. For analysis, a sample was recrystallized from EtOAc to yield a white solid: m.p. 125–126°; IR (KBr) 1709 (broad, CH_3CO, CO), 1600, 1100 cm^{-1}; UV max (CH_3OH) 318 (15,800) nm; NMR ($CDCl_3$) δ 7.46, 6.91 (q, 2H, Ar–H), 5.95, 5.3 (m, 3H, CH–CH_2), 4.64 (m, 2H, CH_2CH–CH_2), 2.73 (m, 2H, CH_2), 2.59 (s, 3H, CH_3), 2.55 (m, 2H, CH_2), 1.81 (m, 4H, CH_2CH_2); mass spectrum m/e 298 (M^+), 280 (M^+-H_2O), 243 (base); Anal. ($C_{18}H_{18}O_4$, 298.34) C,H.

3-(*Allyloxy*)-7, 8, 9, 10-*tetrahydro*-4-*hyroxy*-6H-*dibenzo*-[b, d]*pyran*-6-*one* (**11**). A suspension of 117 g (0.39 mol) of **10** in 495 mL 2N NaOH was heated under reflux for 0.75 hr, cooled to 0° and treated dropwise at that temp with 109 mL 30% H_2O_2. After 2 hr, the reaction was acidified with 3N HCl to pH 1 and 106.1 g (100%) of **11**, was filtered off and air-dried. The material was used directly in the next step. For analysis, a sample was recrystallized from abs EtOH to give a white solid: m.p. 213–214°; (IR (KBr) 3425 (OH), 1690 (CO), 1652 cm^{-1}; UV max (CH_3OH) 260 (12,200), 313 (13,800) nm; NMR (DMSO) δ 9.21 (s, 1H, OH), 6.58, 6.44 (q, 2H, Ar–H), 6.2–5.3 (m, 3H, CH–CH_2), 4.63 (m, 2H, CH_2CH–CH_2), 2.70, 2.39 (m, 4H, 2 × CH_2), 1.72 (m, 4H, CH_2CH_2); mass spectrum *m/e* 272 (M^+), 231 (M^+-allyl, base), 203; Anal. ($C_{16}H_{16}O_4$, 272.30) C, H.

3 - (*Allyloxy*)7,8,9,10 - *tetrahydro* - 4 - *methoxy* - 6H - *dibenzo*[b, d] *pyran*-6-*one* (**12**). A soln of 129.8 g (0.45 mol) of **11** in 1.5L acetone was treated with 56.4 mL (0.60 mol) and 91 g K_2CO_3, anhy. The reaction was heated under reflux for 5 hr cooled, and the solid was filtered off and washed well with acetone. The filtrate and washings were combined, evaporated, and the residue was triturated with abs EtOH to afford 114.8 g (89%) of **12**. Recrystallization from EtOH afforded a first crop of 59.0 g of pure **12** as a white solid: m.p. 103–104°; IR (KBr) 1707 (CO), 1606, 1260, 1145, 1098 cm^{-1}; UV max (CH_3OH), 205 (52,500), 246 (6300), 255 (6400), 315 (15,000) nm; NMR ($CDCl_3$)δ 7.16, 6.80 (q, 2H, Ar–H), 6.2–5.2 (m, 3H, CH–CH_2), 4.67 (m, 2H, CH_2CH–CH_2), 3.97 (s, 3H, OCH_3), 2.8–2.5 (m, 4H, 2 × CH_2), 1.80 (m, 4H, CH_2CH_2); mass spectrum *m/e* 286 (M^+), 245 (M^+–CH_2CH–CH_2, base), 217, 185; Anal. ($C_{17}H_{18}O_4$, 286.33) C, H.

2 - *Allyl* - 3 - *hydroxy* - 4 - *methoxy* - 7,8,9,10 -*tetrahydro* - 6H - *dibenzo*[b, d] - *pyran* - 6 - *one* (**13**). A soln of 52.9 g (0.185 mol) of **12** in 0.5 L N, N-dimethylaniline was heated under reflux for 6 hr and then cooled. The reaction was partitioned between 6N HCl(ice) and CH_2Cl_2. The aqueous phase (pH = 1) was extracted 2 × with CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, and evaporated. The residue was recrystallized from $EtOa_2$ to afford a first crop of 15.2 g of **13**. The mother liquors were chromatographed over 1.5 kg silica gel, eluting with EtOAc/hexane, 2:3. Fractions containing the product were combined and evaporated to yield 20.7 g. The total yield of **13** was 35.9 g (68%) as a white solid, m.p. 183–184° (EtOAc). IR(KBr) 3240 (OH), 1684 (CO), 1643 cm^{-1}; UV max (CH_3OH) 207 (55,800), 325 (15,300) nm; NMR ($CDCl_3$) δ 6.98 (s, 1H, Ar–H), 6.23 (s, 1H, OH), 6.1–4.9 (m, 3H, CH–CH_2), 4.06 (s, 3H, OCH_3), 3.42 (bd, 2H, $ArCH_2$), 2.8–2.5 (bm, 4H, 2 × CH_2), 1.79 (m, 4H, CH_2CH_2); mass spectrum *m/e* 286 (M^+, base), 271, 258, 230; Anal. ($C_{17}H_{18}O_4$, 286.33) C, H.

(±) - 1,2,3,4,9,10 - *Hexahydro* - 9 - *hydroxy* - 7 - *methoxy*-5H-*benzofuro*- [6, 5-c][2]*benzopyran*-5-*one* (**14**). A soln of 15.2 g (53.0 mmol) of 13 in 300 mL of the tertiary solvent system of MeOH/EtOAc/water, 3:2:1 was treated with 60 g potassium *meta*-periodate and 35 mL of an aqueous soln of osmium tetroxide containing 10 mg of O_5O_4/ml. The reaction was stirred vigorously (mechanical stirring) at 25° for 5 hr and was then partitioned between water/CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, and evaporated to yield 15.3 g (100%) of **14**. For analysis, a sample was recrystallized from EtOAc to yield pure **14** as a white solid: m.p. 138–139°; IR (KBr) 3335 (OH), 1693 (CHO), 1662 cm^{-1}; UV max (CH_3OH) 207 (50,800), 256 (5500), 325 (16,000) nm; NMR ($CDCl_3$) δ 9.75 (t, < 1H, CHO tautomer), 7.05 (s, 1H, Ar–H), 6.21 (m, < 1H, CHOH), 4.5 (s, < 1H, OH), 4.07 (s, 3H, CH_3), 3.75 (m, 2H, Ar–CH_2), 2.8–2.5 (m, 4H, 2 × CH_2), 1.80 (m, 4H, CH_2CH_2); mass spectrum *m/e* 288 (M^+), 259 (base), 231; Anal. ($C_{16}H_{16}O_5$, 288.30) C, H.

1,2,3,4 - *Tetrahydro* 7 - *methoxy* - 5H - *benzofuro*[6, 5-c][2]*benzopyran*-5-*one* (15). A soln of 16.7 g (57.93 mmol) of **14** in 225 mL formic acid was heated under reflux for 1 hr, cooled, and evaporated to dryness. The residue was chromatographed over silica, eluting with EtOAc/hexane, 2:3 to afford 8.40 g (54%) of pure **15** as a white solid: m.p.

194–195° (ethyl acetate); IR (KBr) 1706 (CO), 1205, 1123 cm^{-1}; UV max (CH_3OH) 210 (29,500), 248 (24,000), 263 (16,600), 299 (11,300) nm; NMR ($CDCl_3$) 7.63, 6.78 (q, 2H, HC–CH), 7.39 (s, 1H, Ar–H), 4.29 (s, 3H, OCH_3), 2.9–2.6 (m, 4H, 2 × CH_2), 2.0–1.8 (m, 4H, CH_2CH_2); mass spectrum *m/e* 270 (M^+–CH_3), 242, 227, 214; Anal. ($C_{16}H_{14}O_4$, 270.28) C, H.

7-Methoxy-5H-benzofuro[6, 5-c][2]*benzopyran-5-one* (**4**). A soln of 5.0 g (18.5 mmols) of **15** in 100mL diphenyl ether was treated with 2.0 g 10% Pd/C and heated under reflux for 5 hr. The reaction was cooled, filtered through Celite to remove the catalyst, diluted with 2L pet. ether (b.p. 38–57°) and allowed to stir overnight at room temp. The product was filtered off, washed with EtOH and dried to afford 2.80 g (57%) of crude **4**. Further purification was effected by recrystallization from abs. EtOH to give pure **4** as a white solid: m.p. 185–186°; IR (KBr) 1718 (CO), 1262, 1110 cm^{-1}; UV max (CH_3OH + DMSO, 99:1) 323 (7700) nm; NMR ($CDCl_3$ + DMSO) δ 8.35 (dd, 1H, C(4)–H), 8.12 (dd, 1H, C(1)–H), 7.91 (s, 1H, (C(11)–H), 7.81 (ddd, 1H, C(2)–H), 7.68 6.85 (q, 2H, C(9)–H and C(10)–H), 7.54 (ddd, 1H, C(3)–H), 4.29 (s, 3H, OCH_3); mass spectrum *m/e* 266 (M^+, base), 251 (M^+–CH_3), 223, 195, 167, 139; Anal. ($C_{16}H_{10}O_4$, 266.25) C, H.

3-Hydroxy-4-methyl-7,8,9,10-tetrahydro-6H-dibenzo[b, d]*pyran-6-one* (**16**). A suspension of 32.09 g (0.259 mol) 2-methyl resorcinol in 42.5 mL α-carbethoxycyclohexanone was treated dropwise at 0° with 200 mL conc H_2SO_4 (mechanical stirring) over 15 min. The reaction proceeded at 0° for 2.5 hr and was then diluted with 1.5 L ice water and stirred vigorously for 1 hr. The product was filtered off, triturated with EtOH and yielded 59.0 g (99%) of **16**. For analysis, a sample was recrystallized from abs EtOH to afford pure **16** as a white solid: m.p. 268–269° (lit. m.p. 268°); IR (KBr) 3270 (OH), 1675 (CO), 1100 cm^{-1}; UV max (CH_3OH) 247 (5100), 256 (5000), 321 (15,700) nm;NMR (DMSO) δ 7.23, 6.75 (q, 2H, Ar–H), 2.8–2.4 (m, 4H, 2 × CH_2), 2.16 (s, 3H, CH_3), 1.8–1.6 (m, 4H, CH_2CH_2); mass spectrum *m/e* 230 (M^+, base), 215 (M^+–CH_3), 202, 174; Anal. ($C_{14}H_{14}O_3$, 230.26) C, H.

3-(Benzoyloxy)-4-methyl-7,8,9,10-tetrahydro-6H-dibenzo[b, d]*pyran-6-one* (**17**). A soln of 46.0 g (0.02 mol) of **16** in 300 mL pyridine was heated to 90°, treated with 28.0 mL (0.02 mol) benzoyl chloride, and allowed to cool to room temp. The product separated upon the addition of 2L ice water and was filtered off, washed well with dil HCl and air-dried Recrystallization from EtOAc yielded 50.6 g (76%) pure 17 as a white solid: m.p. 217–218°; IR (KBr) 1736 (PhCO), 1712 (CO), 1275, 1125 cm^{-1}; UV max (CH_3OH) 229 (24,100), 280 (15,600 nm; NMR ($CDCl_3$) δ 8.2–7.0 (m, 7H, Ph + Ar–H), 2.8–2.5 (m, 4H, 2 × CH_2), 2.33 (s, 3H, CH_3), 2.0–1.8 (m, 4H, CH_2CH_2); mass spectrum *m/e* 334 (M^+), 229, (M^+–PhCO), 105 ($PhCO^+$, base), 77; Anal. ($C_{21}H_{18}O_4$, 334.37) C, H.

3-Acetoxy-4-methyl-7,8,9,10-tetrahydro-6H-dibenzo[b, d]*pyran-6-one* (**18**). A soln of 36.48 g (0.159 mol) of **16** in 100 mL pyridine was treated at 90° with 50 mL Ac_2O and set aside to cool. After 3 hr at 25°, the product was filtered off, washed with ether, and recrystallized from EtOAc to yield 28.61 g (66%) pure **18** as a white solid: m.p. 162–163°; IR (KBr) 1765 (Ac), 1716(CO), 1210, 1090 cm^{-1}; UV max (CH_3OH) 277 (11,700), 309 (9200) nm; NMR ($CDCl_3$) δ 7.36, 6.93 (q, 2H, Ar–H), 2.8–2.5 (m, 4H, 2 × CH_2), 2.35 (s, 3H, Ac), 2.27 (s, 3H, Ar–CH_2), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 272 (M^+), 244, 230 (M^+–CH_2CO, base), 215, 202, 174; Anal. ($C_{16}H_{16}O_4$, 272.30) C, H.

2-Benzoyl-3-hydroxy-4-methyl-7, 8, 9, 10-*tetrahydro*-6H-*dibenzo*[b, d]-*pyran*-6-*one* (**19**). An intimate mixture of 50.60 g (0.152 mol)of **17** and 150 g $AlCl_3$, anhy was heated at 150° for 1.5 hr. The reaction was quenched with 2L ice/water and cooled to room temp. The crude product was filtered off, washed with water and air-dried. The material was purified by recrystallization from abs EtOH to yield 37.82 g (75%) pure **19** as a light yellow solid: m.p. 211–212°; IR (KBr) 1720 (CO), 1622 (PhCO), 1120 cm^{-1}; UV max (CH_3OH) 274 (30,400), 351 (8100) nm; NMR)$CDCl_3$) δ 12.45 (s, 1H, OH), 7.7–7.4 (m, 6H, Ph + Ar–H), 2.6–2.5 (m, 4H, 2 × CH_2), 2.30 (s, 1H, CH_3), 1.9–1.6 (m, 4H, CH_2CH_2); mass spectrum *m/e* 334 (M^+, base), 319, 305, 105, ($PhCO^+$), 77; Anal. ($C_{21}H_{18}O_4$, 334.37) C, H.

2-Acetyl-3-hydroxy-4-methyl-7,8,9,10-tetrahydro-6H-dibenzo-[b, d]*pyran-6-one* (**20**). An intimate mixture of 28.60 g (0.105 mol) of **18** and 75 g $AlCl_3$, anhy was heated at 150° for 1.5 hr. The reaction was quenched with 1L ice/water and allowed to cool to room temp. The product was filtered off, washed well with water, and air-dried to yield 27.8 g (97%) of **20**. For analysis, a sample was recrystallized from abs EtOH to yield pure **20** as a white solid: m.p. 235–236°; IR (KBr) 1725 (CO), 1639 (Ac), 1400, 1115 cm^{-1}; UV max (CH_3OH) 212 (16,750) 261 (28,700), 244 (8600) nm; NMR ($CDCl_3$) δ 12.5 (s, 1H, OH), 7.70 (s, 1H, Ar–H), 2.8–2.6 (m, 2H, CH_2), 2.8 (s, 3H, CH, CO), 2.6–2.5 (m, 2H, CH_2), 2.58 (s, 3H, Ar–CH_3), 2.0–1.6 (m, 4H, CH_2CH_2); mass spectrum *m/e* 272 (M^+, base), 257 (M^+–CH_3), 244, 229 (M^+–Ac); Anal. ($C_{16}H_{16}O_4$, 272.30) C, H.

[(2-*Benzoyl*-7,8,9,10-*tetrahydro*-4-*methyl*-6-*oxo*-6H-*dibenzo*[b, d]-*pyran*-3-*yl*)*oxy*]*acetic acid ethyl ester* (**21**). A soln of 37.35 (0.112 mol) of **19** in 550 mL acetone was treated with 13.60 mL (0.123 mol) ethyl bromacetate and 17.54 g K_2CO_3, anhy. The mixture was heated under reflux for 4 hr, cooled to 25°, and filtered. The solid was washed well with warm acetone. The combined filtrate and washings were evaporated to afford 45.97 g (98%) of **21** of sufficient purity for use in the next step. For analysis, a sample was recrystallized from CH_2Cl_2/abs EtOH to yield pure **21** as a white solid: m.p. 144–145°: IR (KBr) 1753 (ester), 1713 (CO), 1673 (PhCO), 1210, 1100 cm^{-1}; UV max (CH_3OH) 265 (26,700) nm; NMR ($CDCl_3$) δ 7.8–7.4 (m, 5H, Ph), 7.40 (s, 1H, C(1)–H), 4.41 (s, 2H, OCH_2CO), 4.14 (q, 2H, OCH_2CH_3), 2.8–2.5 (m, 4H, 2 × CH_2), 2.45 (s, 3H, Ar–Ch_3), 1.9–1.6 (m, 4H, CH_2CH_2), 1.18 (t, 3H, CH_3CH_2); mass spectrum *m/e* 420 (M^+), 402 (M^+–H_2O), 391 (M^+–Et), 374 (M^+–EtO), 347 (M^+–EtOCO), 105 ($PhCO^+$); Anal. ($C_{25}H_{24}O_6$, 420.46) C, H.

[(2-*Acetyl*-7,8,9,10-*tetrahydro*-4-*methyl*-6-*oxo*-6H-*dibenzo*[b, d]-*pyran*-3-*yl*)*oxy*]*acetic acid ethyl ester* (**22**). A soln of 27.8 g (0.102 mol) of **20** in 0.5L acetone was treated with 12.4 mL (0.112 mol) ethyl bromoacetate and 16.0 g K_2CO_3, anhy. The mixture was heated under reflux for 5 hr and filtered while hot. The filtrate was cooled and evaporated to give 34.3 g (94%) crude **22**. Recrystallization from EtOAc afforded 25.53 g (70%) pure **22** as a white solid: m.p. 132–133; IR (KBr) 1758 (ester), 1724 (CO), 1678 (Ac), 1200 cm^{-1}; UV max (CH_3OH) 254 (25,800), 281 (11,400), 314 (8300) nm; NMR $CDCl_3$) δ 7.73 (s, 1H, Ar–H), 4.51 (s, 2H, OCH_2CO), 4.26 (q, 2H, CH_2CH_3), 2.9–2.8 (m, 2H, CH_2), 2.69 (s, 3H, Ac), 2.6–2.5 (m, 2H, CH_2), 2.44 (s, 3H, Ar–CH_3), 1.9–1.6 (m, 4H, CH_2CH_2), 1.30 (t, 3H, CH_3CH_2); mass spectrum *m/e* 358 (M^+), 243 (M^+–CH_3), 285 (M^+–CO_2Et), 269, 43 (CH_3CO^+, base); Anal. ($C_{20}H_{22}O_6$, 358.39) C, H.

[(2-*Benzoyl*-7,8,9,10-*tetrahydro*-4-*methyl*-6-*oxo*-6H-*dibenzo*[b, d]-pyran-3-yl)oxylacetic acid (**23**). A suspension of 40.82 g (97.2 mmol) of **21** in 300 mL N NaOH was heated at 75° for 20 hr cooled, and acidified with 6N HCl to pH 1. The mixture was extracted 3 × with CH_2Cl_2. The organic extracts were pooled, dried over Na_2SO_4, and evaporated to afford 35.30 g (93%) pure **23**. For analysis, a sample was recrystallized from EtOAc/pentane to give a white solid: m.p. 177–178°; IR (KBr) 3220–3060 (CO_2H), 1765 (CO_2H), 1715 (CO), 1665 (PhCO), 1600, 1125 cm^{-1}; UV max (CH_3OH) 265 (23,800) nm; NMR ($CDCL_3$) δ (10.58) bs, 1H, CO_2H), 7.8–7.3 (m, 5H, Ph), 7.44 (s, 1H, C(1)–H), 4.48 (s, 2H, OCH_3), 2.7–2.5 (m, 4H, 2 × CH_2), 2.39 (s, 3H, CH_3), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum 392 (M^+), 374 (M^+–H_2O), 331, 105 ($PhCO^+$, base), 77; Anal. ($C_{23}H_{20}O_6$, 392.41) C, H.

[(2-*Acetyl*-7,8,9,10-*tetrahydro*-4-*methyl*-6-*oxo*-6H-*dibenzo*[b, d]-*pyran*-3-*yl*)*oxy*]*acetic acid* (**24**). A suspension of 21.95 g (61.31 mmol) of **22** in 0.5L N NaOH was heated at 75° for 5 hr, cooled, and acidified with 6N HCl to pH 1. The mixture was extracted 3 × with CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, and evaporated to yield 17.8 g (88%) of **24**. Recrystallization from abs EtOH afforded 12.6 g (62%) pure **24** as a white solid: m.p. 179–180°; IR (KBr) 3240 (OH), 1760 (CO_2H), 1680 (Ac), 1600 cm^{-1}; UV max (CH_3OH) 255 (25,950), 314 (8400) nm; NMR ($CDCl_3$ + DMSO) δ 11–9.5 (bs, 1H, CO_2H), 7.74 (s, 1H, Ar–H), 4.47 (s, 2H, OCH_2), 2.9–2.8 (m, 2H, CH_2), 2.68 (s, 3H, Ac), 2.6–2.4 (m, 2H, CH_2), 2.42 (s, 3H, Ar–CH_3), 2.0–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 330 (M^+, base), 315 (M^+–CH_3), 269, 257, 43 (CH_3CO^+); Anal. ($C_{18}H_{18}O_6$, 330.34) C, H.

1,2,3,4-*Tetrahydro*-7-*methyl*-10-*phenyl*-5H-*benzofuro*[6, 5-c][2]*benzopyran*-5-*one* (**30**).A soln of 21.12 g (53.9 mmol) of 23 in 200 mL Ac_2O was treated with 40 g NaOAc, anhy, and heated under reflux for 3 hr and cooled. The volatiles were removed at the pump and the residue was triturated with ether. The insoluble product was partitioned between water and CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to give 17.0 g (96%) of **30**. For analysis, a sample was recrystallized from CH_2Cl_2/EtOH to yield a pale yellow solid: m.p. 228–229°; IR (KBr) 1710 (CO), 1600, 1120 cm^{-1}; UV max (CH_3OH) 247 (28,000), 300 (15,900) nm; NMR (DMSO) δ 8.36 s, 1H, PhC–CH), 7.88 (bs, 1H, Ar–H), 7.8–7.4 (m, 5H, Ph), 3.0–2.8 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 2.6–2.4 (m, 2H, CH_2), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 330 (M^+, base), 315 (M^+–CH_3), 302, 264; Anal. ($C_{22}H_{18}O_3$, 330.38) C, H.

1,2,3,4 - *Tetrahydro* - 7,10 - *dimethyl* - 5H - *benzofuro*[6, 5-c][2] *benzopyran*-5-*one* (**31**). A soln of 1.8 g (5.45 mmol) of **24** in 25 mL Ac_2O was treated with 3.6 g NaOAc, anhy, heated under reflux for 2 hr, and then cooled to room temp. The volatiles were removed at the pump and the residue was partitioned between water and CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to give 0.86 g (56%) of **31**. For analysis, a sample was recrystallized from abs EtOH to yield pure **31** as a white solid: m.p. 204–205°; IR (KBr) 1707 (CO), 1118 cm^{-1}; UV max (CH_3OH) 211 (31,500), 249 (25,050), 263 (12,580), 301 (12,480) nm; NMR ($CDCl_3$) δ 7.43 (s, 2H, Ar–H) and CH_3C–CHO), 2.9–2.8 (m, 2H, CH_2), 2.7–2.6 (m, 2H, CH_2), 2.54 (s, 3H, Ar–CH_3), 2.24 (d, 3H, CH_3CH–CHO), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 268 (M^+ base), 253 (M^+–CH_3) 239, 225, 212; Anal. ($C_{17}H_{16}O_3$, 268.31) C, H.

3-(*Allyloxy*)-4-*methyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*-[b, d]-*pyran*-6-*one* (**25**). A soln of 27.0 g (0.117 mol) of **16**[16] in 0.5L acetone was treated with 11.25 mL (0.129 mmol) allyl bromide and 19.48 g (0.141 mol) K_2CO_3, anhy. The mixture was heated under reflux for 28 hr and then filtered while hot to remove inorganics. The filtrate was evaporated and the residue was triturated with cold EtOAc to afford 30.89 g (98%) of **25**. Recrystallization from EtOAc yielded 18.78 g pure **25** as a white solid: m.p. 144–145°; IR (KBr) 1710 (CO), 1610, 1115 cm^{-1}; UV max (CH_3OH) 204 (59,300), 244 (5900), 256 (5350), 320 (16,250); NMR ($CDCl_3$) δ 7.32, 6.79 (q, 2H, Ar–H), 6.09 (m, 1H, CH–CH_2), 5.45, 5.30 (m, 2H, CH–CH_2), 4.60 (m, 2H, CH_2CH–CH_2) 2.9–2.6 (m, 4H, 2 × CH_2), 2.33 (s, 3H, CH_3), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 270 (M^+), 229 (M^+–C_3H_5, base), 201, 187, 135; Anal. ($C_{17}H_{18}O_3$, 270.33) C, H.

2-*Allyl*-3-*hydroxy*-4-*methyl*-7,8,9,10-*tetrahydro*-6H-*dibenzo*[b, d]-*pyran*-6-*one* (**26**). A soln of 18.21 g (67.44 mmol) of **25** in 100 mL N, N-dimethylaniline was heated under reflux for 20 hr. The reaction was cooled and poured into a separatory funnel containing ice and an excess 6N HCl. The product was extracted 3 × with CH_2Cl_2. The organic extracts were pooled, dried over Na_2SO_4, and evaporated to yield 11.71 g (64%) pure **26**, m.p. 162–163°, after recrystallization from EtOAc. IR (KBr) 3280 (OH), 1676 (CO), 1605, 1110 cm^{-1}; UV max (CH_3OH), 207 (44,800), 255 (3900), 327 (15,100) nm; NMR ($CDCl_3$) δ 7.13 (s, 1H, Ar–H), 5.99 (m, 1H, CH–CH_2), 5.78 (s, 1H, OH), 5.16 (m, 2H, CH–CH_2), 3.48 (m, 2H, Ar–CH_2), 2.9–2.6 (m, 4H, 2 × CH_2), 2.33 (s, 3H, CH_3), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 270 (M^+, base), 255 (M^+–CH_3), 242, 214; Anal. ($C_{17}H_{18}O_3$, 270.33) C, H.

3-*Acetoxy*-2-*allyl*-7,8,9,10-*tetrahydro*-4-*methyl*-6H-*dibenzo*[b, d]-*pyran*-6-*one* (**27**). A soln of 4.56 g (16.89 mmols) of **26** in 12 mL pyridine was treated at 90° in one portion with 6 mL Ac_2O and allowed to stand at 25° for 0.5 hr. The volatiles were removed at the pump and the residue was triturated with EtOAc/hexane, 3:7, to yield 5.2 g (99%) of **27**. For analysis, a sample was recrystallized from EtOAc to give pure **27** as a white solid: m.p. 125–126°; IR (KBr) 1760 (OAc), 1710 (CO), 1636, 1230, 1140 cm^{-1}; UV max (CH_3OH) 206 (41,700), 278 (11,600), 315 (8300) nm; NMR ($CDCl_3$) δ 7.26 (s, 1H, Ar–H), 5.90 (m, 1H, CH–CH_2), 5.21, 5.11 (m, 2H, CH–CH_2), 3.29 (bs, 2H, Ar–CH_2), 2.8–2.5 (m, 4H, 2 × CH_2), 2.34 (s, 3H, Ac), 3.24 (s, 3H, Ar–CH_3), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 312 (M^+), 270 (M^+–CH_2CO, base), 255, 242, 214; Anal. ($C_{19}H_{20}O_4$, 312.36), C, H.

3-(*Acetyloxy*)-2-(2,3-*dibromopropyl*)-7,8,9,10-*tetrahydro*-4-*methyl*-6H-*dibenzo*[b, d]*pyran*-6-*one* (**28**). A soln of 4.59 g (14.7) mmols) of **27** in 75 mL dry Ca_2Cl_2 was treated dropwise at 25° over 5 min with a soln of 0.764 mL Br in 146 mL of the same solvent. After 2 hr the reaction was evaporated and recrystallized from EtOAc/pentane to yield 4.70 g (68%) pure **28** as a white solid: m.p. 152–153°; IR (KBr) 1755 (OAc), 1713 (CO), 1235, 1140 cm^{-1}; UV max (CH_3OH), 205 (42,500), 276 (12,000), 313 (8200) nm; NMR ($CDCl_3$) δ 7.41 (s, 1H, Ar–H), 4.5–4.2 (m, 1H, CHBr), 3.91, 3.65 (m, 2H, CH_2Br), 3.64, 2.81 (m, 2H, Ar–CH_2), 2.8–2.5 (m, 4H, 2 × CH_2), 2.42 (s, 3H, OAc), 2.25 (s, 3H, Ar–CH_3), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 470 (M^+), 428 (M^+–Ac, base), 349, 270, 243, 215; Anal. ($C_{19}H_{20}Br_2O_4$, 472.17) C, H, Br.

1, 2, 3, 4-*Tetrahydro*-7, 9-*dimethyl*-5H-*benzofuro*[6, 5-c][2] *benzopyran*-5-*one* (**29**). A soln of 6.81 g (14.42 mmols) in 360 mL abs EtOH was treated with 7.2 g KOH and heated at 55° for 5 hr. The reaction was cooled and evaporated. The residue was triturated with abs EtOH and the remaining solid was filtered off and washed well with water. Recrystallization from EtOAc afforded 2.4 g (62%) pure **29** as a white solid: m.p. 174–175°; IR (KBr) 1708 (CO), 1633, 1120 cm^{-1}; UV max (CH_3OH) 209 (27,500), 249 (27,820), 297 (10,480), 328 (7800) nm; NMR ($CDCl_3$) δ 7.37 (s, 1H, C(11)–H), 6.32 (q, 1H, C(10–H), 2.9–2.5 (m, 4H, 2 × CH_2), 2.55 (s, 3H, Ar–CH_3), 2.48 (s, 3H, C(9)–CH_3), 1.9–1.7 (m, 4H, CH_2CH_2); mass spectrum *m/e* 268 (m^+, base), 253 (M^+–CH_3), 240, 225, 221, 212; Anal. ($C_{17}H_{16}O_3$, 268.31) C, H.

Acknowledgements—We wish to thank the following individuals and their staff for the determination of analytical and spectra data: Mr. S. Traiman (IR), Dr. V. Toome (UV), Dr. T. Williams (NMR), Dr. W. Benz (Mass spec), and Dr. F. Scheidl (Microchemistry).

REFERENCES AND NOTES

[1]T. B. Fitzpatrick and M. A. Pathak, *J. Invest. Dermatol.* **32**, 225–238 (1965).

[2]M. Bloomfield, *Sacred Books of the East*: *Hymns of Athara Venda*, Vol. XLII. Clarendon Press, Oxford (1897).

[3]A. F. R. Hoernle, *Bower Manuscript* pp. 1893–1912. Government Printing, Calcutta, India (1924).

[4]J. A. Parrish, T. B. Fitzpatrick, G. Tanenbaum and M. A. Pathak, *N. Eng. J. Med.* **291**, 1207 (1974); K. Wolff, T. B. Fitzpatrick and J. A. Parrish, *Arch. Dermatol.* **112**, 934–950 (1976); G. D. Weinstein, *Drug. Ther.* **6**, 59–61, 65–67 (1976).

[5]F. Dall'Acqua and G. Rodighiero, *Atti. Acad. Naz. Lincei. Cl. Sci. Fis. Mat. Natur. Rend.* **40**, 412–22 (1966).

[6]F. Dall'Acqua, F. S. Marciani, L. Ciavatta and G. Rodighiero, *Z. Naturforsch.* **266**, 561–9 (1971).
[7]See, for example the following review: B. R. Scott, M. A. Pathak, and G. R. Mohn, *Mutat. Res.* **39**, 29–74 (1976); M. T. Melo, D. Averbeck, R. V. Bensasson, E. J. Land and C. Salet, *Photochem. Photobiol.* **30**, 645–651 (1979).
[8]The Δ^3 double bond was selected for sequestering since the following workers predicted greater reactivity for Δ^3 over Δ^4 in the psoralen system in the triplet excited state: P. Song, M. L. Harter, T. A. Moore and W. C. Herndon, *Photochem. Photobiol.* **14**, 521–30 (1971); P. Song and W. H. Gordon, *J. Phys. Chem.* **74**, 4234–40 (1970).
[9]H. Pechmann and B. Duisberg, *Ber. Dtsch Chem. Bis.* **16**, 2119 (1883).
[10]H. K. Sen and U. P. Basu, *J. Indian Chem. Soc.* **5**, 470 (1928).
[11]A. H. Blatt, *Org. Reactions* **1**, 342–69 (1942).
[12]H. D. Dakin, *Org. Syn. Coll.* Vol. **1**, 149 (1941).
[13]D. S. Tarbell, *Org. React.* **2**, 1–48 (1944).
[14]A related sequence was employed by us for the total synthesis of the major metabolite of methoxsalen: P. N. Confalone and D. L. Confalone, *J. Org. Chem.* **45**, 1470–73 (1980). See also T. R. Seshadri and M. S. Sood, *Indian J. Chem.* **1**, 291 (1963).
[15]The production of intermediates of this type was first reported in the synthesis of methylated derivatives of 8-methoxypsoralen: P. N. Confalone, D. Lollar Confalone, G. Pizzolato, and M. R. Uskoković, *U.S. Pat.* 4,130,568 and 4,180,659; Ger.Offen. 2,741,233. Some aldehyde tautomer of **14** was observed in this case in solution as shown by a proton NMR.
[16]M. G. Parekh and K. N. Trivedi, *Austral. J. Chem.* **23**, 407 (1970).
[17]D. N. Shah and N. M. Shah, *J. Chem. Soc.* 1681–85 (1954).
[18]An alternative approach to psoralens of this substitution pattern was reported by C. Antonello, *Gazz. Chim. Ital.*, **88**, 415–29 (1958).
[19]Related methodology was employed by K. D. Kaufman, W. E. Russey and L. R. Worden, *J. Org. Chem.* **27**, 875–79 (1962); K. D. Kaufman, *Ibid.* **26**, 117–121 (1961).
[20]Y. A. Shaikh and K. N. Trivedi, *J. Indian Chem. Soc.* **51**, 755–756 (1974).