76299-72-4; **6**, 56037-77-5; **7**, 22094-23-1; **8a**, 86289-58-9; **8b**, 86289-59-0; **9a**, 86289-60-3; **9b**, 86289-61-4; **10a**, 86289-62-5; **10b**, 86289-63-6; **11**, 86289-64-7; *trans*-**12**, 86289-65-8; *cis*-**12**, 86289-66-9; **14a**, 86289-67-0; **14b**, 86289-68-1; **15**, 86289-69-2; **16**, 86289-70-5; **18**, 86289-71-6; **19b**, 86289-72-7; **19c**, 86289-73-8; **20a**, 86289-74-9; **20b**, 86334-04-5; **20c**, 86334-05-6; **20d**, 86391-04-0; **21a**, 86289-75-0; **21b**, 86334-06-7; **22a**, 86289-76-1; **22b**, 86334-07-8; **22c**, 86334-08-9; **22d**, 86334-09-0; **23**, 86289-77-2; **24**, 86289-78-3; **25**, 86289-79-4; **26**, 86289-80-7; **28**, 86289-81-8; **29**, 86289-82-9; **32**, 86289-83-0; **33**, 86289-84-1; **34**, 86289-85-2; **35**, 86307-80-4; Me_2C=CHOAc, 14478-14-9; Et_2C=CHOAc, 22014-15-9; $C_5H_{10}C$=CHOAc, 23438-53-1; CH_3CH=CHOAc, 3249-50-1; cyclohexylcarboxaldehyde, 2043-61-0; propaldehyde, 123-38-6; thiophenol, 108-98-5; isobutyraldehyde, 78-84-2; 2-ethylbutyraldehyde, 97-96-1.

Synthesis and Derivitization of 8-Acetylpsoralens. Acetyl Migrations during Claisen Rearrangement

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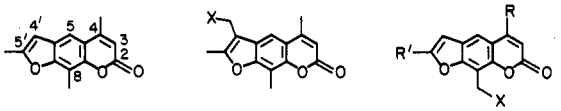
Received January 18, 1983

We have synthesized a series of 8-acetylpsoralens in which methyl and hydrogen substitutions were systematically varied at the 4- and 5′-positions. Claisen rearrangement was employed in developing the furano ring, and acetyl migration during the rearrangement was identified as a major side reaction. This migration was circumvented by applying a diethylaluminum chloride catalyzed Claisen rearrangement to the pyrone ring-opened compound. For the 5′-methyl compounds, furano ring formation was most effectively performed in a sulfuric–acetic acid mixture. The 8-acetyl group, through a series of transformations, was then converted to acetic acid and α-hydroxyethyl, β-hydroxyethyl, α-aminoethyl, aminomethyl, hydroxymethyl, and formyl moieties.

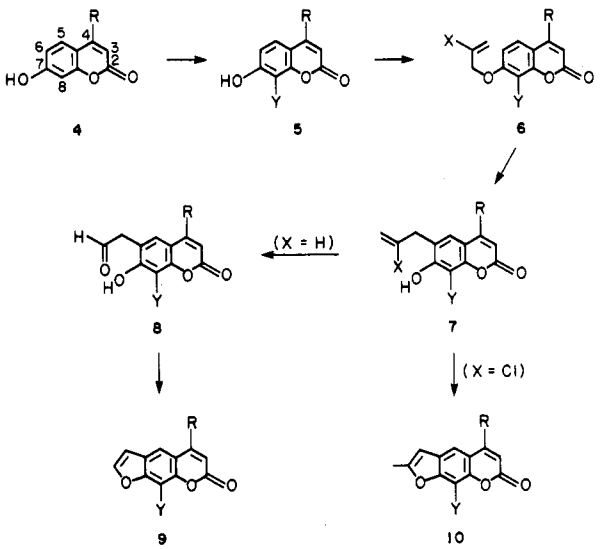
Psoralens **2** in which X = OH or NH_2 are superior to 4,5′,8-trimethylpsoralen (**1**) and 8-methoxypsoralen in their abilities to saturate photoreactive sites on DNA and RNA without repeated addition of reagent.[2] In particular, the 4′-aminomethyl derivatives (**2**, X = NH_2) is highly soluble in water and binds more strongly to DNA than does **1**. Thus **2** (X = NH_2) is a very effective photoreactive cross-linking reagent for both DNA and RNA.[2]



1 **2** **3**

The effectiveness of **2** (X = NH_2) prompted an interest in the dependence of intercalation and photoreactivity on the type and position of substituents on the parent psoralen nucleus.[3] In particular, we wished to examine the extent to which the formation of monoadduct vs. diadduct (cross-link) depends on the substitution pattern on the photoreactive double bonds (C-3, C-4 and C-4′, C-5′).[4] We therefore sought to vary **2** in two ways as depicted in structure **3**. First we wished to move the water-solubilizing group to a nonreacting portion of the psoralen molecule. Placing this group at C-8 instead of C-5 appeared easier in terms of synthetic convenience and also involved the least amount of structural variation with respect to 4,5′,8-trimethylpsoralen (**1**).[5] We then wished to examine the role of the methyl groups at C-4 and C-5′ by making four series of compounds **3**: R = R′ = CH_3; R′ = H, R = CH_3; R′ = CH_3, R = H; R = R′ = H. Characterization of these compounds with respect to DNA and RNA in terms of dark binding constant, ability to saturate photoreactive sites, and ability to cross-link would then establish a basis for a more detailed understanding of the photoreaction of methyl-substituted psoralens with nucleic acids. This understanding could in turn be used as a guide for the

Scheme I. Generalized Routes for Synthesis of Psoralens 3



4 **5** **6** **8** **7** **9** **10**

(1) Fellow of the Jane Coffin Childs Memorial Fund for Medical Research.

(2) Isaacs, S. T.; Shen, C. J.; Hearst, J. E.; Rapoport, H. *Biochemistry* **1977**, *16*, 1058.

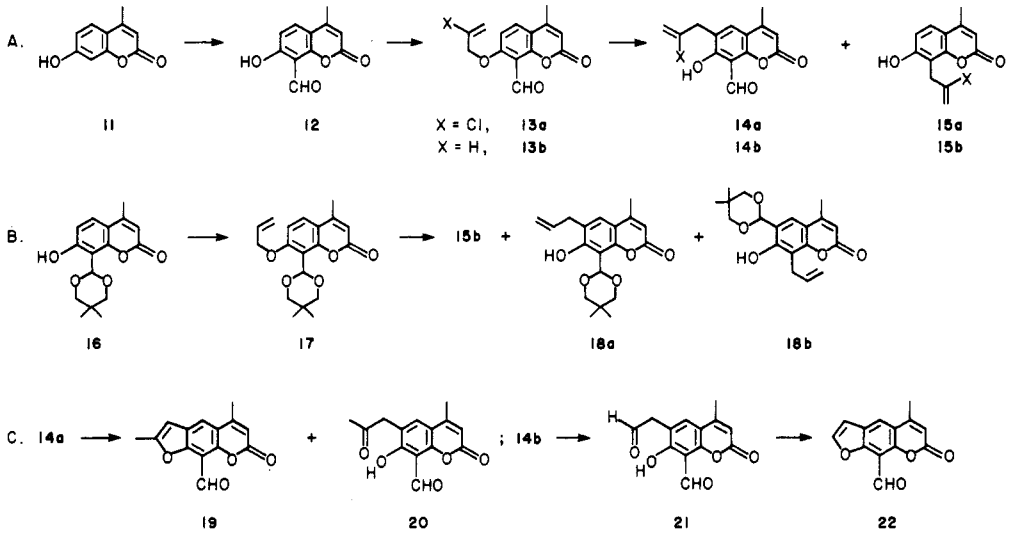
(3) Many psoralens substituted with various alkyl groups and a limited number of psoralens substituted with other groups have been prepared and assayed for their ability to photosensitize skin. None of these psoralens contain a water-solubilizing group, a modification first introduced in ref 2. For a discussion of these compounds see: Musajo, L.; Rodighiero, G.; Caporale, G.; Dall'Aqua, F.; Marciani, S.; Bordin, F.; Baccichetti, F.; Bevilacqua, R. In "Sunlight and Man"; University of Tokyo Press: Tokyo, 1974; p 369.

(4) The complete structural characterizations of psoralen–pyrimidine monoadducts and diadducts have recently been reported (Kanne, D.; Straub, K.; Rapoport, H.; Hearst, J. *Biochemistry* **1982**, *21*, 861. Kanne, D.; Straub, K.; Hearst, J.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 6754). These reports also describe a quantitative method for determining the amounts of mono- and diadducts formed in a given psoralen–nucleic acid photoreaction.

(5) Also, models suggested that X in **3** would lie in a hydrophilic region of the double helix.

0022-3263/83/1948-2709$01.50/0

Scheme II. Synthesis of 8-Formylpsoralens



design of soluble psoralens in which the ability to perform a prescribed function, e.g., the ability to cross-link or to exclusively form monoadducts, is maximized. In this report we discuss the synthesis of 8-acetylpsoralens **44**, **45**, **50**, and **51**. The conversion of these psoralens to compounds having solubilizing functionality at C-8 is also described.

The route by which we planned to make compounds **3** is outlined in Scheme I. Coumarins **4** in which R = H or CH_3 are commerically available[6] and can be readily converted to **5** in which Y equals a variety of groups containing functionalized carbon, including formyl and acetyl.[7] During conversion of **4** to **5**, substitution occurs predominantly or exclusively at C-8.[8] Alkylation of **5** with a suitable allyl halide would give **6**, which in turn would be expected to rearrange on heating to 6-allylcoumarin **7**. For psoralens **3** in which R′ = H, X in **6** and **7** would be a proton, and oxidation of **7** with OsO_4/IO_4^- or with ozone would give **8**. Treatment of **8** with acid would then lead to psoralen **9**. This route has been widely used for the synthesis of psoralens substituted at C-8 and unsubstituted at both C-4′ and C-5′.[9] For psoralens **3** in which R′ = CH_3 we planned to use the route previously described by us for the synthesis of **1**.[10] In this process X in **6** and **7** equals chlorine, and treatment of **7** with acid would be expected to lead directly to psoralen **10**.

Initially we wished to have Y = formyl, anticipating that the resulting psoralens **9** and **10** could be converted simply to psoralens **3**. We also anticipated that formyl could be a useful handle for the synthesis of other derivatives. The required 8-formylcoumarins (**5**, Y = formyl) can be prepared conveniently by reaction with hexamethylenetetramine, although the yields are low.[11] We examined this route for the case of R = CH_3, and the results are summarized in Scheme II.

Formylcoumarin **12** was prepared from **11** in 15% yield.[12] Alkylation of **12** with allyl bromide in refluxing acetone/potassium carbonate was incomplete, and alkylated material in turn underwent aldol condensation with acetone.[13] Alkylation in refluxing ethanol/potassium carbonate did not proceed to completion;[14] however, use of potassium fluoride[15] in DMF at 60 °C led to production of **13b** in high yield within 1 h. Alkylation of **12** with 2,3-dichloro-1-propene required higher temperatures.

When heated in refluxing *p*-diisopropylbenzene, allyl ethers **13** produced not only the desired compounds **14** but also 8-allyl compounds **15**, in which the elements of carbon monoxide had been lost. The yields of **14** and **15** differed depending on X: 50% and 10%, respectively, for X = Cl and 35% each for X = H. Products analogous to **15** have been isolated previously from Claisen rearrangements of allyl ethers of salicylaldehydes.[16] In an attempt to hinder allyl migration to C-8, we prepared the neopentyl glycol

(6) Coumarins **4** in which R ≠ H are also readily prepared by von Pechmann condensation between resorcinol and an appropriate β-keto ester. Coumarin syntheses are reviewed by: Dean, F. M. "Naturally Occurring Oxygen Ring Compounds"; Butterworths: London, 1963; p 176.

(7) Compounds **5** (R = CH_3) which are known include the following. (a) Y = hydroxymethyl: Boshetti, E.; Molho, D.; Aknin, J.; Fontaine, L.; Grand, M. *Chim. Ther.* **1966**, 403. (b) Y = methoxycarbonyl: Limaye, D. B.; Kulkarni, K. M. *Rasayanam* **1943**, *1*, 251. (c) Y = allyl: Baker, W.; Lothian, O. M. *J. Chem. Soc.* **1935**, 628. References for compounds in which Y = formyl or acetyl follow.

(8) 7-Hydroxycoumarins react preferentially at C-8 in electrophilic reactions, and 7-(allyloxy)coumarins rearrange preferentially to C-8. If the aromaticity of the pyrone ring is disrupted, then reaction at C-6 is preferred. See ref 6 for review.

(9) Psoralen syntheses are reviewed by: Mustafa, A. "Furopyrans and Furopyrones"; Wiley-Interscience: New York, 1967.

(10) Bender, D. R.; Hearst, J. E.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2176.

(11) Naik, R. M.; Thakor, V. M. *J. Org. Chem.* **1957**, *22*, 1626, 1630.

(12) (a) Rangaswami, S.; Seshadri, T. R. *Proc.—Indian Acad. Sci., Sect. A* **1937**, *6A*, 112. (b) Nesmeyanov, A. N.; Vompe, A. F.; Zaverich, T. S.; Smolin, D. D. *J. Gen. Chem. USSR (Engl. Transl.)* **1937**, *7*, 2767. (c) Antonello, C. *Gazz. Chim. Ital.* **1958**, *88*, 430. (d) See ref 7a. In all reports except the last, yields of **12** range from 10% to 20%. In ref 7a a yield of 43% is claimed, but in our hands that procedure gave only a 10–15% yield of impure material. Using the procedure described in this report, we consistently obtained pure material.

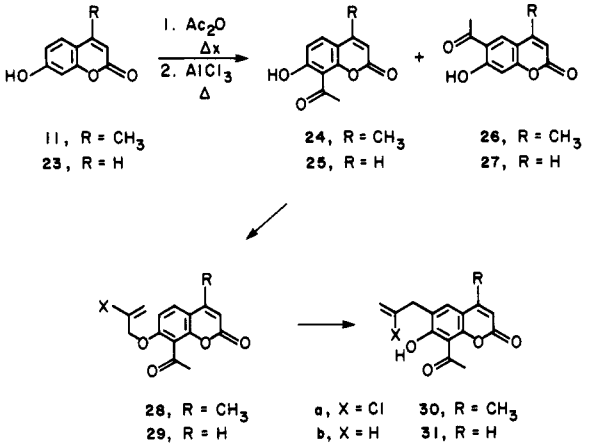
(13) Phenol **12** has been alkylated in refluxing acetone/potassium carbonate with ethyl bromoacetate to give the corresponding 8-formyl ether in 74% yield.[12c] We repeated this work and found that the mass not accounted for appeared to be the alcohol resulting from aldol condensation of the 8-formyl ether with acetone. Using identical reaction conditions, we attempted alkylation of **12** with allyl bromide and recovered a 44% yield of the alcohol which results from aldol condensation of allylated **12** (**13b**) with acetone. The remaining material was unreacted **12**.

(14) Allyl ether **13b** and another component were formed within 1 h. TLC of the reaction solution also indicated presence of starting material. Continued reaction brought no further change. Chromatography on silica gel allowed isolation of **13b** in 25% yield and **12** in 65% yield. The third component apparently had reverted to **12** on the column. When **13b** was refluxed in ethanol/potassium carbonate, it was converted to many unidentified components within 3 h. These results are in contrast to the reported quantitative alkylation of salicylaldehyde under identical reaction conditions (Claisen, L.; Eisleb, O. *Justus liebigs Ann. Chem.* **1913**, *401*, 95).

(15) Clark, J. H.; Miller, J. M. *J. Chem. Soc., Chem. Commun.* **1976**, 229; *J. Am. Chem. Soc.* **1977**, *99*, 498.

(16) Rearrangements involving the displacement of carboxyl and aldehyde groups have been reviewed by: (a) Tarbell, D. S. *Chem. Rev.* **1940**, *27*, 495. (b) Tarbell, D. S. *Org. React.* **1944**, *2*, 1.

Scheme III. Synthesis of 8-Acetyl-6-allyl-7-hydroxycoumarins



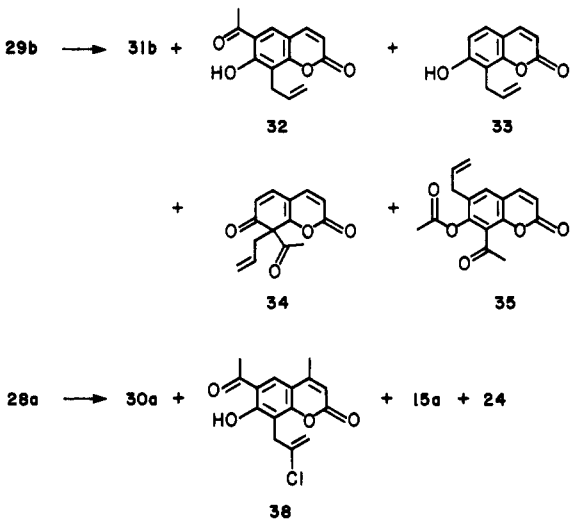
acetal **17**. Heating this allyl ether, however, produced a mixture which still contained 8-allyl compounds **15b** (12%) and **18b** (14%) along with the desired acetal **18a** (58%) as shown in Scheme IIB.

The conversion of compounds **14** to the desired psoralens is shown in Scheme IIC. Reaction of **14a** with concentrated HCl gave mixtures of unidentified products but none of **19**. Use of concentrated or 70% (v/v) aqueous H_2SO_4 at room temperature gave mixtures of psoralen **19** and ketone **20** in a ratio of about 1/3.[17] Oxidation of **14b** with OsO_4/IO_4^- gave unstable material, and examination by NMR indicated that it was undoubtedly the coumarylacetaldehyde **21**.[18] Attempts to convert **21** to **22** were unsuccessful. When **21** was added slowly to hot PPA or 85% phosphoric acid, a very small amount (1% yield from **14b**) of material having a UV spectrum consistent with **22** was obtained.

The need for an alternate approach to psoralens **3** was clear. Use of Y = CH_3CO (Scheme I) appeared attractive not only because two of the four desired 8-acetylpsoralens had been prepared previously (**51**[19] and **44**[20]) but also because we anticipated the ready conversion of the acetylpsoralens to derivatives **3**, to 8-methoxypsoralen derivatives,[21] and also to 8-ethyl derivatives containing functionality at both the α- and β-carbon of the ethyl group.

The initial stages of production of the required 8-acetylpsoralens are shown in Scheme III. Fries rearrangement of the acetate of **11** is known to produce a mixture of **24** and **26**.[22] A mixture of **25** and **27** can be obtained in an analogous manner. In both cases the 8-acetyl isomers predominate.[23] Alkylation of **25** with allyl bromide proceeds in good yield to give **29b**,[19] as does the analogous alkylation of **24** to give **28b**.[20] The conversions of **28b** to **30b**[20] and of **29b** to **31b**[19] by Claisen rearrangement are both reported to proceed in 45–50% yields, and **31b** has been converted to psoralen **51** (**9**; R = H, Y = CH_3CO) by ozonolysis to the coumarylacetaldehyde followed by acid-catalyzed ring closure.[19] We planned to make psoralen **50** (**9**; R = CH_3, Y = CH_3CO) from **30b** in an analogous manner. Psoralen **44** (**10**; R = CH_3, Y = CH_3CO) has been derived from **30b** by bromination of the allylic double bond followed by treatment with sodium ethoxide,[20] but the overall yield was low. Thus we intended to make 5′-methylpsoralens by proceeding via (chloroallyl)coumarins, as described previously.[10] Our results are detailed below.

Scheme IV. Products of Claisen Rearrangement of 8-Acetyl-7-(allyloxy)coumarins



Synthesis of Allyl Ethers 28a,b and 29a,b. 8-Acetyl-7-hydroxy-4-methylcoumarin (**24**) was obtained as described,[22] although a small amount of 6-acetyl isomer **26** remained. Further recrystallization removed this contaminant to give a 42% yield of **24**.[23] The analogous 8-acetylcoumarin **25**[24] was obtained by using the same procedure as for synthesis of **24**. 6-Acetyl isomer **27**[25] was isolated and shown to have a UV spectrum which differs markedly from that of 8-acetyl isomer **25**. In particular, the spectrum of **27** exhibits an intense maximum at 256 nm, whereas the spectrum of **25** shows a minimum at this wavelength. At 310 nm both isomers absorb about equally. Mixtures of **24** and **26**, when examined by HPLC with UV detection at both 256 and 310 nm, exhibit similar behavior. Thus it was possible to show by HPLC with UV detection at 256 nm that our samples of **24** and **25** contained <0.2% of the corresponding 6-acetyl isomers.

Allyl ethers **28b**[20] and **29b**[19] were obtained as described in 92% and 94% yields, respectively. Synthesis of **28a** by reaction of **24** and 2,3-dichloro-1-propene in refluxing acetone/potassium carbonate with 5 mol % of KI proceeded slowly, but substitution of 1/1 (v/v) DMF/benzene as the solvent and reaction at 80 °C led to production of

(17) With concentrated H_2SO_4, **19** and **20** could be obtained in about 50% combined yield, the remainder of material being polymeric; 70% (v/v) H_2SO_4 gave **19** and **20** in greater yield but did not preclude formation of polymeric material. The best conversion should result from the H_2SO_4/HOAc reagent which was developed subsequently.

(18) In psoralen syntheses which use this approach, formylmethylcoumarins analogous to **21** but without a substituent at C-8 capable of hydrogen bonding appear to exist as the hemiacetals. The NMR spectrum of **21** clearly shows two absorptions for the aldehyde protons, thus indicating that **21** exists at least to a significant extent as the unstable coumarylacetaldehyde.

(19) Seshadri, T. R.; Sood, M. S. *Indian J. Chem.* **1963**, *1*, 293.

(20) Kaufman, K. D.; Worden, L. R. *J. Org. Chem.* **1961**, *26* 4721.

(21) Kanne, D.; Rapoport, H.; Hearst, J. E., submitted for publication in *J. Med. Chem.*

(22) Russell, A.; Frye, J. R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 281 and references cited therein.

(23) Although the Fries rearrangement gives a crude product which contains approximately 80% of the desired 8-acetyl compound, purification by repeated crystallization lowers the yield to 50%. Continuing the sequence into the next step with crude material allows utilization of a chemical separation of the allyloxy compounds by opening the pyrone with hot 0.1 N NaOH and then quenching in cold HCl. The 8-acetyl compound **28b** forms coumarinic acid **39** which can be extracted into the aqueous layer with 1 M K_2CO_3. The 6-acetyl isomer, on the other hand, recloses in cold acid and remains in the organic layer. This approach allows the recovery of virtually all of the 8-acetyl compound formed in the Fries rearrangement without the need of multiple recrystallization or chromatographic separation.

(24) Ray, J. N.; Silooga, S. S.; Vaid, V. R. *J. Chem. Soc.* **1935**, 813.

(25) Limaye, D. B.; Joshi, M. C. *Rasayanam* **1943**, *1*, 225.

28a in 92% yield; 29a was prepared similarly in 91% yield.

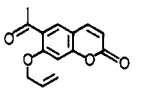
Claisen Rearrangement of Allyl Ethers 28a,b and 29a,b. Acetyl Migrations. As mentioned earlier, the Claisen rearrangements of ethers **28b** and **29b** are reported to give hydroxycoumarins **30b** and **31b** in about 50% yield.[19,20] No comments were made about the nature of the remaining material. In the case of the rearrangement of ether **29b** we examined all products in detail, and their structures are shown in Scheme IV. Most prominant among the minor products was 6-acetyl-8-allylcoumarin **32**, which proved difficult to remove from **31b** by crystallization. Other products were easily removed and included hydroxycoumarin **33** and neutral products **34** and **35**. Examination of products from the rearrangement of **28b** by TLC and GC indicated that an array of products analogous to those shown in Scheme IV had been formed.

When the rearrangement of **29b** was carried out in refluxing *N,N*-diethylaniline, **32** accounted for ~30% of total mass and could not be removed from **31b** to a significant extent even after several crystallizations from 95% ethanol. Yields of the remaining minor products were only a few percent each. When the rearrangement of **29b** was carried out as described[19] by heating neat at 210 °C, the yield of **32** dropped to 13% while the combined yield of **34** plus **35** increased from about 2% to 9%. Although the percent of **31b** in the mixture changed very little, the reduced yield of **32** allowed for isolation of pure **31b** in 44% yield[26] after several recrystallizations. Subsequently, **29b** also was heated in *p*-diisopropylbenzene and in nitrobenzene. The 8-acetyl (**31b**)/6-acetyl (**32**) isomer ratios were 6/4 in *p*-diisopropylbenzene, 6/4 in *N,N*-diethylaniline, 7/3 in nitrobenzene, and 8/2 neat.

To confirm the structure of **32**, we planned to synthesize and rearrange allyl ether **36**, which in turn could be prepared from 6-acetylumbelliferone (**27**)[25] by alkylation with allyl bromide. The detailed published procedure for isolation of **27**[25] appeared accessible only with difficulty. We isolated **27** by first extracting a solution of a mixture of **25** and **27** several times with aqueous sodium carbonate. The higher double bond character at the C7-C8 bond of **25** should increase the resonance stabilization of the 7-O anion of **25** relative to the corresponding anion of **27**. Thus this procedure resulted in preferential extraction of the more acidic 8-acetyl isomer **25**. The enriched material which remained in the organic phase was chromatographed and recrystallized to give a sample of **27** which was shown by HPLC to contain <0.2% of **25**. This material was then converted to **36** by alkylation with allyl bromide in refluxing acetone/potassium carbonate. A separation of **29b** and **36** that exploits the ability of **29b** to form a stable coumarinic acid provided a convenient alternative route to pure **36**.[23]

When **36** was heated in refluxing *N,N*-diethylaniline, at least five products were formed. About 90% of the total mass was the anticipated 8-allyl-6-acetylcoumarin **32**, identical by spectral and chromatographic comparison with **32** obtained from the rearrangement of **29b**. A prominent minor component was 6-allyl-8-acetyl-7-hydroxycoumarin (**31b**) formed in 5% yield and confirmed by NMR and HPLC comparison with authentic material. The formation of **31b** from the rearrangement of **36** demonstrates that even when rearrangement to a single component is highly favored, a product resulting from acetyl migration can still occur.

Characteristic features of the NMR and UV spectra of these acetylcoumarins lend strong support to our structural



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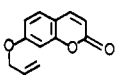

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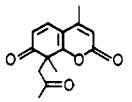
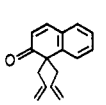
assignments. The position of the acetyl group in coumarin **24** is well established by its conversion to 2-acetylresorcinol.[22] Characteristic absorptions in the NMR spectrum of **24** include a multiplet at δ 6.19 for H-3 and doublets at δ 7.73 and 6.95 for H-5 and H-6. The NMR spectrum of the analogous 8-acetylcoumarin **25** shows similar absorptions for H-5 and H-6 along with a doublet at δ 6.27 for H-3 and an additional doublet at δ 7.67 for H-4. In both compounds the C-8 acetyl methyl absorbs at about δ 3.0: at δ 3.00 for **24** and δ 2.98 for **25**. In contrast the acetyl methyl of 6-acetylcoumarin **27** absorbs at δ 2.68, and from a spectrum of a mix of **24** and **26** it is apparent that the acetyl methyl of **26** absorbs at essentially the same position (δ 2.70). 6-Acetylcoumarin **27** also shows the expected doublets for H-3 (δ 6.27) and H-4 (δ 7.60) along with singlets for H-5 (δ 7.85) and H-8 (δ 6.82).

When compared with the NMR spectrum of **25**, it is evident that the spectrum of 6-allyl-8-acetyl-7-hydroxycoumarin (**31b**) contains absorptions for H-3, H-4, and H-5 that are essentially identical in splitting patterns (except for H-5) and chemical shifts with those seen for **25**. A similar comparison of the spectra of **32** and **27** also shows essential identity of absorptions for H-3,4,5. In addition, the acetyl methyl of **31b** absorbs at δ 2.94, in comparison with δ 2.98 for **25**, and the acetyl methyl of **32** absorbs at δ2.72, in comparison with δ 2.68 for **27**. Additional support for structural assignments can be drawn from a comparison of UV spectra. As mentioned earlier, the UV spectra of **25** and **27** differ markedly, with that of 6-acetylcoumarin **27** showing an intense maximum at 256 nm. The UV spectrum of **32** exhibits a similar maximum at 263 nm, and further comparison shows essential similarity between the spectra of **27** and **32** and between the spectra of **25** and **31b**. Thus there is no doubt about the structural assignments for acetylcoumarins **31b** and **32**. 8-Allylumbelliferone (**33**) was prepared by Claisen rearrangement of 7-(allyloxy)coumarin (**37**),[27] and it was identical with **33** produced from **29b** by TLC comparison and by GC and HPLC coinjection.

The structure of dienone **34** was suggested by its NMR spectrum. Characteristic doublets for H-3,4 and for H-5,6 are present along with absorptions for the allyl group which clearly show it to be bound to carbon and not to oxygen. A sharp singlet assigned to the acetyl methyl appears upfield (δ 2.38) relative to the acetyl methyl absorptions in compounds such as **29b** (δ 2.62), **31b** (δ 2.94), and **32** (δ 2.72), suggesting that the acetyl group of **34** is not conjugated. The UV spectrum of **34** exhibits a maximum at 288 nm (shoulder at 310 nm), suggesting the presence of an extended conjugated system which would be precluded if either the allyl group or the acetyl group was bonded to C-4a. An analogous compound, 1,1-diallyl-2-oxo-1,2-dihydronaphthalene (B), shows an absorption maximum at about the same wavelength (299 nm).[28]



A



B

(26) The reported yield of **31b** is 78%.[19] Our experience suggests that this material was contaminated with 8-allyl-6-acetyl isomer **32**.

(27) Krishnaswamy, B.; Seshadri, T. R. *Proc.—Indian Acad. Sci., Sect. A* **1941**, *13A*, 43.

(28) Green, J.; McHale, D. *Chem. Ind. (London)* **1964**, 1801.

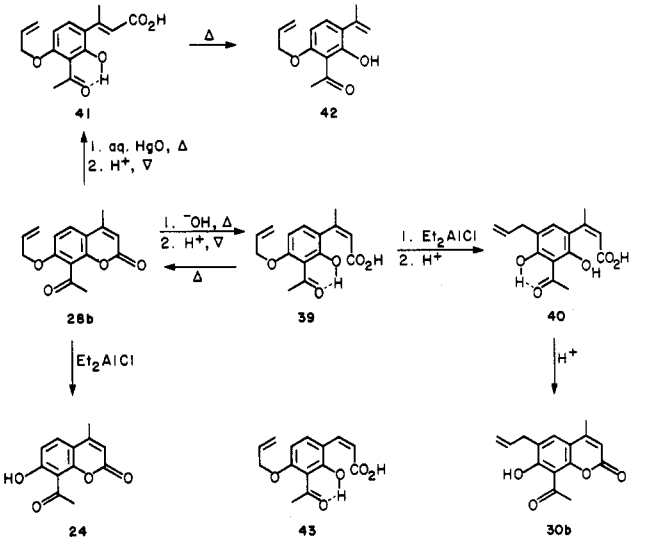
The UV spectrum of **34** is also similar to that of dienone A, isolated previously by us.[10,29] The low-resolution mass spectrum of **34** shows a prominent absorption at *m/e* 244 (M^+) and a base peak at *m/e* 202 (M^+ – acetyl + a proton). A high-resolution mass measurement of the *m/e* 244 absorption was consistent with the molecular formula for **34**. Chemical evidence in support of structure **34** (a 1,3-dione) was provided by its rapid decomposition on silica gel to 8-allyl-7-hydroxycoumarin (**33**). This conversion presumably occurs by attack of water at the acetyl carbonyl followed by expulsion of the resonance stabilized hydroxycoumarin **33**.

Two sharp three-proton singlets were noted in the NMR spectrum of **35**, which is very similar to that of **31b**. Spectral and chromatographic identity with material prepared by acetylation of **31b** confirmed structure **35**.

8-Allylcoumarins **32** and **33** undoubtedly arise from an intermediate which at least approximates dienone **34**.[29] Thermal elimination of the acetyl group as ketene would give **33**,[30] and scavenging of ketene by hydroxycoumarin **31b**, the most abundant component of the mixture, would give rise to **35**. A [1,5]sigmatropic rearrangement of the acetyl group of **34** would give **32**. An analogous cyclohexadiene, 1-acetyl-1-methylcyclohex-2,4-diene, undergoes a similar rearrangement.[31] The association of the Claisen rearrangement with such a [1,5] sigmatropic rearrangement has also been observed with 2-(allyloxy)-4-methyl-5-methoxyacetophenone.[32]

The Claisen rearrangement of chloroallyl ethers **28a** and **29a** gave products analogous to those formed from **29b**, although the relative yields differed. The most useful difference was the production of greater amounts of the desired 6-(chloroallyl)coumarins **30a** and **31a**, allowing isolation of the pure compounds by crystallization in 81% and 72% yields, respectively. In the case of the rearrangement of ether **28a**, other products were examined in some detail by carrying out a series of separations involving crystallizations and chromatography of the mother liquor which remained after isolation of **30a**. 8-(Chloroallyl)-coumarin **15a** was isolated and shown by spectral and chromatographic comparison to be identical with **15a** obtained from the Claisen rearrangement of 8-formyl ether **13a**. 8-Acetylcoumarin **24**, the product of ether cleavage of **28a**, was also isolated. Although 6-acetylcoumarin **38** was not isolated, NMR spectra of mixtures containing **38** along with 8-acetylcoumarin **30a** show the characteristic absorptions expected for **38**. In addition, examination of these materials by HPLC with UV detection at both 256 and 310 nm indicated that the material to which we assign structure **38** shows intense UV absorption at 256 nm, in analogy with 6-acetyl-7-hydroxycoumarins **26**, **27**, and **32**. The hydroxyl protons of coumarins **24**, **30a**, and **38** absorb in the NMR at concentration-independent and distinctively different positions. This information allowed for the determination of yields of products: **30a**, 85%; **38**, 5%; **15a**, 1%; and **24**, 3%.[33] Most of the remaining mass (4%) was starting material **28a**. Chromatographic and NMR inspection of the crude product from the rearrangement of chloroallyl ether **29a** indicated the formation of analogous products in essentially identical yields.

Scheme V. Reaction of Coumarinic Acid 39 with Diethylaluminum Chloride



Treatment of Coumarinic Acid 39 with Diethylaluminum Chloride. The Claisen rearrangement of 7-(allyloxy)coumarins yields, if possible, the 8-allyl isomer as the predominant product.[34] This preference for rearrangement to C-8 instead of to C-6 presumably derives from valence-bond stabilization brought about by the aromatic nature of the pyrone ring of the coumarin.[35] If the pyrone ring of either **28** or **29** could be opened and kept open during Claisen rearrangement, then preference for rearrangement to C-8 would presumably be eliminated. Thus the extent of formation of 8-allylcoumarins (e.g., **32** and **33**) could, in principle at least, be reduced.

The pyrone ring of coumarins can be opened in alkali to the corresponding acid (a coumarinic acid), but the acid generally recloses to the coumarin if the pH is brought from alkaline to neutral. An exception to the strong tendency to reclose occurs if there exists at C-8 a group capable of hydrogen bonding with the ortho phenolic hydroxyl.[36] Accordingly, we treated allyl ether **28b** with warm alkali and carefully acidified the coooled solution to form coumarinic acid **39** (Scheme V) in high yield. By forming **39** we have not only disrupted the initial bond order brought about by fusion to the pyrone ring but have also introduced greater double bond character at C6–C7 which will favor rearrangement to C-6. This effect derives from hydrogen bonding between the phenolic hydroxyl and the acetyl oxygen and has been amply confirmed by the results of Claisen rearrangement of analogous compounds.[7c,37]

(29) Other dienones which have been isolated from Claisen rearrangements include dihydronaphthalene B[28] and a product which arose at room temperature on silica from the 1,1-dimethylallyl ether of 6,7-dimethoxy-5-hydroxycourmarin (Murray, R. D. H.; Sutcliffe, M.; Hasegawa, M. *Tetrahedron* **1975**, *31*, 2966).

(30) A formally equivalent mechanism has been proposed to rationalize elimination of an allyloxy group during the Claisen rearrangement of 1,2-bis(allyloxy)anthraquinone (Bell, K. A.; Flatman, I. J. Golborn, P.; Pachl, A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1978**, 900).

(31) Schiess, P.; Funfschilling, P. *Tetrahedron Lett.* **1972**, 5195.

(32) Falshaw, C. P.; Lane, S. A.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1973**, 491. Also, a similar [1,5] acetyl shift has been reported in the naphthalene series by: Cooper, S. C.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1980**, 633.

(33) The extent of formation of products derived from migration of allyl groups to C-8 would be expected to be less in the case of β-chloroallyl vs. allyl due to the increased congestion introduced by the chloroallyl group in C-8 allyl intermediates such as **34**.

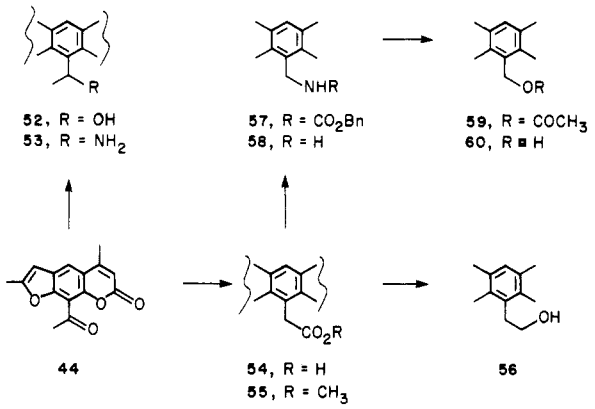
(34) (a) We have heated 7-(allyloxy)-4-methylcoumarin neat at 205 °C and obtained the 6-allyl- and 8-allyl-7-hydroxy-4-methylcoumarin (**15b**) in a ratio of 19/81. (b) The 1,1-bis(methylallyl) ether of umbelliferone (**23**) gave on pyrolysis products of rearrangement to C-8 (74%) and to C-6 (Murray, R. D. H.; Ballantine, M. M.; Mathai, K. P. *Tetrahedron* **1971**, *27*, 1247).

(35) In this respect coumarins can be viewed as analogous to naphthalenes.

(36) (a) Crawford, M.; Rasburn, J. W. *J. Chem. Soc.* **1956**, 2155. (b) Naik, R. M. Thakor, V. M. *J. Org. Chem.* **1957**, *22*, 1240.

(37) Baker, W.; Lothian, O. M. *J. Chem. Soc.* **1936**, 274.

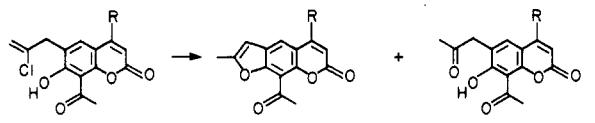
Scheme VI. Derivatization of 8-Acetylpsoralens



Initially we simply heated **39** neat. Not surprisingly, the result was reclosure to **28b**[38] followed by rearrangement to the previously described mixture of products. Similar treatment of the trans acid **41**,[39] which is incapable of reclosing to the pyrone, led to decarboxylaton to the styrene **42**.[40]

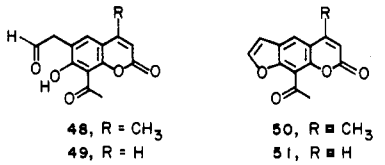
We next investigated rearrangement in the presence of Lewis acids. Treatment of coumarin **28b** with diethylaluminum chloride[41] resulted in ether cleavage to give **24**, but similar treatment of coumarinic acid **39**, where the phenolic hydroxyl is now free to activate electrophilic attack, gave a high yield of the desired 6-allylcoumarin **30b**. None of the 6-acetyl isomer (the 4-methyl analogue of **32**) was observed. The rearrangement presumably proceeds first to **40** which has two hydroxyl groups available for hydrogen bonding with the acetyl group and would therefore be expected to close readily to **30b**. Coumarinic acid **43** was prepared from **29b** in the same manner used for preparation of **39**. However, solubility problems precluded successful use of the Lewis acid catalyzed rearrangement.

Ring Closure of Coumarins 30a and 31a to 5′-Methylpsoralens 44 and 45. Previously we described conditions for the ring closure of 7-acetoxy-6-(β-chloroallyl)-4,8-dimethylcoumarin to 4,5′,8-trimethylpsoralen (**1**).[10] These conditions simply called for treatment of the coumarin with 70% (v/v) sulfuric acid at room temperature. Application of this procedure to **30a** gave the desired psoralen **44** and ketone **46** in 61% and 37% yields, respectively. Recrystallization of the crude psoralen gave **44** in 50% yield. Treatment of **31a** with 70% (v/v) sulfuric acid gave psoralen **45** and ketone **47**, also in about 61% and 37% yield, respectively.



Although the detailed mechanism for the formation of psoralens **44** and **45** and ketones **46** and **47** is not known,[42] it was found that psoralen **44** and ketone **46** exist in equilibrium in 70% sulfuric acid. Thus both pure **44** and pure **46**, when placed in acid, gave mixtures of the two compounds equal in ratio to the ratio obtained from reaction of **30a** with 70% sulfuric acid. By using glacial acetic acid as the diluent for the sulfuric acid (50% v/v) instead of water (the presence of which sets up the equilibrium leading to the undesired keto phenol **46**) a clean conversion of either **30a** or **46** to **44** can be affected.

This equilibrium totally favors ring-closed product with the phenolic aldehydes **48** and **49**. Both aldehydes were obtained from the corresponding allylcoumarins **30b** and **31b** by ozonolysis in formic acid. Treatment with a variety of acids gave complete furan ring formation to psoralens **50** and **51**.



The conversion of 8-acetylpsoralen **44** to the hydroxymethyl **60**, the amino methyl **58**, the β-hydroxyethyl **56**, the α-hydroxyethyl **52**, the α-aminoethyl **53** (Scheme VI), and the 8-methoxypsoralen[21] demonstrates the versatility of this compound. Analysis of the distribution of photoadducts from reaction of a nucleic acid with all four methyl permutations of one of the above psoralens has provided valuable structure–activity information with regard to the effect of peripheral methyl groups on photoaddition at the furan and pyrone side of a furocoumarin. The results of this study are the subject of another report.[21]

Experimental Section

Solvent evaporations were carried out in vacuo by using a Berkeley rotary evaporator after drying the mixtures over $MgSO_4$. All melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 137 spectrometer in $CHCl_3$ unless otherwise indicated. Ultraviolet (UV) spectra were recorded on a Cary Model 14 spectrometer in 95% EtOH, and nuclear magnetic resonance (NMR) spectra were recorded by using $CDCl_3$ solutions (unless otherwise indicated) on a Varian T-60, UCB 200-MHz, or UCB 250-MHz spectrometer with Me_4Si as an internal standard (coupling constants are given in hertz). Mass spectra were obtained on an AE1 MS-12 instrument. All reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Column chromatography was performed on Merck silica gel (70–230 mesh) or Camag Kieselgel (>250 mesh). Normal phase high-performance liquid chromatography (HPLC) was carried out on an Si-60 analytical column with EtOAc/hexanes/2-propanol (50/50/0.3 v/v/v) at a flow rate of 1 mL/min. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

8-Formyl-7-hydroxy-4-methylcoumarin (12). 7-Hydroxy-4-methylcoumarin (**11**; 20 g, 114 mmol), hexamethylenetetramine (40 g, 285 mmol), and glacial acetic acid (150 mL) were combined and stirred at 95 °C for 5.5 h. Aqueous HCl [concentrated HCl/water, 84/100 (v/v), 300 mL] was added, and the solution was heated for 30 min, cooled to 25 °C, and added to water (1.5 L). The resulting solution was extracted with ether (1 × 1 L, 2 × 0.5 L), and the combined extracts were washed with saturated NaCl (0.5 L), dried, and evaporated to yield crude **12** (4.0 g, 17%), which was recrystallized from ethanol: 3.36 g (14.5%); mp 179–181 °C (lit.[12d] mp 180 °C); IR 1650, 1730, 1757 (sh) cm^{-1}; NMR δ 2.43 (3 H, d, J = 2), 6.18 (1 H, m), 6.90 (1 H, d, J = 9), 7.77 (1 H, d, J = 9), 10.61 (1 H, s), 12.20 (1 H, s).

7-(Allyloxy)-8-formyl-4-methylcoumarin (13b). Formylcoumarin **12** (204 mg, 1.0 mmol), DMF (5.0 mL), potassium fluoride (290 mg, 5.0 mmol, fused and repowdered), and allyl bromide (133 mg, 1.1 mmol) were combined in that order and stirred at 60 °C for 1 h. The solvent was evaporated, the residue was taken up in water/$CHCl_3$ (15 mL of each), the aqueous phase was extracted again with $CHCl_3$ (10 mL), and the combined

(38) A 5% yield of styrene **42** resulting from decarboxylation of the cis acid was also obtained.
(39) Dey, B.; Rao, R.; Seshadri, T. *J. Indian Chem. Soc.* **1934**, *11*, 743.
(40) After 60 s at 210 °C the trans acid is decarboxylated to the styrene (66%) with the remaining 33% being starting material. If the reaction is allowed to continue, multiple products are observed, presumably arising from further reaction of the styrene.
(41) Sonnenberg, T. M. *J. Org. Chem.* **1970**, *35*, 3166.
(42) The initial reaction could be hydrolysis directly to the ketone or ring closure to the 5′-chloro-4′,5′-dihydrofuran.

extracts were washed with 1 M potassium carbonate (15 mL), dried, and evaporated. The residue (218 mg) was chromatographed on silica gel (2.0 g) with chloroform to give 213 mg (87%) of **13** which was recrystallized from $CHCl_3$/hexane: yield 105 mg; mp 158–160 °C; IR 1692, 1733 cm^{-1}; NMR δ 2.40 (3 H, d, J = 2), 4.75 (2 H, m), 5.2–6.4 (3 H, m), 6.15 (1 H, q, J = 2), 6.95 (1 H, d, J = 9), 7.75 (1 H, d, J = 9), 10.63 (1 H, s). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 5.0. Found: C, 69.2; H, 5.0.

7-[(β-Chloroallyl)oxy]-8-formyl-4-methylcoumarin (13a). Formylcoumarin **12** (780 mg, 3.82 mmol), DMF (16 mL), potassium fluoride (537 mg, 9.2 mmol, fused and powdered), and 2,3-dichloro-1-propene (646 mg, 5.8 mmol, freshly distilled) were combined in that order and stirred at 100 °C. After 7.5 h, additional KF (279 mg, 4.8 mmol) was added, and heating was continued for 3.5 h. The solvent was evaporated, the residue was taken up in water/$CHCl_3$ (50 mL of each), the aqueous phase was extracted again with $CHCl_3$ (50 mL), and the combined extracts were washed with 1 M Na_2CO_3 (50 mL), dried, and evaporated. The residue (851 mg) was chromatographed on Kieselgel (47 g) with $CHCl_3$ to yield a homogeneous fraction (559 mg, 52%). Recrystallization from $CHCl_3$/hexane yielded 308 mg of **13a**: mp 185–186 °C; IR 1695, 1733 cm^{-1}; NMR (Me_2SO-d_6) δ 2.42 (3 H, d, J = 2), 5.00 (2 H, br s), 5.77 (2 H, m with J_{gem} = 16), 6.33 (1 H, q, J = 2), 7.27 (1 H, d, J = 9), 8.02 (1 H, d, J = 9), 10.55 (1 H, s). Anal. Calcd for $C_{14}H_{11}O_4Cl$: C, 60.3; H, 4.0. Found: C, 60.2; H, 4.1.

6-(β-Chloroallyl)-8-formyl-7-hydroxy-4-methylcoumarin (14a). Allyl ether **13a** (138 mg, 0.5 mmol) and diisopropylbenzene (4.0 mL, distilled from Na) were stirred at reflux under argon for 11 h. The solvent was evaporated, and the residue was chromatographed on Kieselgel (18 g) with $CHCl_3$ to yield **14a** (70 mg, 50%), **12** (24 mg, 23%), **13a** (14 mg, 10%), and **15a** (12 mg, 10%), eluted in that order. Recrystallization from ethanol gave **14a**: mp 129–131 °C; IR 1644, 1732 cm^{-1}; NMR δ 2.45 (3 H, m), 3.75 (2 H, m), 5.33 (2 H, m), 6.22 (1 H, m), 7.71 (1 H, s), 10.66 (1 H, s), 12.63 (1 H, s). Anal. Calcd for $C_{14}H_{11}O_4Cl$: C, 60.3; H, 4.0. Found: C, 60.3; H, 4.1.

6-Allyl-8-formyl-7-hydroxy-4-methylcoumarin (14b). The conversion of allyl ether **13b** to **14b** was carried out in the same fashion as the conversion of **13a** to **14a** described above, giving **14b**: 60% yield; mp 161–162 °C; NMR δ 2.4 (3 H, d, J = 2), 3.45 (2 H, m), 5.0–6.2 (3 H, m), 6.2 (1 H, m), 7.6 (1 H, s), 10.6 (1 H, s), 12.5 (1 H, s); exact mass calcd for $C_{14}H_{12}O_4$ m/z 244.0736, found 244.0736.

6-(Formylmethyl)-8-formyl-7-hydroxy-4-methylcoumarin (21). With continuous stirring, to 6-allyl-8-formyl-7-hydroxy-4-methylcoumarin (**14b**; 1.72 g, 7.05 mmol) dissolved in ethyl acetate (60 mL) and water (50 mL) were added osmium tetraoxide (165 mg, 0.65 mmol) and, after 10 min, 2.95 g (13.8 mmol) sodium metaperiodate over an 80-min period. After 3 h, the mixture was extracted with $CHCl_3$ (3 × 50 mL), and the extracts were washed with water, dried, and evaporated to yield 990 mg (53.6%) of **21**: NMR δ 2.5 (3 H, d, CH_3), 3.9 (2 H, s), 6.3 (1 H, m, C-3 H), 7.6 (1 H, s, C-5 H), 9.8 (1 H, s), 10.7 (1 H, s); mass spectrum, m/z (relative intensity) 246 (M^+, 12), 218 (M^+ – CO, 55); exact mass calcd for $C_{13}H_{10}O_5$ m/z 246.0528, found 246.0528.

8-(5,5-Dimethyl-1,3-dioxan-2-yl)-7-hydroxy-4-methylcoumarin (16). A mixture of 0.95 g (4.6 mmol) of 7-hydroxy-8-formylcoumarin (**12**), 532 mg (4.66 mmol) of neopentylglycol, 0.7 mL of 85% H_3PO_4, 20 mg of $ZnCl_2$, and 12 mL of benzene was refluxed for 2 h with H_2O separation. The reaction mixture was taken up in $CHCl_3$ (25 mL), and the $CHCl_3$ was washed with water (3 × 25 mL) and saturated aqueous sodium chloride, dried, and evaporated to yield 1.12 g (80%) of acetal **16**: mp 192–197 °C; NMR δ 0.90 (3 H, s), 1.6 (3 H, s), 2.4 (3 H, d, J = 2), 3.9 (4 H, s), 6.23 (1 H, m), 6.37 (1 H, s), 7.0 (1 H, d, J = 9), 7.6 (1 H, d, J = 9); exact mass calcd for $C_{16}H_{18}O_5$ m/z 290.1154, found 290.1155.

7-(Allyloxy)-8-(5,5-dimethyl-1,3-dioxan-2-yl)-7-hydroxy-4-methylcoumarins (17). A mixture of 0.233 g (0.78 mmol) of **16**, 95 mg (0.78 mmol) of allyl bromide, 0.21 g (1.50 mmol) of anhydrous potassium carbonate, and 5 mL of acetone was refluxed for 5 h. Isolation was carried out as described above to yield 0.223 g (84%) of **17**: mp 177.5–178.5 °C; NMR δ 0.90 (3 H, s), 1.6 (3 H, s), 2.4 (3 H, d, J = 2), 3.9 (4 H, s), 4.8 (2 H, m), 5.2–6.2 (3 H, m), 6.23 (1 H, m), 6.37 (1 H, s), 7.0 (1 H, d, J = 9), 7.6 (1 H, d, J = 9); exact mass calcd for $C_{19}H_{22}O_5$ m/z 330.1467, found 330.1466.

6-Allyl-8-(5,5-dimethyl-1,3-dioxan-2-yl)-7-hydroxy-4-methylcoumarin (18a). Ether **17** (336 mg, 1.0 mmol) was heated neat at 210 °C for 3 h, applied to a PTLC plate, and eluted three times with CH_2Cl_2. Reverse-phase preparative HPLC (Altex 5-μm Ultrasphere column, isocratic 75% CH_3OH/25% H_2O, flow rate 3 mL min^{-1}) of the front-running material revealed two components with t_R's of 14 and 24 min. The fraction with t_R = 24 min, 80% of the front-running PTLC material (58% overall yield), gave NMR and HRMS spectra consistent with **18a**. The minor component had essentially the same mass spectrum as **18a**, and its NMR spectrum is consistent with **18b** (14%). Educt **17** (5%) and 8-allyl-4-methyl-7-hydroxycoumarin (**15b**, 12%) also were isolated.

15b: mp 198–199 °C (lit.[7c] mp 198–199 °C); NMR (CD_3OD) δ 2.43 (3 H, d, J = 2), 3.6 (2 H, m), 4.8–6.2 (3 H, m), 6.13 (1 H, m), 6.93 (1 H, d, J = 9), 7.53 (1 H, d, J = 9), 10.6 (1 H, s).

18a: NMR δ 0.9 (3 H, s), 1.4 (3 H, s), 2.4 (3 H, s), 3.4 (2 H, m), 3.8 (4 H, s), 5.1 (2 H, m), 6.0 (1 H, m), 6.1 (1 H, m), 6.3 (1 H, s, $HC(OR)_2$), 7.3 (1 H, s), 9.3 (1 H, s); exact mass calcd for $C_{19}H_{22}O_5$ m/z 330.1467, found 330.1465.

18b: NMR δ 0.9 (3 H, s), 1.3 (3 H, s), 2.4 (3 H, s), 3.5–4.0 (6 H, m), 5–5.4 (2 H, m), 5.6 (1 H), 5.9–6.1 (1 H, m), 6.12 (1 H, s), 7.36 (1 H, s), 8.64 (1 H, s); mass spectrum, m/z (relative intensity) 330 (66), 244 (100), 216 (72).

6-Acetonyl-8-formyl-7-hydroxy-4-methylcoumarin (20). Chloroalkene **14a** (836 mg, 3.0 mmol) was shaken with 70% (v/v) H_2SO_4 (15 mL) for 27 min, and the solution was added to water (105 mL) with vigorous stirring, keeping the temperature below 10 °C. The resulting mixture was extracted with $CHCl_3$ (2 × 50 mL), the combined extracts were washed with saturated $NaHCO_3$ (50 mL) and then extracted with cold 1 M NaOH (80 mL), the alkaline extracts was immediately neutralized to pH 5 with 3 M H_3PO_4 and extracted with $CHCl_3$ (2 × 40 mL), and the combined extractions were dried and evaporated to yield ketone **20**: 340 mg; NMR δ 2.32 (3 H, s), 2.42 (3 H, d, J = 2), 3.84 (2 H, s), 6.22 (1 H, m), 7.60 (1 H, s), 10.6 (1 H, s), 12.6 (1 H, s). The original organic layer contained both ketone **20** and psoralen **10**.

4,5′-Dimethyl-8-formylpsoralen (19). By use of the procedure described above, chloroalkene **14a** (139 mg, 0.5 mmol) was treated with 70% (v/v) H_2SO_4. The reaction solution was quenched in water, the mixture was extracted with $CHCl_3$, and the extracts were washed with saturated $NaHCO_3$, dried, and evaporated to yield a residue (141 mg) containing **19** and **20**. NMR spectral analysis indicated that about 75% of the mixture was ketone **20**. A portion of this mixture (10 mg) and 85% H_3PO_4 (0.1 mL) dissolved in diglyme (3.0 mL, distilled from CaH_2) were heated at reflux for 7 h. The cooled solution was diluted with $CHCl_3$ (15 mL), washed with water (15 mL) and saturated $NaHCO_3$ (15 mL), dried, and evaporated to yield a residue (7 mg) which was chromatographed on silica gel (350 mg) with $CHCl_3$, yielding 8-formylpsoralen **19**; 5 mg; NMR δ 2.53 (3 H, d, J = 2), 2.58 (3 H, d, J = 2), 6.39 (1 H, m), 6.54 (1 H, m), 7.97 (1 H, s), 10.9 (1 H, s); IR (Nujol) 1733, 1686 cm^{-1}; UV λ_{max} 240 nm (ϵ 20700), 292 (9700), 355 (5730); mass spectrum, m/z (relative intensity) 243 (10), 242 (M^+, 40), 214 (19), 213 (14), 186 (44), 185 (40), 43 (100); exact mass calcd for $C_{14}H_{10}O_4$ m/z 242.0579, found 242.0576.

8-Acetyl-7-hydroxy-4-methylcoumarin (24). 7-Hydroxy-4-methylcoumarin (**11**; 176 g, 1.0 mol) was converted as described[22] to 198 g (91%) of 7-acetoxy-4-methylcoumarin. The acetate (112 g, 0.51 mol, powdered) and $AlCl_3$ (254 g, 1.9 mol) gave a crude product which was recrystallized from 2.2 L of 95% EtOH to yield 67.3 g (60%) of material which contained 7% of 6-acetyl isomer **26**. Two more recrystallizations from 1.2 and 2.0 L of 95% EtOH gave 47.5 g (42%) of 8-acetyl isomer **24** free of 6-acetyl isomer **26**: mp 167–168 °C (lit.[22] mp 162–163 °C); NMR δ 2.45 (3 H, d, J = 2), 3.00 (3 H, s), 6.19 (1 H, m), 6.95 (1 H, d, J = 9), 7.73 (1 H, d, J = 9), 13.6 (1 H, s); UV λ_{max} 211 nm (ϵ 24000), 240 (sh), 268 (9300), 273 (9200), 312 (10500), 334 (9500).

8-Acetyl-7-hydroxycoumarin (25). By use of the procedure referred to above, 7-hydroxycoumarin (**23**; 162 g, 1.0 mol) was converted to the crude acetoxy derivative (200 g, 98%). This material (197 g, powdered) was converted as described above to crude product which was recrystallized from 95% EtOH (3.5 L) to yield crude **25** (137 g, 70%), free of the 6-acetyl isomer. It was chromatographed on silica gel (200 g), eluting with $CHCl_3$, and

then recrystallized from 95% EtOH (3.6 L) to yield 123 g (62%) of **25**: mp 167–168 °C (lit.[24] mp 167 °C); NMR δ 2.98 (3 H, s), 6.27 (1 H, d, J = 9), 6.90 (1 H, d, J = 9), 7.55 (1 H, d, J = 9), 7.67 (1 H, d, J = 9), 13.7 (1 H, s); UV λ_{max} 209 nm (ε 16800), 233 (8100), 242 (8400), 267 (8500), 317 (11600), 344 (sh, 8600).

8-Acetyl-7-[(β-chloroallyl)oxy]-4-methylcoumarin (28a). 8-Acetylcoumarin **24** (79.3 g, 0.364 mol) was dissolved in DMF (450 mL), and then benzene (450 mL), K_2CO_3 (100 g, 0.73 mol), KI (3.5 g, 0.02 mol), and 2,3-dichloro-1-propene (44.6 g, 0.40 mol, freshly distilled) were added in that order. The mixture was stirred at 85 °C for 6 h, cooled, and evaporated, and the residue was taken up in $CHCl_3$ (1 L) and water (1 L). The aqueous layer was extracted with $CHCl_3$ (200 mL), and the combined extracts were washed with cold 1 M NaOH (1 L) and saturated $NaHCO_3$ (0.8 L), dried, and evaporated. The residue in $CHCl_3$ (350 mL) was chromatographed on silica gel (500 g) with $CHCl_3$. The initial fractions (88.2 g) were recrystallized from 95% EtOH (700 mL) to yield 85.4 g (80%) of **28a**. The later fractions (10 g) and the mother liquor from the first recrystallization were combined, rechromatographed (60 g silica), and recrystallized (95 mL, 95% EtOH) to yield another 12.5 g of **28**: total yield 92%; mp 130–131 °C; NMR δ 2.42 (3 H, d, J = 2), 2.67 (3 H, s), 4.70 (2 H, m), 5.50 (2 H, m), 6.13 (1 H, m), 6.83 (1 H, d, J = 9), 7.52 (1 H, d, J = 9); UV λ_{max} 297 nm (ε 10900), 318 (15200). Anal. Calcd for $C_{15}H_{13}ClO_4$: C, 61.6; H, 4.5. Found: C, 61.6; H, 4.5.

8-Acetyl-7-[(β-chloroallyl)oxy]coumarin (29a). Coumarin **25** (51.0 g, 0.25 mol) was converted as described above to **29a**: 63.5 g (91%); mp 113–114 °C; NMR δ 2.67 (3 H, s), 4.73 (2 H, m), 5.60 (2 H, m), 6.32 (1 H, d, J = 9), 6.91 (1 H, d, J = 8), 7.53 (1 H, d, J = 8), 7.72 (1 H, d, J = 9); UV λ_{max} 304 nm (sh, ε 12300), 321 (14800). Anal. Calcd for $C_{14}H_{11}ClO_4$: C, 60.3; H, 4.0. Found: C, 60.3; H, 4.2.

8-Acetyl-6-(β-chloroallyl)-7-hydroxy-4-methylcoumarin (30a). [(Chloroallyl)oxy] coumarin **28a** (52.7 g, 0.18 mol) was heated at reflux in *p*-diisopropylbenzene (720 mL) for 8 h. The cooled reaction mixture was evaporated, and the residue was recrystallized from 95% EtOH (1.9 L) to give **30a**: 42.8 g (81%); fine yellow needles; mp 153–154 °C; IR 1733 (br), 1631 (br) cm^{-1}; NMR δ 2.42 (3 H, d, J = 2), 2.97 (3 H, s), 3.70 (2 H, br s), 5.24 (2 H, m), 6.10 (1 H, m), 7.59 (1 H, s), 14.6 (1 H, s); UV λ_{max} 226 nm (ε 13000, sh), 245 (9000, sh), 272 (10900), 276 (10700, sh), 311 (10000), 348 (10200). Anal. Calcd for $C_{15}H_{13}ClO_4$: C, 61.6; H, 4.5. Found: C, 61.7; H, 4.5.

8-Acetyl-6-(β-chloroallyl)-7-hydroxycoumarin (31a). [(Chloroallyl)oxy]coumarin **29a** (62.0 g, 0.22 mol) was heated in *p*-diisopropylbenzene (710 mL) at reflux for 11.5 h. The cooled mixture was evaporated, and the residue was recrystallized from 95% EtOH (500 mL) to yield material (53.8 g) which contained some of the 6-acetyl isomer as indicated by TLC. Two more recrystallizations, each from 95% EtOH (500 mL), gave **31a** (44.7 g, 72%) free of the 6-acetyl isomer as indicated by HPLC: mp 126–127 °C; IR 1736 (br), 1623 (br) cm^{-1}; NMR δ 2.97 (3 H, s), 3.70 (2 H, br s), 5.25 (2 H, m), 6.20 (1 H, d, J = 9), 7.44 (1 H, s), 7.57 (1 H, d, J = 9), 14.5 (1 H, s); UV λ_{max} 228 nm (sh, ε 10800), 234 (sh, 10400), 247 (9900), 271 (10000), 277 (sh, 9200), 319 (10900), 346 (10000), 353 (sh, 9900). Anal. Calcd for $C_{14}H_{11}ClO_4$: C, 60.3; H, 4.0. Found: C, 60.1; H, 4.2.

8-Acetyl-4,5′-dimethylpsoralen (44) and 6-Acetonyl-8-acetyl-7-hydroxy-4-methylcoumarin (46). (A) Coumarin **30a** (29.25 g, 0.10 mol) and 70% (v/v) sulfuric acid (700 mL of concentrated H_2SO_4/300 mL of water, 933 mL) were shaken for 40 min and then added to cold water (6.5 L), keeping the temperature below 20 °C. The mixture was extracted with two 750-mL portions of $CHCl_3$, and the combined extracts were washed with saturated $NaHCO_3$ (1 L) and then extracted twice with cold 1 M NaOH (1 and then 0.5 L). The combined alkaline extracts were immediately neutralized to pH 5 with 3.0 M H_3PO_4 (400 mL) with cooling to <20 °C. This mixture was extracted with $CHCl_3$ (2 × 500 mL), and the combined extracts were dried and evaporated to yield **46** (10.2 g, 37%). Recrystallization from 95% ethanol gave fine yellow needles: mp 173–174 °C; IR 1745 (sh), 1730, 1634 cm^{-1}; NMR δ 2.30 (3 H, s), 2.42 (3 H, d, J = 2), 2.97 (3 H, s), 3.82 (2 H, s), 6.17 (1 H, m), 7.56 (1 H, s), 14.1 (1 H, s); UV λ_{max} 213 nm (ε 23500), 246 (8600, sh), 273 (10300), 277 (10200, sh), 311 (9300), 348 (9500). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.7; H, 5.2. Found: C, 65.4; H, 5.2.

The organic layer which remained after the extraction with alkali was washed with saturated $NaHCO_3$ (500 mL), dried, and evaporated. The residue was recrystallized from 95% EtOH (320 mL) to give 13.5 g (53%) of **44**: mp 165–165.5 °C (lit.[20] mp 165–165.5 °C); IR 1730 (br), 1621 (br, w), 1587 (w) cm^{-1}; NMR δ 2.52 (6 H, br s), 2.84 (3 H, s), 6.26 (1 H, m), 6.48 (1 H, m), 7.77 (1 H, s); UV λ_{max} 238 nm (ε 24800), 240 (sh, 24600), 260 (15000), 287 (sh, 10800), 346 (7500).

(B) Coumarin **30a** (2.5 g, 8.5 mmol) and 50% H_2SO_4/HOAc (40 mL of concentrated H_2SO_4/40 mL of glacial acetic acid) were shaken for 45 min and then added with stirring to 400 mL of ice–water, keeping the temperature <15 °C. The aqueous layer was extracted with $CHCl_3$ (3 × 400 mL), and the combined extracts were washed with saturated $NaHCO_3$ and 1 M NaOH, dried, and evaporated to yield 2.04 g (94%) of **44**.

8-Acetyl-5′-methylpsoralen (45). Coumarin **31a** (106 mg, 0.38 mmol) and 70% (v/v) sulfuric acid (1.9 mL) were shaken for 25 min and then added dropwise to cold water (14 mL), keeping the temperature <15 °C. The resulting mixture was extracted with $CHCl_3$ (2 × 5 mL), the combined extracts were washed with saturated $NaHCO_3$ (20 mL) and then with cold 1 M NaOH (20 mL), and the alkaline extract was immediately neutralized to pH 5 with 3.0 M H_3PO_4 and extracted with $CHCl_3$ (2 × 10 mL). Both $CHCl_3$ extracts were then dried and evaporated separately. The alkali-soluble residue was ketone **47** (35 mg, 35%) and was not examined further. The residue containing neutral material (58 mg, 63%) was recrystallized from 95% EtOH (1 mL) to yield 36 mg (39%) of psoralen **45**: mp 149–150 °C; IR 1742, 1724 cm^{-1}; NMR δ 2.48 (3 H, d, J = 2), 2.85 (3 H, s), 6.37 (1 H, d, J = 9), 6.45 (1 H, m), 7.60 (1 H, s), 7.77 (1 H, d, J = 9); UV λ_{max} 236 nm (ε 24900), 240 (sh, 24000), 270 (15500), 295 (sh, 9800), 349 (6800). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.4; H, 4.2. Found: C, 69.5; H, 4.3.

8-Acetyl-6-allyl-7-hydroxycoumarin (31b). Allyl ether **29b**[19] (4.0 g, 16.4 mmol) was heated neat at 210 °C for 2.0 h. The cooled melt was recrystallized from 95% EtOH (60 mL) to yield 2.38 g (60%) of material which contained 1–2% of **32** (see below) as indicated by HPLC. Two more recrystallizations, each from 50 mL of 95% EtOH, yielded pure **31b**: 1.76 g (44%, 0.1% of **32**); mp 134–135 °C; (lit.[19] mp 127–128 °C); NMR δ 2.94 (3 H, s), 3.40 (2 H, m), 5.1 (2 H, m), 5.9 (1 H, m), 6.20 (1 H, d, J = 9.5), 7.33 (1 H, s), 7.56 (1 H, d, J = 9.5), 14.0 (1 H, s); UV λ_{max} 213 nm (ε 22200), 255 (9800), 272 (10000), 324 (10700), 347 (10000), 357 (sh, 9600).

8-Acetyl-6-(formylmethyl)-7-hydroxycoumarin (49) and 8-Acetyl-6-(formylmethyl)-7-hydroxy-4-methylcoumarin (48). 8-Acetyl-6-allyl-7-hydroxycoumarin (**31b**; 411 mg, 1.7 mmol) was dissolved in 100 mL of formic acid, and ozone was passed through the solution until the starting material was consumed [TLC (eluant, EtOAc/cyclohexane, 1/1 v/v) R_f (**31b**) 0.66, R_f (**49**) 0.47]. To the reaction mixture was added 160 mol % of Me_2S, and the mixture was left under N_2 for 12 h. A rapid flow of N_2 was then passed through the solution for 1.5 h, 50 mL of $CHCl_3$ and 50 mL of H_2O were added, and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The organic layer was washed (saturated $NaHCO_3$, 2 × 50 mL), dried, and evaporated to yield 362 mg (92% crude yield) of product. Recrystallization twice from MeOH yielded 63% of **49**: NMR δ 2.86 (s, 3 H), 3.7 (s, 2 H), 6.13 (d, 1 H, J = 10), 7.36 (s, 1 H), 7.53 (d, 1 H, J = 10), 9.6 (s, 1 H), 13.6 (s, 1 H); exact mass calcd for $C_{13}H_{10}O_5$ m/z 246.0528, found 246.0530.

8-Acetyl-6-allyl-7-hydroxy-4-methylcoumarin (**30b**)[20] was converted in a similar fashion to the corresponding 6-formylmethyl compound **48**: NMR δ 2.43 (3 H, d, J = 2), 3.0 (3 H, s), 3.8 (2 H, d, J = 2), 6.2 (1 H, m), 7.57 (1 H), 9.85 (1 H); exact mass calcd for $C_{14}H_{12}O_5$ m/z 260.0685, found 260.0683.

8-Acetyl-4-methylpsoralen (50) and 8-Acetylpsoralen (51). Conversion of the 6-(formylmethyl)-7-hydroxy compounds **48** and **49** to the corresponding furocoumarins can be accomplished with a number of acid catalysts such as 85% H_3PO_4, polyphosphoric acid, 70% (v/v) H_2SO_4, or methanesulfonic acid. The following is a typical example: 280 mg (1.07 mmol) of 6-(formylmethyl)-8-acetyl-7-hydroxy-4-methylcoumarin (**48**) was added to 6 mL of polyphosphoric acid, and the mixture was heated for 20 min at 100 °C with stirring. The mixture was then cooled to 20 °C, water and ice were added with vigorous stirring, it was extracted with $CHCl_3$, the extracts were combined, dried and

evaporated, and the residue was chromatographed on Kieselgel to yield 156 mg (60%) of **50**: mp 179–180 °C; NMR δ 2.53 (3 H, d, J = 2), 2.87 (3 H, s), 6.33 (1 H, m), 6.90 (1 H, d, J = 3), 7.80 (1 H, d, J = 3), 7.97 (1 H, s). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.4; H, 4.2. Found: C, 69.5; H, 4.2. 8-Acetyl-6-(formylmethyl)-7-hydroxycoumarin (**49**) was converted in a similar fashion to the corresponding psoralen **51**: mp 207–208 °C (lit.[19] mp 206–207 °C); NMR δ 2.82 (3 H, s), 6.32 (1 H, d, J = 9), 6.78 (1 H, d, J = 2), 7.72 (1 H, d, J = 2), 7.74 (1 H, s), 7.77 (1 H, d, J = 9).

Isolation of Byproducts from Claisen Rearrangement of 29b. A portion of the mother liquor from the first recrystallization of the crude product resulting from Claisen rearrangement of **29b** was evaporated to a residue (0.61 g) which was chromatographed on Kieselgel (30 g) with ethyl acetate. A fraction containing only the major components was evaporated, and the residue (0.17 g) was rechromatographed on Kieselgel (10 g) with ethyl acetate/CH_2Cl_2 (1/4 v/v) to give pure fractions. One of these was the 6-allylcoumarin **31b**. Another appeared from its NMR spectrum to be the 8-allyl isomer **32**, which was confirmed by synthesis as described below. A third rfraction was 8-allyl-7-hydroxycoumarin (**33**), and its characterization was confirmed by chromatographic (TLC, GC, HPLC) comparison with authentic material prepared as described below.

Another portion of mother liquor was evaporated to a residue (0.24 g) which was taken up in $CHCl_3$ (15 mL) and extracted with cold 1 M NaOH (3 × 15 mL). The combined alkaline extracts were immediately neutralized to pH 5 with 3.0 M H_3PO_4 and extracted with $CHCl_3$ (25 mL). Both $CHCl_3$ solutions were dried and evaporated separately to yield from the neutral fraction 102 mg of product and from the phenolic fraction 122 mg of product. The neutral fraction residue was chromatographed on Kieselgel with $CHCl_3$ to yield **29b** and two other compounds which appeared from their NMR spectra to be **34** and **35**. The properties of **34** and the synthesis and properties of **35** are described below.

Isolation of 6-Acetyl-7-hydroxycoumarin (27). Mother liquors containing 7-hydroxycoumarin (**23**), **25**, and **27** (60 g, obtained from recrystallization of the crude product from Fries rearrangement of 7-acetoxycoumarin) were chromatographed on silica gel (250 g) with $CHCl_3$ to yield 34.4 g of a mixture of **25** and **27** (60/40, as indicated by the NMR). A portion of this mixture (10 g) was dissolved in $CHCl_3$ (245 mL), extracted with 2.0 M Na_2CO_3 (3 × 245 mL), washed with saturated $NaHCO_3$ (100 mL), dried, and evaporated to a residue of 1.66 g, containing 65% of **27**. This sample, combined with another sample (0.98 g) of similar composition, was dissolved in 65 mL of $CHCl_3$ and further extracted with 2 M Na_2CO_3 (2 × 65 mL). Material further enriched in **27** was recovered as described above to yield 0.98 g of residue. HPLC showed this residue to contain **25** (25%) and **27** (68%). Preparative chromatography on Kieselgel with $CHCl_3$ and crystallization from 95% EtOH yielded 196 mg of **27**: mp 173–174 °C (lit.[25] mp 177 °C); NMR δ 2.68 (3 H, s), 6.27 (1 H, d, J = 9.5), 6.82 (1 H, s), 7.60 (1 H, d, J = 9.5), 7.85 (1 H, s), 12.7 (1 H, s); UV λ_{max} 207 nm (ε 11 100), 227 (14 100), 256 (29 200), 309 (10 500), 341 (11 600).

6-Acetyl-7-(allyloxy)coumarin (36). 6-Acetyl-7-hydroxycoumarin (**27**; 153 mg, 0.75 mmol), acetone (7.5 mL), allyl bromide (0.19 g, 1.6 mmol), and K_2CO_3 (0.28 g, 2.0 mmol) were stirred at reflux for 5.5 h. The cooled reaction mixture was evaporated and the residue taken up in $CHCl_3$ (25 mL) and water (25 mL). The aqueous layer was extracted again with $CHCl_3$ (15 mL), and the combined extracts were washed with cold 1 M NaOH (25 mL) and saturated $NaHCO_3$ (25 mL), dried, and evaporated to a residue which was chromatographed on silica gel (2.5 g) with $CHCl_3$. The major fraction (175 mg, 96%) was recrystallized from 95% EtOH (5 mL) to yield 112 mg (61%) of **36**: mp 138–139 °C; NMR δ 2.69 (3 H, s), 4.73 (2 H, m), 5.5 (2 H, m), 6.0 (1 H, m), 6.30 (1 H, d, J = 9.5), 6.87 (1 H, s), 7.69 (1 H, d, J = 9.5), 7.93 (1 H, s); UV λ_{max} 217 nm (ε 18 100), 253 (22 300), 307 (12 600), 328 (14 100). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 5.0. Found: C, 68.9; H, 5.1.

6-Acetyl-8-allyl-7-hydroxycoumarin (32). Allyl ether **36** (85 mg, 0.35 mmol) was heated in *N,N*-diethylaniline (6 mL) at reflux for 3 h, the solvent was evaporated, and the residue (84 mg) on HPLC showed the presence of five components: major components **32** (t_R = 4.6 min) and **31b** (t_R = 2.3 min), confirmed by coinjection of authentic material, and three minor components, with t_R = 2.1, 2.8, and 3.2 min. The relative yields, in order of elution and assuming equal extinction coefficients at 310 nm, were 0.7%, 5.7%, 1.4%, 2.1%, and 90.0%.

The crude residue was crystallized twice from 95% EtOH to give **32**: 20 mg (23%); mp 157–158 °C; NMR δ 2.72 (3 H, s), 3.60 (2 H, m), 5.08 (2 H, m), 5.9 (1 H, m), 6.22 (1 H, d, J = 9.5), 7.62 (1 H, d, J = 9.5), 7.80 (1 H, s), 13.4 (1 H, s); UV λ_{max} 228 nm (ε 14 300), 263 (34 700), 308 (sh 11 400), 326 (11 900), 347 (11 600). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 5.0. Found: C, 69.0; H, 5.2.

8-Allyl-7-hydroxycoumarin (33). 7-Hydroxycoumarin (**23**; 1.075 g, 6.63 mmol) was converted to 7-(allyloxy)coumarin (**37**) as described:[27] 74% yield; mp 84–85 °C (lit.[27] mp 79–80 °C). 7-(Allyloxy)coumarin (**37**, 0.77 g) was in turn heated at reflux in *N,N*-diethylaniline for 4 h. When the mixture was allowed to stand at room temperature, the product precipitated and was recrystallized from absolute EtOH (2 mL), giving 0.322 g of **33**: mp 162.5–164 °C (lit.[27] mp 162–163 °C); UV λ_{max} 252 nm (63 800), 260 (4200), 339 (16 300).

8-Acetyl-6-allyl-7-acetoxycoumarin (35): mp 95.5–96 °C; NMR 2.37 (3 H, s), 2.75 (3 H, s), 3.4 (2 H, m), 5.3 (2 H, m), 5.9 (1 H, m), 6.5 (1 H, m), 6.5 (1 H, d, H-3, J = 9), 7.5 (1 H, H-5), 7.7 (1 H, d, H-4, J = 9); mass spectrum, m/z (relative intensity) 286 (M^+, 55), 249 (100). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 67.4; H, 4.9. The identical compound was obtained in quantitative yield by refluxing **31b** in acetic anhydride for 10 min.

8-Acetyl-8-allyl-7-oxo-7,8-dihydrocoumarin (34): mp 91.5–92 °C; NMR δ 2.38 (3 H, s), 3.65 (2 H, m), 5.2 (2 H, m), 6.0 (1 H, m), 6.45 (1 H, d, H-3, J = 9), 7.1 (1 H, d, H-6, J = 9), 7.45 (1 H, d, H-5, J = 9), 7.8 (1 H, d, H-4, J = 9); exact mass calcd for $C_{14}H_{12}O_4$ m/z 244.0736, found 244.0737.

8-(β-Chloroallyl)-7-hydroxy-4-methylcoumarin (15a) and Other Products Formed on Heating 28a. The mother liquors from recrystallization of the crude product resulting from heating **28a** in *p*-diisopropylbenzene were evaporated and recrystallized from 95% EtOH (100 mL). These crystals (5.60 g, a mixture of three components) constitute sample a. The mother liquor was evaporated, the residue was taken up in $CHCl_3$ (90 mL) and MeOH (1 mL), this solution was washed with cold 1 M NaOH (1 × 75 mL, 2 × 50 mL), the alkaline extract was immediately neutralized to pH 5 with 3.0 M H_3PO_4 (35 mL) and extracted with $CHCl_3$ (50 mL, 30 mL), and the combined, dried $CHCl_3$ extracts were evaporated.

The $CHCl_3$ solution which had been washed with alkali was washed with saturated $NaHCO_3$ (50 mL), dried, and evaporated to yield 2.0 g (4%) of educt **28a**.

The residue containing alkali-soluble material was taken up in $CHCl_3$ (30 mL) and filtered to remove an insoluble residue (200 mg, sample b). The filtrate was evaporated, and the residue was chromatographed on silica (15 g) with $CHCl_3$ to give front-running fractions and material (60 mg) identical with sample b which was added to sample b (combined mass 0.26 g, 0.6%) and crystallized from 95% EtOH (5 mL) to yield **15a** (identical by spectral and chromatographic comparison with **15a** obtained from Claisen rearrangement of 8-formyl ether **13a**): mp 213–214 °C dec; single blue fluorescent spot on TLC ($CHCl_3$), R_f 0.2); IR (Nujol) 1684 cm^{-1}; NMR ($CDCl_3$, CD_3OD) δ 2.43 (3 H, d, J = 2), 3.92 (2 H, m), 5.14 (2 H, m, J_{gem} = 9), 6.15 (1 H, m), 6.92 (1 H, d, J = 9), 7.50 (1 H, d, J = 9); UV λ_{max} 248 nm (ε 4200), 258 (4500), 326 (15 400). Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.3; H, 4.4. Found: C, 62.0; H, 4.5.

The combined early fractions from the chromatography were evaporated, and the residue was chromatographed on Kieselgel (17 g) with CH_2Cl_2. Initial (sample c), middle (sample d), and late fractions were collected. The latter on recrystallization from 95% EtOH (5 mL) yielded **24** (416 mg), identical with authentic material.

Detailed TLC and NMR analysis of all other fractions and samples led to the conclusion that the products formed in the Claisen rearrangement of **28a** are as follows: **30a**, 86%; **38**, 5% [NMR δ 2.45 (3 H, J = 2), 2.72 (3 H, s), 3.87 (2 H, br s), 5.10 (2 H, m), 6.12 (1 H, m), 7.92 (1 H, s), 13.4 (1 H, s)]; **24**, 3%; educt **28a**, 4%; **15a**, 1%.

3-Acetyl-4-(allyloxy)-β-methylcoumarinic Acid (39). 8-Acetyl-7-(allyloxy)-4-methylcoumarin (**28b**; 3.37 g, 13.1 mmol) was

heated with 40 mL of 5% sodium hydroxide to complete dissolution, and the solution at 0 °C was carefully acidified and immediately extracted with chloroform (3 × 50 mL). The combined, dried extracts were evaporated to yield 3.34 g (92%) of **39**: mp 128 °C; NMR δ 2.2 (3 H, d, J = 2), 2.75 (3 H, s), 4.6 (2 H, m), 5.2–6.2 (3 H, m), 5.95 (1 H, m), 6.35 (1 H, d, J = 9), 7.12 (1 H, d, J = 9), 13.6 (1 H, s); exact mass calcd for $C_{15}H_{16}O_5$ m/z 276–0998, found 276.0996.

3-Acetyl-4-(allyloxy)-β-methyl-*o*-coumaric Acid (41). A solution of 8-acetyl-7-(allyloxy)-4-methylcoumarin (**28b**, 1.025 g) in 60 mL of 0.2 M sodium hydroxide was boiled for 1 h with powdered red HgO (72 mg). The mercury was precipitated with H_2S, and the filtrate was treated as in the isolation of coumarinic acid **39**. The product was recrystallized twice from 95% EtOH to yield 0.85 g (78%) of **41**: mp 154–155 °C; NMR δ 2.53 (3 H, d, J = 2), 2.72 (3 H, s), 4.65 (2 H, m), 5.4–6.2 (3 H, m), 5.98 (1 H, m), 6.38 (1 H, d, J = 9), 7.28 (1 H, d, J = 9), 13.7 (1 H, s). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.2; H, 5.8. Found: C, 65.4; H_2 6.0.

2-Hydroxy-3-acetyl-4-(allyloxy)-α-methylstyrene (42). When coumaric acid **41** was heated at 210 °C, the initial product formed was styrene **42**: NMR δ 2.13 (3 H, m), 2.7 (3 H, s), 4.6 (2 H, m), 5.08–6.2 (5 H, m), 6.38 (1 H, d), 7.3 (1 H, d); mass spectrum, m/z (relative intensity) 232 (M^+, 10), 191 ($M - C_3H_5$, 100); exact mass calcd for $C_{14}H_{16}O_3$ m/z 232.1099, found 232.1098.

Reaction of Diethylaluminum Chloride with Coumarinic Acid 39 To Produce 30b. To 250 mg (0.9 mmol) of 3-acetyl-4-(allyloxy)-β-methylcoumarinic acid (**39**) in 3.0 mL of $CHCl_3$ was added 5.4 mmol of diethylaluminum chloride (DEAC, as a 25% solution in heptane). After being stirred for 3 h, the reaction mixture was cooled to 5 °C and hydrolyzed with dilute HCl. The aqueous phase was extracted with chloroform (3 × 15 mL), and the combined dried extracts were evaporated to yield 203 mg (87%) of pure 8-acetyl-6-allyl-7-hydroxy-4-methylcoumarin (**30b**): mp 133–134 °C (lit.[20] mp 134 °C); NMR δ 2.5 (3 H, d, J = 2), 3.0 (3 H, s), 4.55 (2 H, m), 5–6.2 (3 H, m), 6.2 (1 H, m), 7.6 (1 H, s), 15.4 (1 H, s).

4,5′-Dimethylpsoralen-8-acetic Acid (54). A mixture of 8-acetyl-4,5′-dimethylpsoralen (**44**; 645 mg, 2.5 mmol), sulfur (80 mg, 2.5 mmol), and 2 mL of morpholine was heated at reflux for 4 h after which the morpholine was evaporated, 10 mL of a mixture of glacial acetic acid, concentrated H_2SO_4, and water (80/12/18 v/v/v) was added, and refluxing was continued for 6 h. To the cooled mixture was added 40 mL water, and it was extracted with $CHCl_3$/isopropyl alcohol (IPA) (5/1, 4 × 50 mL). The organic layer was evaporated to 100 mL and extracted with saturated $NaHCO_3$ (4 × 60 mL), and the aqueous layer was then acidified with 6 N HCl to pH 1 and extracted with $CHCl_3$/IPA (5/1, 4 × 60 mL). The final organic extracts were combined, washed with water and saturated NaCl, dried, and evaporated to yield 380 mg (56%) of **54** which was crystallized from 95% ethanol: mp 284–286 °C dec; NMR δ 2.5 (6 H, m), 4.2 (2 H, s), 6.3 (1 H, m), 6.5 (1 H, m), 7.7 (1 H, m).

Methyl 4,5′-Dimethylpsoralen-8-acetate (55). To 544 mg (2 mmol) of the 8-acetic acid **54** in 10 mL of $CHCl_3$ was added thionyl chloride (6 mmol), and the mixture was stirred at 20 °C for 1 h and then at reflux for 3.5 h after which the solution was evaporated. The residue was dissolved in $CHCl_3$ and evaporated, repeating this solution–evaporation four times. To the residue in $CHCl_3$ were added a large excess of MeOH, and the solution was refluxed for 1 h, washed with water and saturated NaCl, dried, and evaporated to yield 457 mg (80%) of the methyl ester **55**: mp 176–178 °C; NMR δ 2.47 (6 H, m), 3.8 (3 H, s), 4.25 (2 H, s), 6.3 (1 H, m), 6.5 (1 H, m), 7.62 (1 H, m). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 67.4; H, 4.9.

8-(β-Hydroxyethyl)-4,5′-dimethylpsoralen (56). To a solution of 272 mg (1.0 mmol) of acid **54** in 5 mL dry THF cooled to 0 °C was added 1 mL (1.0 mmol) of 1 M borane solution in THF. The ice bath was replaced by a water bath at 25 °C, and after 1 h ice–water (5 mL) was added, the solution was extracted with $CHCl_3$ (4 × 5 mL), and the combined $CHCl_3$ extracts were shaken with aqueous $NaHCO_3$ (3 × 20 mL). The aqueous phase was acidified with dilute HCl and then extracted with $CHCl_3$/IPA (5/1, 4 × 40 mL) to yield 130 mg (48%) of unreacted **54**. The original organic layer was dried and evaporated to yield 123 mg (92% based on reacted **54**) of 8-(β-hydroxyethyl)-4,5′-dimethylpsoralen (**56**): mp 205–207 °C; NMR δ 2.5 (6 H, m), 3.45 (2 H, t), 4.1 (2 H, t), 6.25 (1 H, m), 6.45 (1 H, m), 7.6 (1 H, m). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.7; H, 5.4. Found: C, 69.7; H, 5.4.

8-(α-Hydroxyethyl)-4,5′-dimethylpsoralen (52). To 280 mg (1.08 mmol) of 8-acetyl-4,5-dimethylpsoralen (**44**) dissolved in 3 mL of ethanol was added sodium borohydride (0.27 mmol). After 10 min, 5 mL of methanol was added, and the solvents were evaporated. This addition–evaporation was repeated two more times, and the residue was then partitioned between methylene chloride and water. The organic phase was dried and evaporated to yield 270 mg (96%) of **52**: mp 217–218 °C; NMR δ 1.77 (3 H, d, J = 7), 2.48 (3 H, s), 2.51 (3 H, s), 5.7 (1 H, m), 6.24 (1 H, m), 6.43 (1 H, m), 7.59 (1 H, s). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.8; H, 5.4. Found: C, 69.8; H, 5.5.

8-(α-Aminoethyl)-4,5′-dimethylpsoralen (53). A solution of 285 mg (1.1 mmol) of 8-acetyl-4,5′-dimethylpsoralen (**44**) in formamide (2 mL) and formic acid (96%, 0.2 mL) was heated at 165 °C for 2 h, 10 mL of 6 N HCl was added, and the solution was heated at 80 °C for 30 min. The cooled solution was brought to pH 12 with concentrated sodium hydroxide then extracted twice with equal volumes of $CHCl_3$. Drying and evaporating the $CHCl_3$ left a residue which was chromatographed on silica, eluting with ethyl acetate, to yield 157 mg (60%) of **53**: mp 198 °C; NMR δ 1.73 (3 H, d, J = 7), 2.49 (3 H, s), 2.51 (3 H, s), 4.95 (1 H, q), 6.22 (1 H, m), 6.42 (1 H, m), 7.57 (1 H, s). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 69.5; H, 6.6. Found: C, 69.6; H, 6.6.

8-[[(Benzyloxycarbonyl)amino]methyl]-4,5′-dimethylpsoralen (57). A solution of 150 mg (0.55 mmol) of the 8-acetic acid **54** and 151 mg (0.55 mmol) of diphenylphosphoryl azide in 15 mL of dry benzene was concentrated to 5 mL, and triethylamine (0.55 mmol) was then added. After 3 h at 25 °C, the temperature was raised to 80 °C, after 2.5 h, 1000 mol % of dry benzyl alcohol was added, and reflux was continued for 10 h. The solution was cooled and washed successively with aqueous $NaHCO_3$, water, and saturated NaCl. The dried organic phase was evaporated, and the residue was chromatographed (5 g of TLC grade Kieselgel) with $CHCl_3$/MeOH (98/2) as the eluent to yield 107 mg (52%) of carbamate **57** which was recrystallized from $CHCl_3$/hexane: mp 174 °C; NMR δ 2.58 (6 H, m), 4.96 (2 H, d, J = 6), 5.2 (2 H, s), 6.24 (1 H, m), 6.5 (1 H, m), 7.65 (1 H, m). Anal. Calcd for $C_{22}H_{19}O_5N$: C, 70.0; H, 5.1; N, 3.7. Found: C, 69.9; H, 5.1; N, 3.7.

8-(Aminomethyl)-4,5′-dimethylpsoralen (58). A saturated solution (3 mL) of HBr in glacial acetic acid was added to 30 mg (0.079 mmol) of the carbamate **57**, and after 1 h 10 mL of ether was added. The supernatant was discarded, and the solid residue was triturated with 5 mL of ether four times. The amine hydrobromide was then dissolved in 2 mL of H_2O, 2 mL of 0.2 M NaOH was added along with 4 mL of $CHCl_3$, the phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 4 mL). After the combined $CHCl_3$ extracts were dried and evaporated, there was obtained 17 mg (89%) of **58** which was chromatographed on silica gel: mp 177–178 °C; NMR δ 1.37 (2 H, s), 2.5 (6 H, m), 4.4 (2 H, s), 6.3 (1 H, m), 6.5 (1 H, m), 7.62 (1 H, m); exact mass calcd for $C_{14}H_{13}NO_2$ m/z 243.0895, found 243.0894.

4,5′-Dimethyl-8-(hydroxymethyl)psoralen (60) and 4,5′-Dimethyl-8-(acetoxymethyl)psoralen (59). To 100 mg (41 mmol) of the 8-(aminomethyl)psoralen **58** dissolved in 4 mL of glacial acetic acid and 0.75 mL of water and cooled to 0–5 °C was added a concentrated aqueous solution of $NaNO_2$ (0.49 mmol). After the evolution of nitrogen ceased, the solution was heated for 30 min on a steam bath, made alkaline, and extracted with chloroform (3 × 10 mL), after which the chloroform layer was dried and evaporated to yield a mixture of the alcohol **60** (42%) and the acetate **59** (40%). The acetate was readily converted to the alcohol by treatment with 0.1 N KOH in EtOH for 2 h.

Alcohol **60**: mp 250–251 °C; NMR δ 2.45 (3 H, d), 5.2 (2 H, s), 6.25 (1 H, m), 6.45 (1 H, m), 7.66 (1 H, s); exact mass calcd for $C_{14}H_{12}O_4$ m/z 244.0736, found 244.0734.

Acetate **59**: mp 198 °C; NMR δ 2.1 (3 H, s), 2.45 (3 H, d), 5.6 (2 H, s), 6.25 (1 H, m), 6.45 (1 H, m), 7.68 (1 H, s); exact mass calcd for $C_{16}H_{14}O_5$, m/z 286.0841, found 286.0843.

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Registry No. 11, 90-33-5; 11 acetate, 2747-05-9; 12, 14003-96-4; 13a, 86290-39-3; 13b, 86290-40-6; 14a, 86290-41-7; 14b, 86290-42-8; 15a, 86290-43-9; 15b, 1616-54-2; 16, 86290-44-0; 17, 86290-45-1; 18a, 86290-46-2; 18b, 86290-47-3; 19, 86290-48-4; 20, 86290-49-5; 21, 86290-50-8; 23, 93-35-6; 23 acetate, 10387-49-2; 24, 2555-29-5; 25, 6748-68-1; 27, 6835-55-8; 28a, 86290-51-9; 29a, 86290-52-0; 29b, 72939-36-7; 30a, 86290-53-1; 30b, 86290-54-2; 31a, 86290-55-3; 31b, 86290-56-4; 32, 86290-57-5; 33, 55136-72-6; 34, 86290-58-6; 35, 86290-59-7; 36, 86290-60-0; 38, 86290-61-1; 39, 86290-62-2; 41, 86290-63-3; 42, 86290-64-4; 44, 14256-46-3; 45, 86290-65-5; 46, 86290-66-6; 47, 86290-67-7; 48, 86290-68-8; 49, 86308-27-2; 50, 86290-69-9; 51, 86290-70-2; 52, 86290-71-3; 53, 86290-72-4; 54, 86290-73-5; 55, 86290-74-6; 56, 86290-75-7; 57, 86290-76-8; 58, 86290-77-9; 59, 86290-78-0; 60, 86290-79-1; 2,3-dichloro-1-propene, 78-88-6; neopentyl glycol, 126-30-7.

Halogenation of Pyrimidine 6-*O*-Cyclonucleosides

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Pyrimidine 6-*O*-cyclonucleosides (**1**, **5**, **8**, **11**, and **15**) were treated with halogen (Cl_2, Br_2, or I_2) or *N*-halosuccinimide to afford the corresponding 5-monohalogeno derivatives (**2**, **6**, **9**, and **12**), together with a novel type of 6,2′:6,5′-, 6,3′:6,5′-, and 6,2′:6,3′-dianhydro-5,5-dihalo-5,6-dihydro-6,6-dihydroxyuracil nucleosides (**3**, **7**, **13**, and **16**). The structure of each dihalogeno compound was elucidated on the basis of elemental analysis, mass spectrum, and proton magnetic resonance spectrum. The ease of an additional cyclization of pyrimidine 6-*O*-cyclonucleoside depends on the close proximity of the nucleophilic hydroxyl group in the sugar moiety to C-6 in the pyrimidine base. The mass spectra of these halogeno compounds were also discussed.

Halopyrimidine nucleosides provide useful pathways to a wide variety of interesting nucleoside analogues.[1] In addition, some of them have potent medicinal properties; 5-iododeoxyuridine[2] and 1-(tetrahydro-2-furanyl)-5-fluorouracil[3] have been used clinically as antiviral and antitumor agents, respectively. As part of our program concerned with the synthesis and biological test of pyrimidine 6-*O*-cyclonucleosides,[4] we report halogenation of these nucleosides, which led to monohalogeno derivatives, together with a novel type of dihalogeno nucleosides possessing two oxygen bridges between the base and the sugar.

I. Bromination of Pyrimidine 6-*O*-Cyclonucleosides

Reaction of 6,2′-*O*-cyclouridine[5] (**1a**) with bromine water[6] at room temperature afforded two products. A major compound was isolated from the reaction mixture in 46% yield, which had a molecular formula $C_9H_8N_2O_6Br_2$ on the basis of elemental analysis and mass spectrum (MS). It had no ultraviolet (UV) absorption maximum in the B_{2U} region, showing the loss of the 5,6 double bond of the pyrimidine base. The proton magnetic resonance (^1H NMR) spectrum (Me_2SO-d_6) revealed that the two C-5′ protons were shifted downfield[7] compared with those of **1a** and upfield[8] compared with those of 8 and could be analyzed as the AB part of an ABX spin system due to the coupling with C-4′ proton.[7] The C-2′ proton was shifted upfield[8] compared with that of **1a**. The structure was thus established as 6,2′:6,5′-dianhydro-1-(β-D-arabinofuranosyl)-5,5-dibromo-5,6-dihydro-6,6-dihydroxyuracil (**3a**). This is the first example of a novel type of cyclonucleoside with two oxygen bridges between the base and the sugar, starting from the mono-*O*-cyclonucleoside.[9] A minor compound was isolated by successive treatment of the mother liquor in 32% yield, which was identified as the 5-bromo derivative **2a** on the basis of elemental analysis ($C_9H_9N_2O_6Br \cdot {}^1/_2H_2O$) and MS ($m/z$ 320, 322 (M^+)). A plausible mechanism for the formation of **3a** is as follows. An additional bromination at the 5-position of the intermediate **2a** would be initiated by an electrophilic attack of the bromonium cation on the 5,6 double bond of the pyrimidine base, followed by nucleophilic attack of the 5′-hydroxyl group on the electron-deficient 6-position (trans addition), which would result in the intramolecular 6,5′-*O*-cyclization. This interpretation receives support from the fact that the reaction of **2a** with bromine water leads to the formation of **3a**. The ease of intramolecular nucleophilic attack of the 5′-hydroxyl group on C-6 might depend on the close proximity of the two groups. Reaction of **1a** with a small excess of *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) at room temperature provided **3a** as a sole product in 52% yield. Reaction of 6,2′-*O*-cyclocytidine (**1b**) with bromine water did not afford the corresponding dibromo derivative (**4**), but **3a**. Such a deamination would be due to susceptibility of the intermediate **4** to deamination.[10]

A similar bromination of 6,3′-*O*-cyclouridine (**5**) with bromine water gave two compounds in yields of 5.3% and 75%, respectively, which were assigned 5-bromo-6,3′-*O*-cyclouridine (**6a**) and 6,3′:6,5′-dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-xylofuranosyl)uracil (**7a**), respectively, based on the elemental analyses, the ^1H NMR spectra, and the mass spectra. The structure of **7a** was

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