Reactions of Furocoumarins. I. 4,5′,8-Trimethylpsoralene

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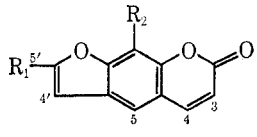
Several reactions of the photosensitizing drug 4,5′,8-trimethylpsoralene (IV) have been studied. Nitration, chlorosulfonation, and bromination all take place by initial substitution of the furan ring β hydrogen. A second nitro group is introduced in the benzene ring (5 position), whereas the second bromine atom is introduced in the 3 position of the pyrone ring. Chromic acid oxidation and catalytic hydrogenation both involve primary attack on the furan double bond, although continued hydrogenation also reduces the pyrone double bond. As expected, alkali opens the pyrone ring, which enables methylation of the pyrone ring oxygen to occur. Bromination of 4′,5′-dihydro-4,5′,8-trimethylpsoralene (V) gives a 3-bromo derivative (VII) which can be dehydrogenated.

The potent dermal photosensitizing activity of psoralene (I) and many of its derivatives is well known and is the basis for their clinical use to treat vitiligo as well as to encouraging sun tanning and to prevent sun burning.[2] Several methods for the synthesis of psoralenes have been developed. Although some studies have been devoted to their photochemical reactivity,[3] very little has been reported about the chemical behavior of the psoralenes, beyond degradative reactions employed in structure proofs.[3] Xanthotoxin (8-methoxypsoralene, II) has been shown[4] to undergo substitution (*e.g.*, nitration, chlorosulfonation, or halogenation) in the 5 position and addition (*e.g.*, hydrogenation) to the 4′,5′ double bond. It is likely, however, that the methoxy group alters the inherent reactivity of the basic ring system, particularly in view of the report[5] that anhydromarmesin (5′-isopropylpsoralene, III) is probably brominated in the 4′ position.



I, $R_1 = R_2 = H$
II, $R_1 = H$; $R_2 = OCH_3$
III, $R_1 = i\text{-}C_3H_7$; $R_2 = H$

At this time, we wish to report the results of a study of the chemistry of 4,5′,8-trimethylpsoralene (IV), which is available in large quantity by synthesis[6] and is currently the psoralene derivative most employed for the treatment of vitiligo and sun sensitivity in the United States.[7] Its natural occurrence has been reported in celery diseased with the fungus *Sclerotinia sclerotiorum*,[8] but no other natural source has been reported.

Hydrogenation of IV, over 5% palladium on charcoal, gave 72% 4′,5′-dihydro derivative V after chromatographic separation from small amounts of the tetrahydro derivative VI and unreacted starting material. Structure V was easily assigned on the basis of the intensive ultraviolet (uv) absorption peak at 335 mμ, characteristic[4a] of coumarins and furocoumarins in which the pyrone ring double bond is intact. Corroboration was found in the infrared (ir) spectrum, which showed the two carbonyl absorption bands (not completely resolved) characteristic[9] of α-pyrones. Reduction of IV with 2 molar equiv of hydrogen gave the tetrahydro derivative VI. Its uv spectrum contained no absorption peaks beyond 300 mμ, indicating[4a] the absence of the pyrone ring double bond. To obtain a monobromo derivative of known structure, the dihydro compound V was brominated. The product, obtained in 83% yield, was assigned the structure of 3-bromo-4′,5′-dihydro-4,5′,8-trimethylpsoralene (VII) on the basis of its nuclear magnetic resonance (nmr) spectrum which, upon integration, showed one aromatic proton (C_5; see Table I) and twelve aliphatic protons. Furthermore, VII underwent rearrangement upon treatment with aqueous potassium hydroxide to give the furocoumarilic acid VIII, which confirms the assignment of the bromine atom to the 3 position. Dehydrogenation of VII over 5% palladium on charcoal in refluxing diphenyl ether was attempted but led to a mixture of at least six compounds observable on a thin layer chromatogram. Heating VII with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[10] in dry chlorobenzene gave better results and led to pure 3-bromo-4,5′,8-trimethylpsoralene (IX) of mp 240–241.5°. (See Scheme I.)

Direct bromination of 4,5′,8-trimethylpsoralene (IV) was carried out to determine whether the product was identical with the 3-bromo derivative IX already synthesized indirectly. A monobromo compound was obtained in 80% yield. Although its melting point (248–249°) was close to that of IX, nmr and ir spectra and mixture melting point clearly showed it to be 4′-bromo-4,5′,8-trimethylpsoralene (X). Its nmr spectrum showed nine aliphatic protons and the C_5 proton (Table I) as a singlet at δ 7.38. The 4′-bromo substituent is quite unreactive toward alkali. Although it slowly dissolved in boiling aqueous potassium hydroxide, X was recovered unchanged upon acidification and was converted into the bromoacrylic acid XI in 70% yield by the action of potassium hydroxide and dimethyl sulfate. Although the 4′-bromo derivative X

(1) National Science Foundation Undergraduate Research Participants, Grants: (a) GE-4097; (b) GY-208; (c) GY-2120.

(2) Psoralenes and Radiant Energy, Proceedings of a Symposium, *J. Invest. Dermatol.*, **32**, 131 (1951).

(3) A. Mustafa, *Chem. Heterocycl. Compds.*, **23**, 14 (1967).

(4) (a) M. E. Brooke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958); (b) *ibid.*, **24**, 523 (1959).

(5) E. A. Abu-Mustafa and M. B. E. Fayez, *Tetrahedron*, **23**, 1305 (1967).

(6) K. D. Kaufman, U. S. Patent 3,201,421 (1965).

(7) Trade name: Trisoralen® (Trioxsalen-Elder). The cooperation of the Paul B. Elder Co., Bryan, Ohio, who supplied quantities sufficient for this study, is gratefully acknowledged.

(8) L. D. Scheel, V. B. Perone, R. L. Larkin, and R. E. Kuppl, *Biochemistry*, **2**, 1127 (1963).

(9) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 92.

(10) For a discussion of the use of quinones as dehydrogenating agents, see L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960).

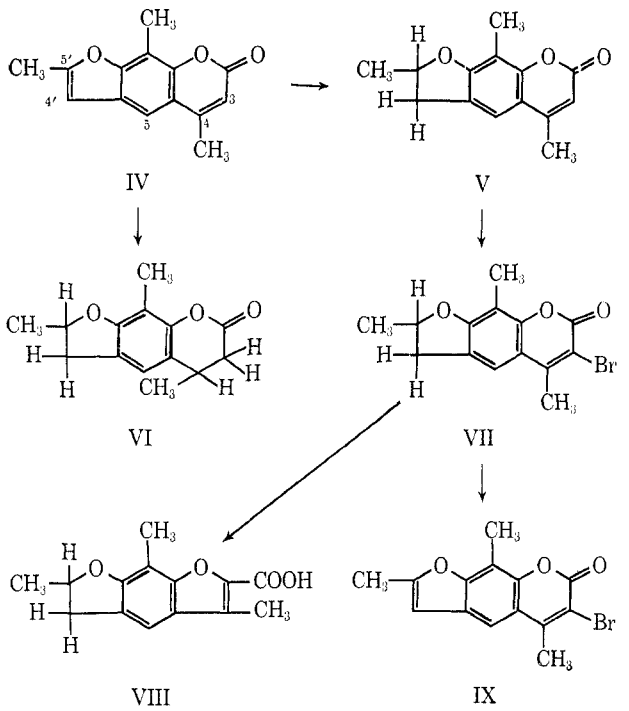
TABLE I

VINYL AND AROMATIC PROTON CHEMICAL SHIFTS[a]

No.	Compound	δ_3	δ_5	$\delta_{4'}$
IV	4,5′,8-Trimethylpsoralene	6.22[b]	7.51	6.41[b]
VII	3-Bromo-4′,5′-dihydro-4,5′,8-trimethylpsoralene		7.28	
IX	3-Bromo-4,5′,8-trimethylpsoralene		7.53	6.43[b]
X	4′-Bromo-4,5′,8-trimethylpsoralene	6.26[b]	7.38	
XII	3,4′-Dibromo-4,5′,8-trimethylpsoralene		7.38	
XIII	4,5′,8-Trimethylpsoralene-4′-sulfonyl chloride	6.32[b]	7.88	
XV	4′-Nitro-4,5′,8-trimethylpsoralene	6.34[b]	8.16	
XVI	4′,5-Dinitro-4,5′,8-trimethylpsoralene	6.45[b]		

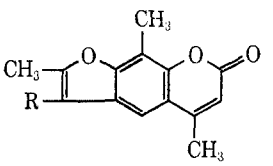
[a] Relative to tetramethylsilane. Solvent, deuteriochloroform. [b] Doublet (J = *ca.* 1 Hz); all of the other peaks were singlets.

SCHEME I

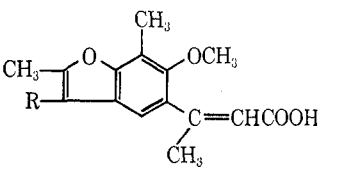


was somewhat resistant to further bromination, 3,4′-dibromo-4,5′,8-trimethylpsoralene (XII) was obtained in 23% yield. Location of the second bromo substituent in the 3 position was apparent from the nmr spectrum. Comparison of the nmr spectra of IV, IX, and X (Table I) confirmed the chemical-shift assignments for the C_3 and $C_{4'}$ protons of IV. It also is apparent that the 4′-bromo substituent shields the C_5 proton slightly but that the 3-bromo substituent does not, although the latter would appear to be more directly conjugated with the 5 position.

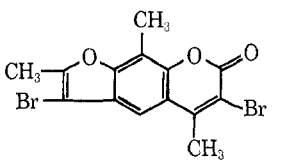
Substitution of bromine in the 4′ position probably occurs by addition to the furan double bond followed by dehydrohalogenation, rather than by direct electrophilic displacement. Brooke and Christensen,[4a] for example, have obtained a stable tribromo derivative of xanthotoxin (II) in which two of the bromine atoms have added to the furan double bond. Benzofuran is known[11] to add bromine to the furan double bond to give an unstable dibromide that subsequently loses hydrogen bromide. To study direct electrophilic substitution, 4,5′,8-trimethylpsoralene (IV) was treated with chlorosulfonic acid to obtain the 4′-sulfonyl chloride (XIII) in 95% yield. Its structure was established by hydrolysis to the sulfonic acid (XIV) followed by bromodesulfonation to 4′-bromo-4,5′,8-trimethylpsoralene (X).[12] Corroboration of the structure



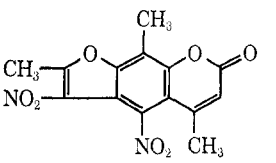
X, R = Br
XIII, R = SO_2Cl
XIV, R = SO_3H
XV, R = NO_2



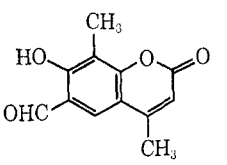
XI, R = Br
XVII, R = H



XII



XVI



XVIII

of XIII was obtained from its nmr spectrum (Table I). As another example of electrophilic substitution, the nitration of IV was studied. Nitric acid in sulfuric acid gave a mixture of products from which a pure mononitro compound was obtained in 18% yield. Better results were obtained by the use of nitric acid in acetic anhydride, which gave the same mononitro compound in 33% yield. It was assigned the structure of 4′-nitro-4,5′,8-trimethylpsoralene (XV) on the basis of its nmr spectrum which clearly showed the protons at C_3 and C_5, deshielded by the nitro group. Assignment of the nitro group to the 3 position is unreasonable because that would require the assumption that the nitro group shields the $C_{4'}$ proton and deshields the C_5 proton. With an excess of nitric acid in sulfuric acid, IV was converted into 4′,5-dinitro-4,5′,8-trimethylpsoralene isolated in 50% yield as a monohydrate and identified by its nmr spectrum.

Two degradative reactions of 4,5′,8-trimethylpsoralene (IV) were studied. As expected, heating with potassium hydroxide and dimethyl sulfate in aqueous acetone opened the pyrone ring and methylated the

(11) R. C. Elderfield and V. B. Meyer in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1951, p 21.

(12) L. Cannell [*J. Amer. Chem. Soc.*, **79**, 2927 (1957)] has established that bromine directly replaces the sulfonic acid group in this reaction.

pyrone oxygen atom to give a methoxybenzofuranacrylic acid (XVII). The course of oxidation with potassium dichromate in dilute sulfuric acid was less predictable but gave a mixture of products, from which a very small yield of 4,8-dimethyl-6-formylumbelliferone (XVIII) was isolated.

Experimental Section

All melting points are corrected. Unless otherwise noted, thin layer chromatograms were run on microscope slides prepared by spreading a slurry of silica gel GF_{254} in 0.3 *M* aqueous sodium acetate and allowing the slides to dry for 1 hr at 50°. Methylene chloride was employed as the moving phase. Samples were introduced onto Florisil columns for chromatography by allowing the solvent to evaporate from a stirred, heated (water bath) suspension of Florisil (*ca.* 5% of the total weight used) in a solution of the sample in methylene chloride. The coated Florisil was then added to the top of a column packed under hexane and elution with hexane or hexane–acetone mixtures was carried out in the usual manner. The uv, nmr, and ir spectra of most of the compounds described below are on file. Photocopies will be supplied upon request.

4′,5′-Dihydro-4,5′,8-trimethylpsoralene (V).—A solution of 4,5′,8-trimethylpsoralene (IV, 0.456 g, 0.0020 mol) in glacial acetic acid (55 ml) was shaken at 25° with hydrogen at atmospheric pressure in the presence of 5% palladium on charcoal until 0.0022 mol of hydrogen had been absorbed. Filtration and removal of the solvent gave a crude product (0.455 g), mp 143–145°. The crude product (0.228 g) was chromatographed on a Florisil (73.2 g) column and was eluted with 5% acetone in hexane. The third fraction (0.164 g, 72%), mp 158.5–159.5°, was shown by thin layer chromatography to be free of contamination by the first two fractions, which were identified (in order of elution) as 3,4,4′,5′-tetrahydro-4,5′,8-trimethylpsoralene (VI) and unreacted starting material. Recrystallization from 95% ethanol gave an analytical sample of colorless needles: mp 159.5–160.5°, ir ($CHCl_3$) 5.89 and 5.85 (α-pyrone carbonyl) and 6.31 μ (strong, conjd C=C); uv max (95% ethanol) 226 mμ (log ε 4.16), 248 (3.62), 260 (3.55), and 335 (4.22).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.34; H, 5.97.

3,4,4′,5′-Tetrahydro-4,5′,8-trimethylpsoralene (VI).—A solution of 4,5′,8-trimethylpsoralene (IV, 0.300 g, 0.00131 mol) in glacial acetic acid (43 ml) was shaken at 25° with hydrogen at atmospheric pressure in the presence of 5% palladium on charcoal (0.150 g) until hydrogen uptake had ceased (0.0027 mol absorbed). Filtration and removal of the solvent gave a crude product (0.300 g), mp 68–94°. Two recrystallizations of the crude product (0.180 g) from 95% ethanol gave colorless needles (0.040 g, 22%): mp 80–81.5°; ir ($CHCl_3$) 5.69 μ (lactone carbonyl); uv max (95% ethanol), 286 mμ (log ε 3.47) and 291 (3.50).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.52; H, 7.24.

3-Bromo-4′,5′-dihydro-4,5′,8-trimethylpsoralene (VII).—A solution of bromine (0.736 g, 0.0046 mol) in chloroform (25 ml) was added dropwise to a stirred solution of 4′,5′-dihydro-4,5′,8-trimethylpsoralene (V, 0.961 g, 0.00418 mol) in chloroform (10 ml). After 4 hr, the solution was extracted with 5% aqueous sodium bisulfite, washed with water, dried ($MgSO_4$), and concentrated to an off-white residue (1.288 g, 100%), mp 245–247°. Recrystallization from 95% ethanol gave colorless plates (1.068 g, 83%), mp 246–247°, which showed a single spot on a thin layer chromatogram.

Anal. Calcd for $C_{14}H_{13}O_3Br$: C, 54.39; H, 4.24; Br, 25.85. Found: C, 54.24; H, 4.30; Br, 25.98.

2,3-Dihydro-2,5,8-trimethylbenzo[1,2-*b*,5,4-*b*′]difuran-6-carboxylic Acid (VIII).—A suspension of 3-bromo-4′,5′-dihydro-4,5′,8-trimethylpsoralene (VII, 0.050 g, 0.16 mmol) in 1 *N* aqueous potassium hydroxide (1 ml) was heated under reflux. The suspended solid gradually dissolved and, after 2 hr, the cooled, clear solution was acidified with 6 *N* hydrochloric acid to obtain a solid (0.025 g, 63%), mp 224–228°. An analytical sample, mp 243–244.5°, was obtained by recrystallization from a mixture of chloroform and petroleum ether: ir ($CHCl_3$) 3.41 (broad) and 11.00 (acid dimer OH), 6.00 (aryl acid C=O), and 7.56 μ (acid C—O).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.33; H, 5.86.

3-Bromo-4,5′,8-trimethylpsoralene (IX).—2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.706 g, 0.00311 mol) was added to a refluxing solution of 3-bromo-4′,5′-dihydro-4,5′,8-trimethylpsoralene (VII, 0.702 g, 0.00227 mol) in chlorobenzene (7 ml) freshly distilled from P_2O_5. After the mixture had been stirred for 34 hr at 140° (oil-bath temperature) under anhydrous conditions, a light tan precipitate of 2,3-dichloro-5,6-dicyanohydroquinone was removed by filtration and washed with chloroform. The combined filtrate and washes were concentrated to a dark gum. Chromatography on a Florisil (700 g) column with 3% acetone in hexane as an eluent produced as the first compound to be eluted a nearly colorless solid (0.128 g, 18%), mp 234.5–237.5°. Recrystallization of 0.102 g from 95% ethanol gave colorless needles (0.082 g, 14%), mp 240–241.5°. A thin layer chromatogram on formamide-impregnated silica gel slides developed with dibutyl ether[13] showed a single spot and established the absence of starting material. The ir spectrum of this compound was significantly different from that of the 4′-bromo isomer and a mixture of the two had mp 202–215°.

Anal. Calcd for $C_{14}H_{11}O_3Br$: C, 54.75; H, 3.61; Br, 26.02. Found: C, 54.62; H, 3.99; Br, 26.12.

4′-Bromo-4,5′,8-trimethylpsoralene (X). A.—A solution of bromine (3.68 g, 0.0230 mol) in chloroform (10 ml) was added dropwise to a stirred solution of 4,5′,8-trimethylpsoralene (IV, 5.00 g, 0.0219 mol) in chloroform (110 ml). After 6 hr, the solvent was allowed to evaporate *in vacuo* to obtain a crude product (6.97 g), mp 243–248°. Recrystallization from 95% ethanol gave fine, colorless needles (5.38 g, 80%), mp 248–249°, which showed a single spot on thin layer chromatography. Additional recrystallization failed to raise the melting point but produced an analytical sample.

Anal. Calcd for $C_{14}H_{11}O_3Br$: C, 54.75; H, 3.61; Br, 26.02. Found: C, 54.55; H, 3.68; Br, 26.38.

B.—A solution of bromine (1.17 g, 0.00732 mol) in chloroform (50 ml) was added to a suspension of 4,5′,8-trimethylpsoralene-4′-sulfonic acid dihydrate (XIV, 1.00 g, 0.00291 mol) in chloroform (150 ml). The mixture was heated under reflux for 7.5 hr, additional bromine (0.25 g) was added, and refluxing was continued for a total of 16 hr. The cooled solution was extracted with 5% aqueous sodium bisulfite, washed with water, dried ($MgSO_4$), and concentrated to dryness to leave a residue (0.681 g). Chromatography of the residue (0.347 g) on Florisil (168 g) with 2–4% acetone in hexane gave, as the first compound to be eluted, 3,4′-dibromo-4,5′,8-trimethylpsoralene (XII, 0.077 g, 13%), identified by comparison with an authentic sample (*vide infra*) through their thin layer chromatograms and their ir spectra. The second compound to be eluted was 4′-bromo-4,5′,8-trimethylpsoralene (X, 0.212 g, 46%), mp 248–249.7°. It was identical with the sample obtained by method A (thin layer chromatography, ir spectra, and mixture melting point).

3-Bromo-6-methoxy-2,7,β-trimethyl-5-benzofuranacrylic Acid (XI).—A mixture of 4′-bromo-4,5′,8-trimethylpsoralene (X, 1.343 g, 0.00438 mol), dimethyl sulfate (10 ml), 20% aqueous potassium hydroxide (50 ml), and acetone (75 ml) was heated under reflux for 15 min and additional portions of dimethyl sulfate (10 ml) and 20% aqueous potassium hydroxide (35 ml) were added. After being refluxed for 4 hr more, the solution was acidified with concentrated hydrochloric acid and the acetone was removed under water aspirator pressure. A white precipitate was collected by filtration and slurried with 5% aqueous sodium hydroxide. The insoluble residue was removed by filtration and the filtrate was acidified with concentrated, hydrochloric acid to obtain an off-white solid (1.038 g, 70%), mp 202–207°. Recrystallization from ligroin gave colorless needles, mp 208–209.5°.

Anal. Calcd for $C_{15}H_{15}O_4Br$: C, 53.11; H, 4.46; Br, 23.56. Found: C, 53.57; H, 4.31; Br, 23.59.

3,4′-Dibromo-4,5′,8-trimethylpsoralene (XII).—A solution of 4′-bromo-4,5′,8-trimethylpsoralene (X, 0.458 g, 0.00149 mol) and bromine (0.27 g, 0.0017 mol) in chloroform (30 ml) was stirred at room temperature for 72 hr, extracted with 5% aqueous sodium bisulfite and water, dried ($MgSO_4$), and concentrated to a residue (0.548 g) that was shown by thin layer chromatography to be a mixture of product and starting material. Chromatography of 0.290 g on an 8-in. square, 1.5-mm thick, sodium acetate buffered silica gel GF_{254} slide enabled the isolation of

(13) T. Beyrich, *J. Chromatogr.*, **20**, 173 (1965).

product (0.070 g, 23%), mp 224.5–226°, uncontaminated by starting material. Recrystallization from 95% ethanol gave pale yellow needles, mp 227–228°.

Anal. Calcd for $C_{14}H_{10}O_3Br_2$: C, 43.55; H, 2.61; Br, 41.40. Found: C, 43.64; H, 2.89; Br, 41.93.

4,5′-8-Trimethylpsoralene-4′-sulfonyl Chloride (XIII).—Chlorosulfonic acid (18.4 ml) was added slowly to solid 4,5′,8-trimethylpsoralene (IV, 2.00 g, 0.00877 mol) without external cooling or heating. After 7 min, ice (450 g) was added to the dark purple reaction mixture. A light yellow solid (2.73 g, 95%), mp 186–187.5°, precipitated and a portion (2.501 g) of it was recrystallized from ethyl acetate to obtain tan needles (2.206 g, 84%), mp 190–192°.

Anal. Calcd for $C_{14}H_{11}O_5SCl$: C, 51.47; H, 3.39; S, 9.82; Cl, 10.85. Found: C, 51.85; H, 3.65; S, 9.70; Cl, 11.08.

4,5′,8-Trimethylpsoralene-4′-sulfonic Acid (XIV).—A suspension of 4,5′,8-trimethylpsoralene-4′-sulfonyl chloride (XIII, 1.825 g, 0.00588 mol) in water (275 ml) was heated under reflux for 15.5 hr, filtered, and concentrated to a white residue (2.120 g, quantitative), mp 167.9–168.3°. A portion (0.171 g) was recrystallized from 2-butanone to obtain long tan needles (0.100 g, 61%), mp 169.5–170.5°, of a dihydrate which was air dried for combustion analysis. Upon being dried *in vacuo* at 120°, a sample (0.0593 g) lost 92% (0.0057 g) of the weight expected for a dihydrate.

Anal. Calcd for $C_{14}H_{12}O_6S \cdot 2H_2O$: C, 48.82; H, 4.68; S, 9.31. Found: C, 48.52; H, 4.75; S, 9.46.

4′-Nitro-4,5′,8-trimethylpsoralene (XV). A.—Concentrated nitric acid (3.95 g of 69.9%, 0.0438 mol) was added to a chilled (ice bath), stirred suspension of finely powdered 4,5′,8-trimethylpsoralene (5.00 g, 0.0219 mol) in acetic anhydride (20.7 ml) at such a rate as to keep the temperature below 10°. After the addition was complete, the mixture was allowed to stand at room temperature for 5 hr and a small amount (0.51 g) of product was collected by filtration. The filtrate was decomposed with aqueous sodium acetate to obtain the rest of the crude product (5.81 g), mp 110–125°. The combined products crystallized from 95% ethanol as light yellow needles (1.96 g, 33%), mp 241–242°.

Anal. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.68; H, 3.70; N, 5.13.

B.—A solution of concentrated nitric acid (1.18 g of 69.9%, 0.013 mol) in concentrated sulfuric acid (3 ml) was added dropwise to a stirred solution of 4,5′,8-trimethylpsoralene (2.00 g, 0.0088 mol) in concentrated sulfuric acid (30 ml) at −10°. After several minutes, the solution was poured onto ice (150 g) and the yellow precipitate was collected by filtration and recrystallized several times from 95% ethanol to obtain yellow needles (0.44 g, 18%), mp 241–242°, which were shown to be identical with the material obtained by method A (ir spectra and mixture melting point).

4′,5-Dinitro-4,5′,8-trimethylpsoralene (XVI).—Concentrated nitric acid (4.0 ml of 69.9%, sp gr 1.42, 0.063 mol) was added dropwise to a stirred solution of 4,5′,8-trimethylpsoralene (IV, 4.00 g, 0.0175 mol) in concentrated sulfuric acid (60 ml) kept at 0°. Addition of ice (*ca.* 500 g) caused the separation of a light yellow precipitate which was converted by several crystallizations from 95% ethanol into off-white needles (2.94 g, 50%), mp 182.5–183.5°, of a monohydrate.

Anal. Calcd for $C_{14}H_{12}N_2O_8$: C, 50.00; H, 3.60; N, 8.33. Found: C, 50.29; H, 3.81; N, 8.28.

6-Methoxy-2,7,β-trimethyl-5-benzofuranacrylic Acid (XVII).—A mixture of 4,5′,8-trimethylpsoralene (1.00 g, 0.00438 mol), dimethyl sulfate (10 ml), 20% aqueous potassium hydroxide (50 ml), and acetone (75 ml) was heated under reflux. After 15 min, more dimethyl sulfate (10 ml) and 20% potassium hydroxide (35 ml) were added and the solution was allowed to continue refluxing for 4 hr. Acidification with hydrochloric acid and evaporation of the acetone under reduced pressure gave a white precipitate, which was washed with 5% aqueous sodium hydroxide to obtain 0.54 g of starting material. Acidification of the alkaline wash solutions gave colorless crystals (0.39 g, 74% based on recovered starting material), mp 168.5–169.0°. Recrystallization from dilute acetic acid did not change the melting point.

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.19; H, 6.20.

6-Formyl-4,8-dimethylumbelliferone (XVIII).—Potassium dichromate (1.00 g) in 10% aqueous sulfuric acid (10 ml) was added slowly to a stirred solution of 4,5′,8-trimethylpsoralene (IV, 1.00 g, 0.00438 mol) in glacial acetic acid (35 ml) at 70°. After 90 min, the solution was allowed to cool to room temperature for 3 hr and was diluted with water (*ca.* 250 ml) to obtain a precipitate which was collected and washed with 5% aqueous sodium hydroxide. Acidification of the alkaline solution gave a brown solid (0.32 g), mp 227–232°. Several recrystallizations from 2-butanone gave pale yellow needles (0.035 g, 4%), mp 251.5–252.5°. The compound gave an orange precipitate with 2,4-dinitrophenylhydrazine reagent.

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.29; H, 4.90.

Registry No.—IV, 3902-71-4; V, 21902-10-3; VI, 21902-45-4; VII, 21902-46-5; VIII, 21902-47-6; IX, 21902-48-7; X, 21902-49-8; XI, 21902-50-1; XII, 21902-51-2; XIII, 21927-80-0; XIV, 21927-81-1; XV, 21902-52-3; XVI, 21902-53-4; XVII, 21902-54-5; XVIII, 6736-54-5.

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