# Reactions of Furocoumarins. II (1). Synthetic Aminomethyl Psoralens *via* Chloromethylation or Benzylic Bromination

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Several psoralen derivatives have been synthesized in order to evaluate their efficacy as photochemotherapeutic (PUVA) agents, including a variety of 4′-substituted-4,5′,8-trimethypsoralen compounds (**1d-j**). Improved synthesis of the very potent photosensitizers 8-methylpsoralen (**6a**) and 4,8-dimethylpsoralen (**6b**) are described and **6a** has been shown to undergo formylation in the 4′-position. Free radical bromination of **6a** and **6b** with NBS affords primarily 8-bromomethyl derivatives (**8a** and **d**), which are readily converted into the 8-aminomethyl derivatives (**8c** and **f**) by the Gabriel method. If the 4′-position is blocked, electrophilic substitution apparently occurs primarily in the 5′-position of the psoralen system. At least, chloromethylation of 4′-methylpsoralen (**9**) affords mainly 5′-chloromethyl derivatives (**10a** and **d**), which also lead to aminomethylpsoralens (**10c** and **f**).

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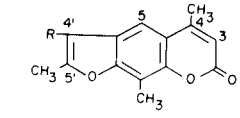
Linear furocoumarins of the type known as psoralens have attracted much attention as probes for nucleic acid secondary structure *in vivo*. Their photochemistry and photobiology has recently been reviewed (2). Apparently, they can penetrate cells or viruses, without disrupting normal processes, and intercalate into DNA helices (3) or RNA helices (4). Irradiation by long-wavelength ultraviolet light (320 to 400 nanometers) causes cycloaddition reactions between the psoralen 3,4- or 4′,5′-double bond and the 5,6-double bond of an adjacent pyrimidine base (5). If pyrimidine bases are appropriately located on opposite strands, both double bonds of a psoralen molecule can react to form a diadduct which results in a covalent interstand cross-link (4,6,7).

Such reactions are probably involved in the psoralen photosensitization of biological systems (8), including the photochemical inactivation of both DNA and RNA viruses by 4,5′,8-trimethylpsoralen (**1a**) (9). Dermatologists have made extensive use of psoralen photosensitization therapy (PUVA) for the treatment of a variety of pathological skin conditions, including psoriasis (10), vitiligo (11), atopic eczema (12), and neurodermatitis (13), as well as mycosis fungoides in the tumor stage (14). Some insight into the risk of cutaneous carcinoma associated with PUVA therapy has been provided by an extensive (1373 patients) five-year follow-up study (15). Preliminary results, after an average post-PUVA observation time of 2.1 years, indicate that the overall risk of cutaneous cancer is not significantly higher than that in a normal population unless the patient has a previous history of cutaneous carcinoma or of exposure to ionizing radiation.

Use of PUVA usually involves ultraviolet irradiation two hours after ingestion of the psoralen, to allow time for the skin to reach peak photosensitization levels. With 8-methoxypsoralen therapy (10) of psoriasis, human doses of 20 to 50 mg are required and the patient remains photo sensitive for at least eight hours. One set of objectives in the present study was to synthesize non-toxic psoralens that are more potent PUVA agents than 8-methoxypsoralen, that photosensitize the skin more rapidly, and that are rapidly metabolized so that skin photosensitization levels decline soon after therapy. Data pertaining to the biological characterization of these compounds will be published at a later date.

This study also provides new information about electrophilic substitution and free-radical bromination of several methylated psoralens. Electrophilic substitution patterns were studied some time ago using 8-methoxypsoralen (16) and 4,5′,8-trimethylpsoralen (trioxsalen, **1a**) (1) which are the two most readily available psoralens. Such reactions as nitration or chlorosulfonation were shown to take place primarily in the 4′-position of **1a**, although the second nitro group enters the 5-position (1). More recently chloromethylation was shown to occur at the 4′-position and the chloromethyl compound (**1b**) was converted to several derivatives, including 4′-(aminomethyl)trioxsalen (**1c**) which is more water soluble and binds more strongly to DNA *in vitro* than **1a** (4). We have now utilized **1b** to prepare a variety of 4′-substituted trioxsalens (**1d-j**) including a nitrile (**1d**) which was subsequently converted to the ester (**1e**) and the caboxylic acid (**1f**). Two quaternary ammonium salts (**1g** and **1h**) were also prepared as well as 4′-([β-hydroxyethoxy]methyl)trioxsalen (**1i**) and 4′-([β-hydroxyethylamino]methyl)trioxsalen (**1j**).




Preliminary unpublished *in vivo* photosensitizing studies using compounds **1a-j**, led to an interest in aminomethyl derivatives of other psoralens, including

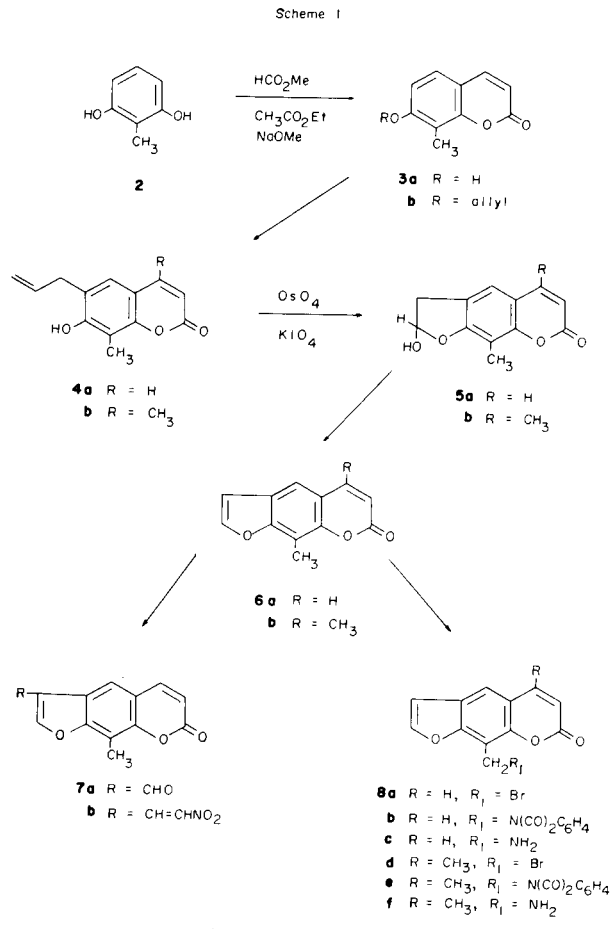
8-methylpsoralen (**6a**) which is the most photodynamic methylfurocoumarin known (17). We have prepared **6a** by a five-step process (Scheme 1) that is much more efficient than the seven-step process reported (18) earlier. 2-Methylresorcinol (**2**) condensed readily with the sodium salt of ethyl formylacetate following directions reported for resorcinol (19). The 9-methylumbelliferone (**3a**) was converted to the allyl ether and rearranged to give the 6-allyl derivative (**4a**) which was cyclized to form **5a** upon oxidation with osmium tetroxide-potassium iodate (20). Dehydration with hot phosphoric acid gave 8-methylpsoralen (**6a**). 4,8-Dimethylpsoralen (**6b**) was prepared in a similar manner from 6-allyl-4,8-dimethylumbelliferone (**4b**).

To convert a 8-methylpsoralen to an aminomethyl derivative, chloromethylation was attempted but a mixture of several products was obtained. Vilsmeier formylation (phosphorous oxychloride, *N,N*-dimethylformamide) at an elevated temperature gave good yields of 4′-formyl-8-methylpsoralen (**7a**) on a small scale (500 mg), which confirms earlier (1,4) conclusions that the 4′-position is the preferred point of electrophilic attack. Yields on a larger scale were disappointing, so **7a** was not used extensively as a synthetic intermediate although it was condensed with nitromethane to give **7b**.

A better approach to the conversion of 8-methylpsoralen to an aminomethyl derivative was discovered by treating **6a** with *N*-bromosuccinimide and dibenzoyl peroxide which gave 8-(bromomethyl)psoralen (**8a**) in 64% yield. Similary, 4,8-dimethylpsoralen (**6b**) was converted to 8-(bromomethyl)-4-methylpsoralen (**8d**) in 57% yield. The assignment of structure **8b** was based initially on the reported (21) behavior of dimethylcoumarins toward *N*-bromosuccinimide, in which methyl groups in other positions are brominated in preference to the 4-methyl group. It was confirmed by the nmr spectrum, which clearly shows allylic splitting of the 4-methyl signal at $\delta$ 2.50, caused by the $C_3$-proton, and a sharp singlet at $\delta$ 4.95 corresponding to the 8-methylene bromide protons. Treatment with potassium phthalimide converted both bromomethyl compounds into the corresponding phthalimides (**8b** and **8e**) which were cleaved by hydrazine acetate to obtain the 8-aminomethyl derivatives (**8c** and **8f**). These 8-(aminomethyl)psorlens are remarkably sensitive to aqueous alkali. Within five minutes, **8c** dissolves completely at 20° in 5% aqueous sodium hydroxide, in contrast to other furocoumarins which require hot aqueous base to open their lactone rings rapidly. Although slightly more stable, the 4-methyl homolog (**8e**) dissolves in 5% aqueous sodium hydroxide in about 15 minutes.

Although it is evident that the 4′-position is most reactive toward electrophilic substitution, the behavior of psoralens in which the 4′-position is blocked has not been reported. Using chloromethyl methyl ether, we have found

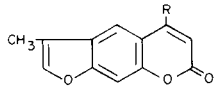
Scheme I



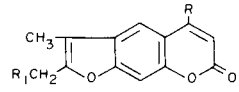

that 4′-methylpsoralens (**9**) undergo substitution in the 5′-position. The chloromethyl derivatives (**10a, 10d**) served as useful intermediates to prepare 5′-aminomethylpsoralens (**10c, 10f**) for evaluation of their photosensitizing activity. 4′-Methylpsoralen (**9a**) and its 4-methyl homolog (**9b**) were obtained readily using the procedure developed by MacLeod (21). Chloromethylation, followed by treatment with potassium phthalimide, gave the 5′-phthalimido derivatives (**10b, 10e**). Cleavage of the phthalyl group from **10e** was accomplished with hydrazine hydrate alone in hot ethanol to obtain 5′-aminomethyl-4, 4′-dimethylpsoralen (**10f**). To obtain 5′-aminomethyl-4′-methylpsoralen (**10c**), acetic acid was added to the hydrazine solution for the cleavage of **10b** in order to decrease the possibility that hydrazine might attack the unsubstituted 4-position, as is known to happen with coumarin (22).

Structure assignments are based on nmr spectra of the psoralen starting materials (**9a, 9b**), which show allylic coupling (J ~ 1 Hz) between the 4′-$CH_3$ protons ($\delta$ 2.25-2.3) and the 5′-proton ($\delta$ 7.36-7.4). Decoupling experiments confirmed that the incompletely resolved splitting of both signals is due to their coupling with each other. The absence of the unresolved doublet at $\delta$ 7.36-7.4

and the absence of splitting in the 4'-$CH_3$ signal at $\delta$ 2.2-2.3 in the spectra of compounds **10a, c, d,** and **f** enable the determination that their 5'-position has been substituted. The spectrum of **10f** was particularly convincing because allylic coupling between 4-$CH_3$ group and the 3-proton was clearly seen.



**9a** R = H
**b** R = $CH_3$



**10a** R = H, $R_1$ = Cl
**b** R = H, $R_1$ = $N(CO)_2C_6H_4$
**c** R = H, $R_1$ = $NH_2$
**d** R = $CH_3$, $R_1$ = Cl
**e** R = $CH_3$, $R_1$ = $N(CO)_2C_6H_4$
**f** R = $CH_3$, $R_1$ = $NH_2$

Evaluation of the photosensitizing activity of the psoralens in this series is presently underway and will be reported as soon as it is completed.

## EXPERIMENTAL

Melting points below 300° were determined in soft glass capillary tubes using a Thomas-Hoover apparatus or between cover glasses using a Fisher Digital Melting Point Analyzer. Those above 300° were determined in soft glass capillaries using a Gallenkamp apparatus with an electrically heated metal block. All melting points are uncorrected. Thin layer chromatography (tlc) was performed on Analtech, 250 micrometer, glass-backed, silica gel $GF_{254}$ slides using 15% 2-butanone in benzene unless otherwise indicated. Nmr spectra were run on a Perkin-Elmer model R24B, using tetramethylsilane as an internal standard. Combustion analyses were carried out by Schwartzkopf Microanalytical Laboratory or by Spang Microanalytical Laboratory.

*N*-(4'-Methylene-4,5',8-trimethylpsoralen)trimethylammonium Chloride (**1h**).

Trimethylamine was allowed to pass through a solution of **1b** (4) (4 g, 14.5 mmoles) in *N,N*-dimethylformamide (400 ml) for two hours. At that time, tlc (ether) showed that the reaction was complete. The product was collected by filtration, 4.615 g (95%), mp 278°. Recrystallization from absolute ethanol gave an analytical sample, mp 276-277°; nmr (deuterium oxide): $\delta$ 2.0 (3H, s, $CH_3$); 2.3 (3H, s, $CH_3$); 2.6 (3H, s, $CH_3$); 3.2 (9H, s, $N(CH_3)_3$); 4.4-4.7 (partially obscured by water, $CH_2$); 5.8 (1H, s, $C_3H$); 7.4 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{18}H_{22}ClO_3$: C, 64.37; H, 6.60; N, 4.17; Cl, 10.56. Found: C, 64.26; H, 6.57; N, 4.17; Cl, 10.38.

*N*-(4'-Methylene-4,5',8-trimethylpsoralen)pyridinium Chloride (**1g**).

A solution of **1b** (4) (200 mg, 0.72 mmole) and pyridine (1 ml) in deuterium oxide (50 ml) was kept at 80° for 60 minutes and stirred overnight at room temperature. The product was collected by filtration, 243 mg (95%), mp 274-276°; nmr (deuterium oxide) $\delta$ 1.4 (3H, s, $CH_3$); 1.9 (3H, s, $CH_3$); 2.5 (3H, s, $CH_3$); 5.4 (1H, s, $C_3H$); 5.75 (2H, s, $CH_2$); 6.9 (1H, s, $C_5H$); 7.8-8.9 (5H, m, pyridine).

*Anal.* Calcd. for $C_{20}H_{18}ClO_3$: C, 67.51; H, 5.10; N, 3.94; Cl, 9.97. Found: C, 67.78; H, 5.12; N, 3.67; Cl, 9.97.

4-([$\beta$-Hydroxyethoxy]methyl)-4,5',8-trimethylpsoralen (**1i**).

A solution of **1b** (4) (3 g, 10.8 mmoles) in ethylene glycol (750 ml) was kept at 90° for four hours and then distilled at 90°/1 torr. Recrystallization of the residue from water gave colorless cyrstals, 2.26 g (69%), mp 151-152°; nmr (deuteriochloroform): $\delta$ 2.4 (10 H, s, OH and $CH_3$); 3.5-3.9 (4H, m, $CH_2CH_2$); 4.6 (2H, s, $CH_2$); 6.1 (1H, s, $C_3H$); 7.5 (1H, 2, $C_5H$).

*Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.26; H, 6.16.

4'-[*N*($\beta$-Hydroxyethyl)aminomethyl]-4,5',8-trimethylpsoralen (**1j**).

After stirring for two hours at 90°, a solution of **1b** (4) (2 g, 7.23 mmoles) in aminoethanol (25 ml) was concentrated, using a rotary evaporator at 1 torr. The residue was suspended in 5% aqueous hydrochloric acid and was then made alkaline by the addition of 20% aqueous sodium hydroxide. The precipitate was collected, washed with 10% aqueous sodium chloride until free of base, once with water, and was recrystallized from 1-butanol to obtain colorless prisms 1.204 g (55%), mp 174-177°, which tlc (50% methanol in benzene) showed to contain a trace of starting material. Another recrystallization from 1-butanol failed to raise the mp but gave an analytical sample; nmr (deuteriochloroform): $\delta$ 2.05 (2H, broad s, OH and NH); 2.42 (6H, s, $CH_3$'s); 2.47 (3H, s, $CH_3$); 2.80 (2H, t, J = 6 Hz, $CH_2CH_2N$); 3.65 (2H, t, J = 6 Hz, $CH_2CH_2O$); 3.85 (2H, s, $CH_2N$); 6.09 (1H, broad s, $C_3H$); 7.49 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.67; H, 6.42; N, 4.33.

4'-Cyanomethyl-4,5',8-trimethylpsoralen (**1d**).

Sodium cyanide (194 mg, 3.96 mmoles) was added to **1b** (1g, 3.6 mmoles) dissolved in dimethylsulfoxide (25 ml) and the solution was stirred at 75° for 2.5 hours and poured into water (125 ml). The precipitate was collected by filtration, washed with 6 normal hydrochloric acid and then with water to obtain 955 mg (99%), mp 267-272° dec. Sublimation at 200°/0.25 torr gave and analytical sample, mp 272-277° dec in 86% yield; nmr (DMSO-$d_6$): $\delta$ 2.40 (9H, s, $CH_3$'s); 4.05 (2H, s, $CH_2$); 6.25 (1H, s, $C_3H$); 7.80 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.87; H, 5.03; N, 5.01.

4'-Carbethoxymethyl-4,5',8-trimethylpsoralen (**1e**).

Dry hydrochloric acid was allowed to bubble through a solution of **1d** (7.238 g, 27 mmoles) in 95% ethanol (2.4 l) for three hours, until the solution was saturated. After a two hour reflux, the solution was concentrated with a rotary evaporator and a chloroform (1.2 l) solution of the residue was filtered and washed with 5% sodium hydroxide (300 ml), 5% hydrochloric acid (300 ml), and water (200 ml). After drying over magnesium sulfate, the soltuion was concentrated to a yellow solid, which crystallized from 95% ethanol, 5.917 g (70%), mp 178-180.5°. Tlc showed one spot ($R_f \sim 0.5$); nmr (deuteriochlorform): $\delta$ 1.24 (3H, t, J = 7 Hz, $CH_2CH_2$); 2.50 (6H, d, J < 1 Hz, $CH_3$'s); 2.58 (3H, s, $CH_3$); 3.62 (2H, s, $CH_2CO_2$); 4.17 (2H, q, J = 7 Hz, $CH_2CH_3$); 6.19 (1H, d, J < 1 Hz, $C_3H$); 7.46 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.72; H, 5.93.

4'-Carboxymethyl-4,5',8-trimethylpsoralen (**1f**).

A suspension of finely ground **1e** (2.4 g, 7.64 mmoles) in 0.1 normal potassium hydroxide (458 ml) was protected from light and heated under reflux until all of the solid had dissolved (1.5 hour). After it had cooled to room temperature in an ice-water bath, the reaction mixture was filtered and acidified, using concentrated hydrochloric acid. Filtration yielded a white solid, more of which precipitated from the filtrate later. Combined, the two precipitates weighed 1.665 g. Recrystallization of a portion (1.600 g) from 95% ethanol (80 ml) gave 1.066 g (51%), mp 273-274°, tlc (2-butanone) showed one spot ($R_f \sim 0.7$).

*Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.92; neutralization equivalent, 286. Found: C, 67.03; H, 5.21; neutralization equivalent, 292.

8-Methylumbelliferone (**3a**).

Methyl formate (141 ml, 2.295 moles) was added at the rate of 5 ml every four minutes to a stirred mixture of sodium methoxide (184.5 g, 3.42 moles) and ethyl acetate (375 ml) cooled in an ice-water bath. After 15 hours, the atmosphere was replaced with argon, a solution of **2** (99.3 g, 0.8 mole) in ethyl acetate (150 ml) was added, the stirred mixture was kept between 60-70° for six hours, and it was then acidified with 3 normal hydrochloric acid (1.3 l). The next day, a precipitate was collected by filtration, 170.75 g (76%), mp 253-256° (reported (23) 258-259°).

7-Allyloxy-8-methylcoumarin (**3b**).

A mixture of **3a** (100 g, 0.57 mole), allyl bromide (260 ml, 3 moles), anhydrous potassium carbonate (372 g, 2.7 moles) and acetone (2.5 l) was heated under reflux for 10 hours, filtered, and concentrated to obtain 105 g (85%), mp 125-126° (reported (23) 125-125.5°).

6-Allyl-8-methylumbelliferone (**4a**).

A solution of **3b** (100 g, 0.46 mole) in *N,N*-diethylaniline (500 ml) was heated under reflux for two hours, allowed to cool, and diluted with pet ether (bp 30-60°, 1 l). Filtration gave 89 g (89%), mp 148-150° (reported (23) 153-154°). Tlc showed two minor contaminants, but the material is suitable for use in the next step.

8-Methylpsoralen (**6a**).

A solution of osmium tetroxide (40 mg) in water (20 ml) was added to a vigorously stirred mixture of potassium periodate (10 g, 43.5 mmoles) and **4a** (4 g, 18.5 mmoles) in methanol (120 ml). After 18.5 hours of stirring, the mixture was diluted with dichloromethane (200 ml), filtered, and the residue was washed with two portions (50 ml) of dichloromethane. The combined filtrate and washes were washed with two portions (100 ml of saturated brine, which were backwashed with dichloromethane (200 ml). All dichloromethane layers were combined, dried (sodium sulfate), and concentrated *in vacuo* to obtain 3.8 g (94%) of crude 4',5'-dihydro-5'-hydroxy-8-methylpsoralen (**5a**). Tlc showed that the product contains no starting material but a small amount of a contaminant. Without further purification, it was heated on a steam bath for 30 minutes in 85% phosphoric acid (60 ml), poured into water (300 ml), and filtered to obtain 2.83 g, which dissloved in chloroform (150 ml) and was chromatographed on alumina (Fisher A-540, 280 g) using chloroform for elution. Fractions (50 ml each) 7 through 15 were combined and concentrated *in vacuo* to obtain pure (one spot on tlc) white crystals, 1.7 g (46%), mp 150-151° (reported (18) 150°).

4,8-Dimethylpsoralen (**6b**).

The procedure used to prepare **6a** was repeated, using **4b** (23) (23 g, 0.1 mole), potassium periodate (54 g, 0.23 mole), osmium tetroxide (1 g in 100 ml water), and methanol (650 ml). The reaction time was reduced to 4.5 hours and crude 4',5'-dihydro-5'-hydroxy-4,8-dimethylpsoralen (**5b**) was obtained in 96% yield. Heating with phosphoric acid gave **6b**, 12.8 g (60%), mp 203-204° (reported (18) 206°), after chromatography on alumina.

4'-Formyl-8-methylpsoralen (**7a**).

Redistilled phosphorus oxychloride (1.84 ml, 20 mmoles) was added to a stirred solution of **6a** (500 mg, 2.5 mmoles) in dry (3 angstrom molecular sieves) dimethylformamide (1.5 ml, 20 mmoles) at 90° . After heating for 24 hours, the mixture was allowed to cool, water (30 ml) was added, and a precipitate was collected by filtration, 485 mg (85%), mp 262-270°. Sublimation (200°/0.25 torr) gave an analytical sample in 73% recovery, mp 271.5-274.5°; nmr (deuteriochloroform): $\delta$ 2.60 (3H, s, $CH_3$); 6.30 (1H, d, J = 10 Hz, $C_3H$); 7.50 (1H, s, $C_5H$); 7.65 (1H, s, $C_5'H$); 7.65 (1H, d J = 10 Hz, $C_4H$); 9.80 (1H, s, CHO).

*Anal.* Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found: C, 68.55; H, 3.81.

4'-($\beta$-Nitrovinyl)-8-methylpsoralen (**7b**).

Nitromethane (0.35 ml, 6.5 mmoles) was added to a solution of **7a** (1 g, 4.38 mmoles) and *n*-hexylamine (0.58 ml, 4.4 mmoles) in boiling glacial acetic acid (50 ml), which was protected by a calcium sulfate drying tube. After refluxing for 2.5 hours and cooling overnight, 5% hydrochloric acid (200 ml) was added and the mixture was extracted with eight portions (100 ml each) of chloroform, which were washed with 5% sodium bicarbonate, 5% hydrochloric acid, and water, dried (magnesium sulfate), and concentrated *in vacuo*. Chromatography of the residue (1.154 g) on silica gel (Baker 3405, 346 g), using 50% chloroform in benzene gave 0.692 g (58%), from which an analytical sample, mp 274-276° dec, was prepared by recrystallization from 1,2-dichloroethane. Tlc showed a single spot of $R_f \sim 0.56$.

*Anal.* Calcd. for $C_{14}H_9NO_5$: C, 61.99; H, 3.34; N, 5.16. Found: C, 61.89; H, 3.41; N, 4.96.

8-Bromomethylpsoralen (**8a**).

A mixture of N-bromosuccinimide (4.446 g, 25 mmoles), carbon tetrachloride (500 ml), **6a** (5 g, 25 mmoles), and benzoyl peroxide (0.606 g, 2.5 mmoles) was stirred and heated under reflux while guarded by a calcium sulfate tube. After four hours, a negative test was obtained with moist potassium iodide-starch paper, the hot mixture was filtered, and the filtrate was refrigerated. The cool filtrate deposited crystals which were taken up in chloroform and washed with four portions (50 ml) of water to remove succinimide. Each water portion was backwashed with chloroform (10 ml). All chloroform layers were combined, dried (magnesium sulfate), and concentrated *in vacuo* to obtain 4.493 g (64%), mp 191-195°. Sublimation (190°/1 torr) gave an analytical sample, mp 202.7-203.5°; nmr (deuteriochloroform): $\delta$ 4.98 (2H, s, $CH_2$); 6.37 (1H, d, J = 10 Hz, $C_3H$); 6.82 (1H, d, J = 2 Hz, $C_4'H$); 7.63 (1H, s, $C_5H$); 7.72 (1H, d, J = 2 Hz, $C_5'H$); 7.74 (1H, d, J = 10 Hz, $C_4H$); ms: m/e (relative intensity) 280 (9.76), 278 ($M^+$, 10.55), 200 (13.13), 199 (100), 171 (28.94).

*Anal.* Calcd. for $C_{12}H_7BrO_3$: C, 51.64; H, 2.53; Br, 28.63. Found: C, 51.79; H, 2.67; Br, 28.60.

8-Bromomethyl-4-methylpsoralen (**8d**).

The procedure used to prepare **8a** was repeated, using **6b** (5.5 g, 25.7 mmoles) to obtain 4.315 g (57%), mp 194-196°. Sublimation *in vacuo* gave an analytical sample, mp 193.5-195°; nmr (deuteriochloroform): $\delta$ 2.50 (3H, d, J ~ 1 Hz, $CH_3$); 4.95 (2H, s, $CH_2$); 6.24 (1H, d, J ~ 1 Hz, $C_3H$); 6.82 (1H, d, J = 3 Hz, $C_4'H$); 7.70 (1H, d, J = 3 Hz, $C_5'H$); 7.75 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{13}H_9BrO_3$: C, 53.26; H, 3.09; Br, 27.27. Found: C, 53.00; H, 2.85; Br, 27.05.

8-Phthalimidomethylpsoralen (**8b**).

Potassium phthalimide (1.132 g, 6.11 mmoles) was added to a mixture of **8a** (1.432 g, mp 191-195°, 5.13 mmoles) and dry dimethylformamide (143 ml) which was stirred and heated at 100° for six hours, while being protected by a calcium sulfate drying tube. After cooling, the dark solution was poured into ice-water (300 ml) and a tan solid was collected by filtration, 1.507 g (85%), mp 248-253°. One recrystallization from glacial acetic acid (82% recovery) gave prisms, mp 253-254°.

*Anal.* Calcd. for $C_{20}H_{11}O_5N$: C, 69.57; H, 3.21; N, 4.06. Found: C, 69.33; H, 3.46; N, 4.00.

8-Phthalimidomethyl-4-methylpsoralen (**8e**).

The procedure used to prepare **8b** was repeated, using **8b** (1g, mp 194-196°, 3.411 mmoles) to obtain a crude product, 1.047 g (85%), mp 220-224°. An analytical sample was obtained from ethanol in 55% recovery, mp 217.5-218°.

*Anal.* Calcd. for $C_{21}H_{13}O_5N$: C, 70.19; H, 3.65; N, 3.90. Found: C, 69.97; H, 3.89; N, 3.76.

8-Aminomethylpsoralen (**8c**).

A stirred mixture of **8b** (250 mg, mp 253-254°, 0.724 mmoles), 95% ethanol (31 ml), glacial acetic acid (0.66 ml, 11.6 mmoles), and 85% hydrazine hydrate (0.33 ml, 5.79 mmoles) was heated under reflux for 3.75 hours, by which time **8b** had completely dissolved and reacted (tlc). Concentration *in vacuo* gave a yellow residue which was acidified with 1 normal hydrochloric acid (27 ml), and a precipitate was collected by filtration and washed with two portions (7 ml) of 1 normal hydrochloric acid. Solid sodium bicarbonate was added to the combined filtrate and washes until their *p*H ~ 8 and that solution was extracted with five portions (25 ml) of chloroform which were combined, dried (sodium sulfate) and concentrated *in vacuo* to a solid that sublimed at 130°/0.5 torr, 61 mg (40%), mp 156-158°; nmr (deuteriochloroform): $\delta$ 2.81 (2H, s, $NH_2$); 4.32 (2H, s, $CH_2$); 6.29 (1H, d, J = 9 Hz, $C_3H$); 6.77 (1H, d, J = 2.5 Hz, $C_4'H$); 7.52 (1H, s, $C_5H$); 7.75 (2H, m, $C_4H$ and $C_5'H$).

*Anal.* Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.74; H, 4.27; N, 6.40.

8-Aminomethyl-4-methylpsoralen (**8f**).

The procedure used to prepare **8c** was repeated, using **8e** (15.5 g, mp 220-224°, 43.14 mmoles) except that the time was extended to six hours and vacuum sublimation was not employed. The crude product weighed 9.2 g (93%), mp 154-155.5°, but tlc (80 chloroform: 20 methanol: 1 triethylamine) showed at least two contaminants. A chloroform solution, containing 4.20 g, was extracted with three portions (200 ml) of 1 normal hydrochloric acid, which were combined, backwashed once with chloroform (200 ml), and neutralized (*p*H ~ 6) with solid sodium bicarbonate. The mixture was extracted repeatedly with chloroform (200 ml portions), which was dried (sodium sulfate) and concentrated *in vacuo* to obtain a light yellow solid, 3.79 g (84% yield), mp 157.5-158.5°. An analytical sample was obtained from a mixture of benzene and ligroin (Eastman Kodak P1628); nmr (deuteriochloroform): δ 1.92 (2H, s, $HN_2$); 2.63 (3H, d, J ~ 1 Hz, $CH_3$); 4.47 (2H, s, $CH_2$); 6.33 (1H, d, J ~ 1 Hz, $C_3H$); 6.90 (1H, d, J = 2.5 Hz, $C_4H$); 7.76 (1H, d, J = 2.25 Hz, $C_5H$); 7.78 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.23; H, 5.07; N, 5.87.

5′-Chloromethyl-4′-methylpsoralen (**10a**).

Two portions (75 ml) of chloromethyl methyl ether were added, 24 hours apart, to a stirred solution of **9a** (21) (8.612 g, 43 mmoles) in glacial acetic acid at room temperature. After 40 more hours, water (3.75 l) was added and a precipitate was separated, 7.60 g (71%), mp 181.7-182.9°. An analytical sample, mp 183.9-184.8°, was obtained from another run by collecting some crystallized product before diluting with water. Nmr (deuteriochloroform): δ 2.3 (3H, s, $CH_3$); 4.7 (2H, s, $CH_2$); 6.35 (1H, d, J = 9 Hz, $C_3H$); 7.35 (1H, s, $C_8H$); 7.50 (1H, s, $C_5H$); 7.75 (1H, d, J = 9 Hz, $C_4H$).

*Anal.* Calcd. for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65; Cl, 14.26. Found: C, 63.07; H, 3.72; Cl, 14.23.

5′-Chloromethyl-4,4′-dimethylpsoralen (**10d**).

The procedure used to prepare **10a** was repeated using **9b** (21) (30 g, 0.14 mole) but, instead of diluting with water, the reaction mixture was concentrated *in vacuo*. A chloroform (1.2 l) solution of the residue was clarified by filtration through Celite, washed with two portions (1 l) of saturated aqueous sodium bicarbonate and then with water, dried (magnesium sulfate), and concentrated *in vacuo*. The residue, suspended in water, was quite acidic, so it was washed repeatedly with water until the wash had *p*H ~ 6, to obtain 35.60 g (97%), which was used to make **10e**. An analytical sample was obtained by sublimation (160°/0.5 torr), mp 170-170.2°; nmr (deuteriochloroform): δ 2.3 (3H, s, 4′-$CH_3$); 2.5 (3H, broad s, 4-$CH_3$); 4.7 (2H, s, $CH_2$); 6.2 (1H, broad s, $C_3H$); 7.3 (1H, s, $C_8H$); 7.6 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 63.80; H, 4.24.

5′-Phthalimidomethyl-4′-methylpsoralen (**10b**).

The procedure used to prepare **8b** was repeated, using **10a** (7.618 g, 30.6 mmoles) but, instead of initial dilution with water, the reaction mixture was concentrated *in vacuo*, diluted with water (400 ml), and extracted with four portions (1 l) of chloroform. After drying (magnesium sulfate) and rotary evaporation, the chloroform extracts yielded 10.013 g (91%) of material suitable for use in the next step. Recrystallization from glacial acetic acid gave an analytical sample, mp 270-270.5°.

*Anal.* Calcd. for $C_{21}H_{13}O_5N$: C, 70.19; H, 3.65; N, 3.90. Found: C, 69.88; H, 3.86; N, 3.73.

5′-Phthalimidomethyl-4′,4-dimethylpsoralen (**10e**).

The procedure for **10b** was repeated using **10d** (35.6 g, 0.135 mole), except that chloroform was not used to isolate the product. After concentration of the reaction mixture and addition of water (800 ml), the product was collected, washed twice with water, and recrystallized twice from glacial acetic acid to obtain 20.7 g (41%), mp 316-318°. Vacuum sublimaton did not change the mp but gave an analytical sample.

*Anal.* Calcd. for $C_{22}H_{15}O_5N$: C, 70.77; H, 4.05; N, 3.75. Found: C, 70.50; H, 4.11; N, 3.63.

5′-Aminomethyl-4′-methylpsoralen (**10c**).

The procedure used to prepare **8c** was repeated, using **10b** (6 g, 16.7 mmoles) to obtain 2.945 g (77%), mp 153-156°. Recrystallization from a mixture of benzene and ligroin (bp 94-105°) gave an analytical sample, mp 154-156°, nmr (deuteriochloroform): δ 1.7 (2H, broad s, $NH_2$); 2.25 (3H, s, 4′-$CH_3$); 3.95 (2H, s, $CH_2$); 6.31 (1H, d, J = 9 Hz, $C_3H$); 7.32 (1H, s, $C_8H$); 7.46 (1H, s, $C_5H$); 7.75 (1H, d, J = 9 Hz, $C_4H$).

*Anal.* Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.94; H, 4.85; N, 5.82.

5′-Aminomethyl-4,4′-dimethylpsoralen (**10f**).

A stirred solution of **10e** (25 g, 0.067 mole) and 85% hydrazine hydrate (31.8 ml, 0.55 mole) in 95% ethanol (3 l) was heated under reflux for six hours and concentrated *in vacuo*. The residue was stirred with 0.1 normal sodium hydroxide (1.5 l) and extracted with three portions (750 ml) of chloroform. An attempt to extract the combined chloroform layer with 1 normal hydrochloric acid produced an insoluble hydrochloride, which was collected by filtration, washed with chloroform (100 ml), and dissolved in warm water (500 ml). Addition of saturated aqueous sodium bicarbonate caused the formation of a precipitate, 11.0 g (67%), mp 186-188°. An analytical sample was obtained by crystallization from a mixture of benzene and ligroin (bp 94-105°); nmr (deuteriochloroform): δ 1.6 (2H, broad s, $NH_2$); 2.2 (3H, s, 4′-$CH_3$); 2.4 (3H, d, J ~ 1 Hz, 4-$CH_3$); 2H, s, $CH_2$); 6.1 (1H, d, J ~ Hz, $C_3H$); 7.2 (1H, s, $C_8H$); 7.45 (1H, s, $C_5H$).

*Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.83; H, 5.50; N, 5.50.

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