Aminomethyl Psoralens. Electrophilic Substitution of Hydroxymethylphthalimide on Linear Furocoumarins

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Received April 24, 1984

A new synthetic route to aminomethylpsoralens, substituted on the furan-ring, has been developed by electrophilic substitution of *N*-hydroxymethylphthalimide and subsequent hydrazinolysis. Hydroxy and methoxy activating functions on the psoralens lead to multi-site substitution and the products of these phthalimidomethylations resist simple cleavage with hydrazine. The two-step introduction of a single CH_2NH_2 group is successful in psoralens containing only methyl substituents.

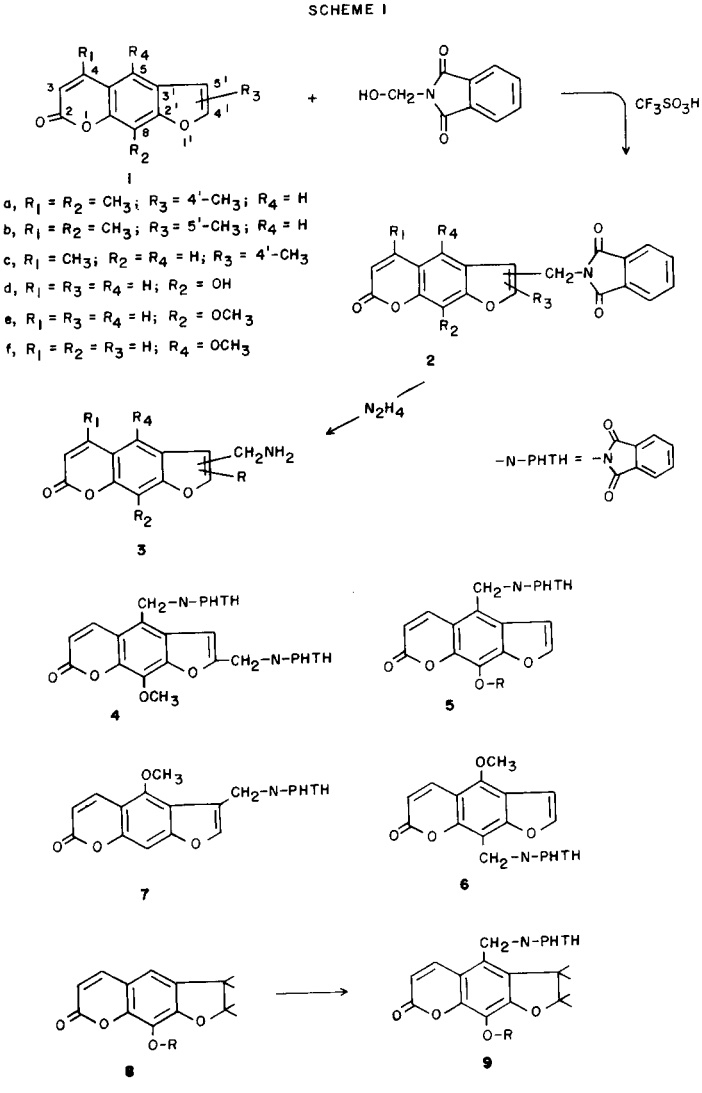
J. Heterocyclic Chem., **22**, 73 (1985).

Psoralens, also known as linear furocoumarins, are phototoxic substances which inhibit cell proliferation in bacterial and eukaryotic cells as well as effecting the inactivation of both DNA and RNA viruses. Their photochemistry and photobiology have been reviewed and the principal mode of action is believed to be light-activated (320-400 nanometers) cyclobutane formation between the 3,4- or 4',5'-double bonds of the psoralens and the 5,6-double bonds in the nucleic acids [1,2].

Several recent publications and patents have claimed impressive photodynamic behavior in viral inactivation [2], in dermal photosensitization [3], in photochemotherapy against L-1210 leukemia in mice [4], in photoactivated DNA binding *in vitro* [5] and in treatment of dermatological diseases [6,7] for the 4'-aminomethyl and 5'-aminomethyl derivatives of certain methylated psoralens. In all cases these aminomethyl psoralens were synthesized by a three-step technique involving initial chloromethylation, displacement of the halide by potassium phthalimide, and subsequent hydrazinolysis of phthalimidomethyl psoralen [3,5,6]. The need to obtain substantial quantities of these aminomethyl psoralens for biologic studies and the reluctance to work with chloromethyl methyl ether, a volatile, toxic, carcinogen [8], caused us to develop an alternative synthesis.

Direct amidomethylation at aromatic carbons with hydroxymethylamides and phthalimides in strong acid has been reported [9]. The reaction can be applied to simple aryl systems and after appropriate cleavage with base and/or hydrazine, generates the primary aminomethyl aromatic [10]. The reaction is well-known to be complicated by multi-substitution with phenol, anisole, and even benzene giving mixture of mono-substituted and di-substituted products [10,11,12]. In psoralens **1a-c** phthalimidomethylation proceeded onto the available position on the furan ring in yields of 60-70% (see Scheme 1) with no evidence of poly-site substitution even when the electrophile was in excess. Proton nmr confirmed the site of substitution by loss of the corresponding furano-proton. Assignment tables have been published for the chemical shifts and coupling constants of most common psoralens [13].

SCHEME I



In methoxy-substituted psoralens **1e** and **1f** initial electrophilic substitution is known to occur on the aromatic ring *para* to the $-OCH_3$ [14]. In methylated psoralens **1a-c** first substitution occurs on either the 4'- or 5'-positions in the furan ring with one claim that the former is favored [3,5,6]. This behavior is parallel to that of benzofuran in

which electrophilic substitution can occur at C-2 or C-3 depending on reaction conditions with C-3 entry favored [15, 16,17]. Polysubstitution effects in the psoralens have not been studied.

Phthalimidomethylation on psoralens (**1d-f**) was polysubstitutional. With **1d** a mixture of three isomeric monophthalimidomethyl products was obtained with substitution at C-5, C-4′ and C-5′ in the ratio (nmr) of 1.7:1.0:2.0. Methylation of the phenolic hydroxy in the C-5 phthalimidomethyl compound **5** (R = H) gave the known methoxypsoralen derivative **5** (R = CH_3). When the 4′,5′-double bond was reduced (*i.e.*, **8**, R = H), electrophilic phthalimidomethylation occurred exclusively at C-5 yielding **9** (R = H) and clearly indicating that the alternative substitution sites were in the furan ring. Phthalimidomethylation of 8-methoxypsoralen (**1e**) also yielded a mixture of the 5-substituted **5** (R = CH_3) and the 5,5′-disubstituted [4] psoralens. Here, too, reduction of the 4′,5′-double bond directed substitution exclusively to the C-5 position. Condensation of *N*-hydroxymethylphthalimide and 5-methoxypsoralen (**1f**) also yielded multiple substitution products **6** and **7**.

Unfortunately, the complexity of multi-site and polysubstitutional attacks on the methoxy and hydroxy substituted psoralens **1d-f** was not the sole factor limiting the utility of these psoralens in the direct aminomethylation. While those psoralens bearing methyl groups **2a-c** smoothly underwent the Ing-Manske [18] hydrazinolysis yielding the aminomethylpsoralens **3a-c** in 59-80% conversions all of the other phthalimidomethylpsoralens behaved anomalously.

Standard hydrazinolysis in ethanol resulted in recovery unchanged of the phthalimidomethylpsoralens **4-7** and **9** if the contact time was short (under 3 hours). Longer (>8 hours) reflux gave a mixture of components whose proton nmr revealed the destruction of the furan and coumarin rings, the formation of phthalhydrazide, and a marked increase in aliphatic resonances. Alternative cleavage methods - aqueous sodium hydroxide, phenylhydrazine/*n*-butylamine, methylamine, 20% aqueous hydrochloric acid - recommended for difficult cases [19], were either unreactive toward the phthalimidomethylpsoralens under mild conditions or totally destroyed the ring system at prolonged reflux. Earlier workers reported that although under certain conditions coumarins with an unsubstituted C-4 undergo nucleophilic addition of hydrazine and subsequent rearrangement, that problem could be avoided by using hydrazine/acetic acid mixtures [6,20]. Hydrazine and acetic acid mixtures on these methoxy-containing phthalimidomethylpsoralens produced similar complex behavior. In fact, other investigators who attempted the hydrazinolysis of **5** (R = CH_3) reported identical findings [21].

While hydrazinolysis according to the Ing and Manske [18] procedure is one of the most effective means of liberating primary amines from phthalimides, some pendant ester and xanthate functions do undergo decomposition [22-23]. At least one study reported that a heterocyclic system, *N*-(5-sulfamoyl-2-thienyl)phthalimide, underwent deep-seated decomposition with evolution of hydrogen sulfide [24]. In other cases, a primary amine being generated in a cleavage produced rearrangement products by reacting with other electrophilic centers in the molecule [25]. This laboratory has reported a ring opening rearrangement of the coumarin ring in a similar amino-containing psoralen [26].

Thus, although phthalimidomethylation and subsequent hydrazinolysis is an attractive, convenient, two-step synthetic route to aminomethylated psoralens, the methoxy and hydroxy-containing psoralens undergo multi-site electrophilic substitution by the phthalimidomethyl group and then resist facile cleavage to the primary amine functionality.

EXPERIMENTAL

General Methods.

Melting points were determined in capillary tubes on a Fisher Meltemp apparatus and are reported uncorrected. Infrared spectra were obtained in potassium bromide discs on a Perkin-Elmer Model 283 spectrometer. The ^{1}H-nmr spectra were obtained in the indicated solvents on a JEOL-FX90Q spectrometer. Elemental analyses were performed by George I. Robertson Microanalytical Laboratory, Florham Park, New Jersey. 4,4′,8-Trimethylpsoralen (**1a**), 4,5′,8-methoxypsoralen (Methoxsalen) (**1e**), and 5-methoxypsoralen (Bergapten) (**1f**) were obtained from the Elder Pharmaceutical Co. of Bryan, Ohio. 4,4′-Dimethylpsoralen (**1c**) was synthesized by a published method [6].

General Preparation of *N*-Phthalimidomethylpsoralens.

A solution of trifluoromethanesulfonic acid (20.0 mmoles) and 25 ml of anhydrous trifluoroacetic acid was added dropwise over 15 minutes to a well-stirred solution (or suspension) of 20.0 mmoles of the requisite psoralen **1** and 30.0 mmoles of *N*-hydroxymethylphthalimide in 100 ml of anhydrous methylene chloride. The addition was carried out with external cooling and the reaction contents were then agitated vigorously at ambient temperature for 6 hours. Evaporation *in vacuo* yielded a dark-colored solid which was stored overnight in an evacuated dessicator over potassium hydroxide pellets to aid in removal of residual acidic volatiles. The solid was then dissolved in the minimal amount of chloroform and washed with 3 × 200 ml of cold water. The chloroform layer was dried over magnesium sulfate, filtered, evaporated to a small volume, and chilled in an ice-water bath. *N*-Phthalimidomethylpsoralens were isolated by filtration and were recrystallized from chloroform to analytical purity.

5′-*N*-Phthalimidomethyl-4,4′,8-trimethylpsoralen (**2a**, 5′-phthal-CH_2).

This compound was obtained in a yield of 70%, mp 273-275°.

Anal. Calcd. for $C_{23}H_{17}NO_5 \cdot 0.25H_2O$: C, 70.48; H, 4.50; N, 3.57. Found: C, 70.15; H, 4.33; N, 3.35.

4′-*N*-Phthalimidomethyl-4,5′,8-trimethylpsoralen (**2b**, 4′-phthal-CH_2).

This compound was obtained in a yield of 61%, mp 274-276°, lit [5] mp 267-274°; ^{1}H nmr (deuteriochloroform): identical to published spectrum [5].

5′-*N*-Phthalimidomethyl-4,4′-dimethylpsoralen (**2c** 5′-phthal-CH_2).

This compound was obtained in a yield of 62%, mp of hydrate 297-299°, mp of sublimed anhydrous material 316-318°, lit mp of anhydrous material 316-318° [6].

Anal. Calcd. for $C_{22}H_{15}NO_5 \cdot 0.75H_2O$: C, 68.31; H, 4.28; N, 3.62. Found: C, 68.00; H, 3.74; N, 3.82.

5,5'-Bis-*N*-Phthalimidomethyl-8-methoxypsoralen (**4**).

Reaction of 8-methoxypsoralen (**1e**) according to the general procedure gave a di-substituted compound as the principal product in 90% yield, (yield based on *N*-hydroxymethylphthalimide as limiting reactant) mp 302-305° (from chloroform); ir: λ max 1765, 1745 (sh), 1720 (sh), 1705 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 4.22 (3H, s, OCH_3), 5.06 (2H, s, CH_2N), 5.14 (2H, s, CH_2N), 6.51 (1H, d, C_3-*H*, J = 10 Hz), 7.7-7.9 (8H, m, phthal Ar*H*), 8.66 (1H, d, C_4-*H*, J = 10 Hz), and 7.36 (1H, s, $C_{4'}$-*H*).

Anal. Calcd. for $C_{30}H_{18}N_2O_8 \cdot 0.25H_2O$: C, 66.79; H, 3.45; N, 5.19. Found: C, 66.98; H, 3.39; N, 5.31.

A crude monophthalimidomethyl compound could be isolated from the concentrated mother liquors but could not be obtained in analytical purity. Its ^{1}H-nmr spectrum was identical to that of **5** (R = CH_3) prepared by methylation of **5** (R = H) as described hereafter.

5-*N*-Phthalimidomethyl-8-hydroxypsoralen (**5**, R = H).

This compound was prepared by a modification of the general method in that equimolar amounts of psoralen (**1d**), trifluoromethanesulfonic acid, and *N*-hydroxymethylphthalimide (20.0 mmoles each) were employed. After removal of acidic contaminants and recrystallization from chloroform, 6.49 g (89% yield) of a mixture of three phthalimidomethyl-8-hydroxypsoralens was obtained, mp 230-250°, tlc on Bakerflex silica gel plates, 2:1 benzene:ethyl acetate eluant, showed three closely spaced spots between R_f 0.32 and 0.45. The ^{1}H nmr of the mixture in DMSO-d_6 showed three *N*-phthalimidomethylenes (-CH_2-) at 4.91, 5.00 and 5.17 ppm. Fractional crystallization from tetrahydrofuran separated **5** (R = H), 35% of the mixture, decomposition without melting 295-310°; tlc silica gel, 2:1 benzene:ethyl acetate R_f = 0.41; ir (potassium bromide): λ max 3300 br (OH), 1770 and 1718 br (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 6.45 (1H, d, C_3-H, J = 10 Hz), 7.19 (1H, d, $C_{4'}$-*H*, J = 2 Hz), 8.06 (1H, d, $C_{5'}$-*H*, J = 2 Hz), 8.62 (1H, d, C_4-*H*, J = 10 Hz), 5.17 (2H, s, -CH_2N), 7.7-7.9 (4H, m, phthal Ar*H*), and 10.7 (1H, br s, O*H*).

Anal. Calcd. for $C_{20}H_{11}NO_6 \cdot 0.25H_2O$: C, 65.62; H, 3.20; N, 3.83. Found: C, 65.60; H, 3.35; N, 4.38.

The remaining *N*-phthalimidomethyl-8-hydroxypsoralens, 65% of the mixture were isolated as non-separated components from the mother liquors of the THF fractional crystallization, mp 275-285°. The loss of coupled furan ring proton resonances (the $C_{4'}$-H and $C_{5'}$-H normally found at *ca.* 7.1 and 8.1 respectively with J = 2 Hz), the appearance of these resonances as shifted singlets at 7.30 and 8.25 ppm, the retention of the C_3-H (6.45 ppm) C_4-H (8.62 ppm) coupled doublets (J = 10 Hz), and the retention of the C_5-H signal at 7.4 ppm, suggested that these isomers are the 4'- and 5'-substituted analogs. A combustion analysis of the mixture confirmed its elemental composition.

Anal. Calcd. for $C_{20}H_{11}NO_6$: C, 66.48; H, 3.06; N, 3.87. Found: C, 66.08; H, 3.27; N, 4.22.

5-*N*-Phthalimidomethyl-8-methoxypsoralen (**5**, R = CH_3).

A suspension of 1.00 g (2.75 mmoles) of **5**, (R = H), 2.0 g of anhydrous potassium carbonate, 2.0 ml of methyl iodide and 50 ml of anhydrous acetone was stirred at reflux for 24 hours. The medium was filtered while hot and the inorganic solids washed on the filter with 50 ml of hot acetone and 50 ml of chloroform. Evaporation *in vacuo* yielded 0.95 g (91% yield) of **5** (R = CH_3), mp 264-265°, (from chloroform), lit [21] mp 261°; ir (potassium bromide): λ max 1770 and 1705 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.22 (3H, s, OCH_3), 5.21 (2H, s, CH_2N), 6.52 (1H, d, C_3-*H*, J = 10 Hz), 7.39 (1H, d, $C_{4'}$-*H*, J = 2 Hz), 7.7-7.9 (4H, m, phthal Ar*H*), 8.15 (1H, d, $C_{5'}$-*H*, J = 2 Hz) and 8.70 (1H, d, C_4-*H*, J = 10 Hz).

Anal. Calcd. for $C_{21}H_{13}NO_6$: C, 67.20; H, 3.49; N, 3.73. Found; C, 67.07; H, 3.47; N, 4.01.

The ir and ^{1}H nmr were identical with those of an authentic sample prepared by chloromethylation and potassium phthalimide displacement on 8-methoxypsoralen [27].

8-*N*-Phthalimidomethyl- and 4'-*N*-Phthalimidomethyl-5-methoxypsoralen (**6** and **7**).

These compounds were prepared by a modification of the general procedure using equimolar (18.0 mmoles) quantities of psoralen **1f**, *N*-hydroxymethylphthalimide and the trifluoromethanesulfonic acid. Product isolation as previously described gave a white solid (from chloroform) which displays three principal spots on tlc (silica gel plates, 50:1 chloroform:ethyl acetate) between 0.73 and 0.37 R_f. The crude product mixture was subjected to flash chromatography on 200-400 mesh silica using the chloroform:ethyl acetate eluant. One fraction (3.0 g, 49% yield) of R_f = 0.73 on tlc was identified as **7**, mp 244-246°; ^{1}H-nmr (deuteriochloroform): δ 4.23 (3H, s, OCH_3), 4.99 (2H, s, CH_2N), 6.20 (1H, d, C_3-*H*, J = 9 Hz), 6.99 (1H, s, $C_{4'}$-*H*), 7.07 (1H, s, C_8-*H*), 7.7-7.9 (4H, m, phthal Ar*H*), and 8.11 (1H, d, C_4-*H*, J = 9 Hz).

Anal. Calcd. for $C_{21}H_{15}NO_6$: C, 66.83; H, 4.00; N, 3.71. Found: C, 66.63; H, 3.74; N, 3.51.

A second fraction (0.91 g, 15% yield) of R_f = 0.43 on tlc was identified as **6**, mp 272-273°; ^{1}H nmr (deuteriochloroform): δ 4.21 (3H, s, OCH_3), 5.31 (2H, s, CH_2N), 6.24 (1H, d, C_3-*H*, J = 9 Hz), 6.98 (1H, d, $C_{4'}$-*H*, J = 2 Hz), 7.50 (1H, d, $C_{5'}$-*H*, J = 2 Hz), 7.7-7.9 (4H, m, phthal Ar*H*), and 8.13 (1H, d, C_4-*H*, J = 9 Hz).

Anal. Calcd. for $C_{21}H_{15}NO_6$: C, 66.82; H, 4.00; N, 3.71. Found: C, 66.68; H, 3.81; N, 3.75.

No other phthalimido products could be isolated in a pure state but a trace of unreacted 5-methoxypsoralen was recovered (R_f *ca* 0.6 in 50:1 chloroform:ethyl acetate on silica plates) and yields expressed above have been corrected. For comparison the ^{1}H nmr in deuteriochloroform of authentic 5-methoxypsoralen (**1f**) from Elder Pharmaceuticals is: δ 4.26 (3H, s, OCH_3), 6.20 (1H, d, C_3-*H*, J = 9 Hz), 7.01 (1H, d, $C_{4'}$-*H*, J = 2 Hz), 7.08 (1H, s, C_8-*H*), 7.58 (1H, d, $C_{5'}$-*H*, J = 2 Hz), and 8.14 (1H, d, C_4-*H*, J = 9 Hz). A very similar spectral analysis has been reported for **1g** in DMSO-d_6/deuteriochloroform mixture [13].

Preparation of 5-*N*-Phthalimidomethyl-4',5'-dihydro-8-hydroxypsoralen (**9**, R = H).

A solution of 10.0 mmoles of trifluoromethane-sulfonic acid, 12.5 ml of trifluoroacetic acid and 10.0 mmoles each of 4',5'-dihydro-8-hydroxypsoralen (**8**, R_1 = H) [13] and *N*-hydroxymethylphthalimide were reacted according to the general procedure given above and 2.77 g, 76% yield of **9** (R = H) were obtained, decomposition wtihout melting 300-310°; ir (potassium bromide): λ max 3350 (OH), 1770 and 1710 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.39 (2H, t, $C_{4'}$-*H'*, J = 8 Hz), 4.65 (2H, t, $C_{5'}$-*H'*, J = 8 Hz), 4.87 (2H, s, CH_2N), 6.29 (1H, d, C_3-*H*, J = 10 Hz), 7.7-7.9 (4H, m, phthal Ar*H*), 8.35 (1H, d, C_4-*H*, J = 10 Hz), and 9.7 (1H, br s, O*H*).

Anal. Calcd. for $C_{20}H_{13}NO_6 \cdot 0.5H_2O$: C, 64.51; H, 3.79; N, 3.76. Found: C, 64.24; H, 3.63; N, 3.90.

Preparation of 5-*N*-Phthalimidomethyl-4',5'-dihydro-8-methoxypsoralen (**9**, R = Me).

A suspension of 1.00 g (2.68 mmoles) of **9** (R = H), 2.0 g of anhydrous potassium carbonate, 2.0 ml of methyl iodide and 50 ml of anhydrous acetone was stirred at reflux for 24 hours, filtered while hot and inorganic solids washed on the filter with 50 ml of chloroform and 50 ml of acetone. The organic phase was evaporated and the crude solids recrystallized from methylene chloride to yield 0.89 g (87%) of **9** (R = Me), mp 274-275°; ir (potassium bromide): λ max 1775 and 1715 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.51 (2H, t, $C_{4'}$-H_2, J = 8 Hz), 4.10 (3H, s, CH_3O), 4.76 (2H, t, $C_{5'}$-H_2, J = 8 Hz), 4.91 (2H, s, CH_2N), 6.33 (1H, d, C_3-*H*, J = 10 Hz), 7.7-7.9 (4H, m, phthal Ar*H*) and 8.31 (1H, d, C_4-*H*, J = 10 Hz).

Anal. Calcd. for $C_{21}H_{15}NO_6$: C, 66.83; H, 4.00; N, 3.71. Found; C, 66.72; H, 3.75; N, 3.71.

Preparation of Aminomethylpsoralens.

A mixture of 2.0 mmoles of the *N*-phthalimidomethylpsoralen (**2**), 4.0 ml of hydrazine hydrate (85% hydrazine in water), and 100 ml of 95% ethanol was heated at reflux for 6 hours and evaporated *in vacuo* to a crude solid mass. This solid was suspended in 250 ml of 0.1 *N* sodium hydroxide solution and extracted with chloroform (2 × 200 ml). The chloroform extracts were combined, washed once with 100 ml of cold water, dried over magnesium sulfate, and evaporated *in vacuo* to a reduced volume. Chilling the solvent precipitated the amines which were recrystallized from chloroform to analytical purity.

5'-Aminomethyl-4,4',8-trimethylpsoralen (**3a**, 5'-CH_2NH_2).

This compound was obtained in a yield of 65%, mp 204-207°, lit [3] mp 197-199°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.77; H, 6.22; N, 5.21.

The ^1H nmr spectrum was identical to published spectrum [3].

4'-Aminomethyl-4,5',8-trimethylpsoralen (**3b**, 4'-CH_2CH_2).

This compound was obtained in a yield of 80%, mp 198-200°. The ^1H nmr spectrum was identical to published spectrum, no mp or analysis reported in previous article [5].

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 69.82; H, 5.75; N, 5.30.

5'-Amino-4,4'-dimethylpsoralen (**3c**, 5'-CH_2NH_2).

This compound was obtained in a yield of 59%, mp 182-185°, lit [6] mp 186-188°; ^1H nmr identical to published spectrum [6].

Acknowledgement.

We acknowledge the assistance of the Elder Pharmaceutical Co., Bryan, Ohio, and the Elsa U. Pardee Foundation.

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[27] We thank Professor Ole Buchardt of the University of Copenhagen for making this comparison.