7,8,4′-trimethoxyflavone which separated from acetone-methanol in colorless, felted needles, m.p. 190° (lit.[28] m.p. 189–190°).

(28) I. C. Badhwar, K. S. Kang, and K. Venkataraman, *J. Chem. Soc.*, 1107 (1932).

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 69.2; H, 5.17; 3 MeO—, 29.8. Found: C, 69.1; H, 5.22; MeO—, 28.8.

Acknowledgment. The author is indebted to L. M. White and Miss G. Secor for the elemental analyses.

ALBANY 10, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KALAMAZOO COLLEGE]

Synthetic Furocoumarins. V.[1] Preparation and Reactions of 8-Amino-4,5′-dimethylpsoralene

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8-Amino-4,5′-dimethylpsoralene (VIa) has been synthesized by a method involving the Claisen rearrangement of 8-acetamido-7-allyloxy-4-methylcoumarin (IIb). Heating in refluxing diethylaniline was found to be a superior method of accomplishing the rearrangement, because heating the *o*-allyloxyacetamido compound alone gave a benzoxazole (VII) as well as the expected 8-acetamido-6-allyl-4-methylumbelliferone (IIIb). Several derivatives of 8-amino-4,5′-dimethylpsoralene have been obtained, most of them *via* diazotization, which was found to proceed satisfactorily in concentrated hydrochloric or hydrobromic acids but not in aqueous sulfuric acid. Reduction of the diazonium salt with hypophosphorous acid gave 4,5′-dimethylpsoralene, which provides an example of the successful use of the amino group as a removable blocking group in the synthesis of linear furocoumarins (psoralenes) from an umbelliferone.

In recent years, intense interest in furocoumarins has been aroused by the discovery that psoralene or 8-methoxypsoralene enhances the rate of pigmentation of human skin.[2] A number of studies[3] have been made of the effect on photosensitizing activity of introducing alkyl substituents in various positions of the basic psoralene system. It has been found that properly located methyl groups do not decrease the activity of psoralene appreciably and particularly that 4,5′,8-trimethylpsoralene (VI. R = CH_3) is as active as psoralene in producing an erythemal response on guinea pig skin irradiated by ultraviolet light.[4] On the other hand, relatively little was known about the activity of psoralenes bearing substituents other than alkyl groups, except for studies on a few naturally occurring compounds, usually methoxy derivatives.[3,4]

This paper describes the synthesis of 8-amino-4,5′-dimethylpsoralene (VIa) from which a number of substituted psoralenes (VIb–g) have been obtained by diazotization and other reactions involving the amino group. The photosensitizing activity of these compounds can now be compared to that of 4,5′,8-trimethylpsoralene (VI. R = CH_3) as, in every case, the only structural difference involves replacement of the 8-methyl group by some other group. The photosensitizing activity of some of the new psoralenes has already been evaluated[4] and data for the others will soon be reported elsewhere. Although not all compounds have been tested as yet, it appears that any substitution which markedly alters the resonance within the psoralene system decreases or eliminates the photosensitizing activity.[4] The general scheme for the preparation of 8-amino-4,5′-dimethylpsoralene is portrayed by structures I through VIa. The starting material was 4-methylumbelliferone (Ia), from which Shah and Mehta[5] have obtained 4-methyl-6-nitroumbelliferone in 24% yield and 4-methyl-8-nitroumbelliferone (Ib) in 32% yield by nitration in sulfuric acid at 5–10°. Their procedure was repeated on a much larger scale (1364 g. of 4-methylumbelliferone), being careful to keep the reaction temperature below 5°. The large amount of crude nitration product was extremely difficult to dry, but it was found possible to use it in the next step without drying or other purification. A small portion was repeatedly crystallized to obtain a yellow solid, m.p. 256°, which was identical with 4-methyl-8-nitroumbelliferone (Ib) prepared by the condensation of 2-nitroresorcinol and ethyl acetoacetate.[6] 4-Methyl-8-nitroumbelliferone (Ib), on treatment with allyl bromide and potassium carbonate in acetone, gave 7-allyloxy-4-methyl-8-nitrocoumarin (IIa). However, all attempts to produce 6-allyl-4-methyl-8-nitroumbelliferone (IIIa) by Claisen rear-

(1) Part IV; K. D. Kaufman and W. E. Russey, *J. Org. Chem., in press.*

(2) Psoralenes and Radiant Energy, proceedings of a symposium, *J. Invest. Dermatol.*, **32**, 131–391 (1959).

(3) K. D. Kaufman, *J. Org. Chem.*, **26**, 117 (1961), (footnote 5 gives a partial bibliography of biological studies on substituted psoralenes).

(4) M. A. Pathak, J. B. Fellman, and K. D. Kaufman, *J. Invest. Dermatol.*, **35**, 165–183 (1960).

(5) N. M. Shah and D. H. Mehta, *J. Indian Chem. Soc.*, **31**, 784–786 (1954).

(6) D. Chakravarti and B. Ghosh, *J. Indian Chem. Soc.*, **12**, 622 (1935).

rangement, either by heating IIa alone or in refluxing diethylaniline, gave only intractable tars.

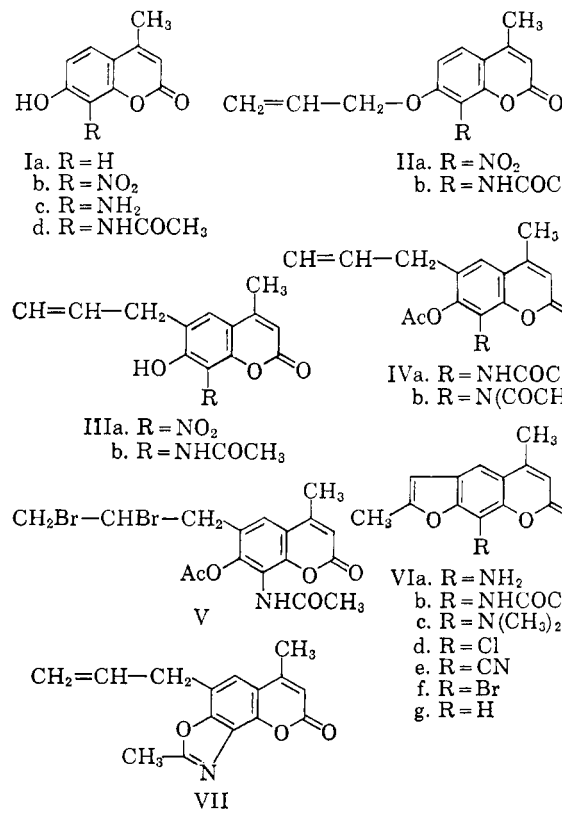
As the rearrangement with a nitro group present was unsuccessful, it was decided to prepare the corresponding acetamido compound (IIb) and attempt its rearrangement. Reduction of the crude, wet nitration product from 4-methylumbelliferone, using sodium hydrosulfite in ammonium hydroxide solution, produced a compound, m.p. 269.5–270°, in 40% yield (two steps) from 4-methylumbelliferone. This material proved to be identical (mixed m.p. and infrared spectra) to 8-amino-4-methylumbelliferone (Ic), prepared by the condensation of 2-aminoresorcinol hydrochloride with ethyl acetoacetate according to the procedure of Fries and Lindemann.[7] Reduction of pure 4-methyl-8-nitroumbelliferone by the sodium hydrosulfite method gave the 8-amino compound in 95% yield. Treatment with acetic anhydride in boiling acetic acid gave an 87% yield of 8-acetamido-4-methylumbelliferone (Id), which dissolves in 5% aqueous sodium hydroxide to give a yellow solution that exhibits blue fluorescence.

Treatment of Id with allyl bromide and potassium carbonate in acetone gave a disappointingly low yield (*ca.* 45%) of 8-acetamido-7-allyloxy-4-methylcoumarin (IIb), undoubtedly because of the low solubility of 8-acetamido-4-methylumbelliferone (Id) in boiling acetone. Better results were obtained by the action of allyl bromide and sodium methoxide in methanol at room temperature. Under the latter conditions, the reaction mixture was allowed to stand for a week, after which both starting material (Id) and 8-acetamido-7-allyloxy-4-methylcoumarin (IIb) were easily isolated. The yield of allyl ether was 70%, based on recovered starting material. It is interesting that opening of the pyrone ring, followed by allylation of the pyrone oxygen atom does not appear to be a major problem under these conditions.

In order to induce 8-acetamido-7-allyloxy-4-methylcoumarin (IIb) to undergo the Claisen rearrangement, a small amount was heated to 210° for two hours. In this way, 8-acetamido-6-allyl-4-methylumbelliferone (IIIb) was obtained in 50% yield, but in addition an alkali insoluble compound, $C_{15}H_{13}NO_3$, was isolated in 26% yield. Its infrared spectrum showed the typical coumarin carbonyl peak at 1699 cm.$^{-1}$ and C=C (vinyl) absorption at 1655 cm.$^{-1}$ as well as several peaks in the region 1490–1640 cm.$^{-1}$, which could be assigned to the C=N system of a benzoxazole. It has been assigned the structure of 4-allyl-2,6-dimethyl-8*H*-pyrano-[2,3-*e*]benzoxazole-8-one (VII) in view of the fact that *o*-amidophenols are known[8] to give benzoxazoles on heating. It is interesting that this compound and other oxazolocoumarins, which are structurally similar to the psoralenes, do not exhibit any photosensitizing activity.[4] This reaction provides an excellent example of the superior results that can be obtained by carrying out Claisen rearrangements in refluxing diethylaniline[9] because, when 8-acetamido-7-allyloxy-4-methylcoumarin (IIb) was treated in that way, the desired rearrangement product (IIIb) was obtained in 80% yield, uncontaminated by the oxazolocoumarin.

Acetylation of crude 8-acetamido-6-allyl-4-methylumbelliferone (IIIb) with one molar equivalent of acetic anhydride in pyridine gave pure 8-acetamido-7-acetoxy-6-allyl-4-methylcoumarin (IVa) in 56% yield. The use of excess acetic anhydride in pyridine, however, produced a compound $C_{19}H_{19}NO_6$, whose infrared spectrum showed no OH or NH absorption. It is undoubtedly 7-acetoxy-6-allyl-8-(*N*,*N*-diacetylamino)-4-methylcoumarin (IVb). From the addition of one molar equivalent of bromine to 8-acetamido-7-acetoxy-6-allyl-4-methylcoumarin (IVa) in chloroform, 8-acetamido-7-acetoxy-6-(2′,3′-dibromopropyl)-4-methylcoumarin (V) was isolated.

Experimental difficulties in the purification of V led to a decision to cyclize the crude dibromo compound and purify the resultant psoralene. In as much as samples of both IVa and IVb were on hand, a mixture of the two in chloroform was treated with just enough bromine to saturate the allyl double bonds of both compounds. After the evaporation of chloroform, the crude brominated ma-



(7) K. Fries and N. Lindemann, *Ann.*, **404**, 68 (1914).

(8) J. W. Cornforth, *Heterocyclic Compounds*, Vol. 5, R. C. Elderfield, ed., Wiley, New York, 1957, p. 420–421.

(9) L. Claisen, *Ann.*, **418**, 72 (1918).

terial was refluxed with sodium ethoxide in absolute ethanol and a mixture was obtained, from which 8-acetamido-4,5′-dimethylpsoralene (VIb) was isolated in 24% yield and 8-amino-4,5′-dimethylpsoralene (VIa) in 17% yield.

Treatment of 8-amino-4,5′-dimethylpsoralene (VIa) with excess methyl iodide in acetone with potassium carbonate suspended gave 8-dimethylamino-4,5′-dimethylpsoralene (VIc). The diazotization of 8-amino-4,5′-dimethylpsoralene (VIa) was attempted in several media. When aqueous sodium nitrite was added to a suspension of the amine in concentrated hydrochloric acid at 0°, the suspended solid readily dissolved and heating the solution with aq. cuprous chloride gave the expected 8-chloro-4,5′-dimethylpsoralene (VId) in 14.5% yield. Neutralization of a similarly diazotized solution with aq. sodium carbonate, followed by heating with aqueous cuprous cyanide gave a 37% yield of 8-cyano-4,5′-dimethylpsoralene (VIe). Similar results were obtained by diazotization in 48% aqueous hydrobromic acid followed by heating with aqueous cuprous bromide, which gave 8-bromo-4,5′-dimethylpsoralene (VIf) in 34% yield. In view of these results, it was interesting that by diazotizing VIa in aq. sulfuric acid and heating the solution, we were unable to isolate any of the expected 4,5′-dimethyl-8-hydroxypsoralene (VI. R = OH) or any other pure compound. The failure appears to be due to an attack on the furocoumarin system by nitrous acid in aqueous sulfuric acid, which is not encountered with nitrous acid in hydrochloric or hydrobromic acids. A sample of 4,5′,8-trimethylpsoralene (VI. R = CH_3), available from previous studies,[3] was found to be insoluble and stable to hydrolysis in 50% aqueous sulfuric acid at 80°. Under the same conditions with sodium nitrite added, the trimethylpsoralene dissolved and was rapidly and completely destroyed. When a suspension of trimethylpsoralene in concentrated hydrochloric acid containing sodium nitrite was heated to 80°, no change was observed and the starting material was recovered in nearly quantitative yield. These experiments indicate that diazotization of aminofurocoumarins should not be carried out in aqueous sulfuric acid solutions.[10]

Diazotization in concentrated hydrochloric acid followed by treatment with hypophosphorous acid converted 8-amino-4,5′-dimethylpsoralene (VIa) to 4,5′-dimethylpsoralene (VIg) in 39% yield. Although the dimethylpsoralene has already been reported,[3] obtaining it by this method represents the successful synthesis of a linear furocoumarin (psoralene) from a 7-hydroxycoumarin by the use of a removable blocking group in the reactive 8-position [7-allyloxy-4-methylcoumarin (II. R = H) and homologs rearrange to give exclusively 8-allylumbelliferones, which lead to angular furocoumarins (isopsoralenes)[3]].

(10) M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958) report the successful substitution of a hydroxyl group, for the amino group of an aminomethoxypsoralene by diazotization in concentrated hydrochloric acid and 95% methanol. We did not try this method for the preparation of VI (R = OH).

EXPERIMENTAL[11]

4-Methyl-8-nitroumbelliferone (Ib). A. Condensation of 2-nitroresorcinol with ethyl acetoacetate, according to the procedure of Chakravarti and Ghosh,[6] gave the product, m.p. 256°, as reported. It gives an intense orange colored solution in 5% aq. sodium hydroxide and an alcohol solution gives no color with aq. ferric chloride.

B. A solution of conc. nitric acid (490 ml., 7.75 moles) in conc. sulfuric acid (510 ml.) was added to a stirred solution of 4-methylumbelliferone[12] (Ia, 1364 g., 7.75 moles) in conc. sulfuric acid (*ca.* 3 l.) at such a rate as to keep the temperature below 5° (ice-salt bath cooling). After warming to 20°, the reaction mixture was poured into a stirred mixture of ice (25 kg.) and water (20 l.) and a yellow precipitate was collected by filtration and thoroughly washed with water. The entire product was only partially dried, because it holds water tenaciously and prolonged heating leads to decomposition. A portion of the product was alternatively recrystallized from glacial acetic acid and methyl ethyl ketone to give material of m.p. 256°, which did not depress the m.p. of the sample from A. The infrared spectra of the two samples were identical. Shah and Mehta[5] also report m.p. 256° for this compound, which they isolated in 32% yield from a smaller scale nitration.

7-Allyloxy-4-methyl-8-nitrocoumarin (IIa). A mixture of 4-methyl-8-nitroumbelliferone (100 g., 0.452 mole), anhydrous potassium carbonate (226 g., 1.64 moles), allyl bromide (118 ml., 1.36 moles), and acetone (2 l.) was stirred and refluxed for 19 hr. Most of the acetone was evaporated under reduced pressure and 1% aq. sodium hydroxide (5 l.) was added to the residue. An undissolved solid was collected by filtration, washed with water, dried, and recrystallized from chloroform to give off-white prisms (37.9 g., 32%), m.p. 158–159°.

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.72; H, 4.32; N, 5.44.

8-Amino-4-methylumbelliferone (Ic). A. Condensation of 2-aminoresorcinol hydrochloride (17.29 g.) and ethyl acetoacetate (27.2 ml.), according to the procedure of Fries and Lindemann,[7] gave 13.90 g. (68%) of crude product, m.p. 266–268°. Recrystallization from 95% ethanol gave the pure compound, m.p. 269.5–270° (reported: 269°). It gave a yellow, nonfluorescent solution in 5% aq. sodium hydroxide and a warm alcohol solution showed an intense green color with aq. ferric chloride.

B. A solution of sodium hydrosulfite (7.0 g., 0.04 mole) in water (30 ml.) was added rapidly to a stirred, orange colored suspension of pure 4-methyl-8-nitroumbelliferone (m.p. 256°, 2.37 g., 0.0107 mole) in 30% aq. ammonia (20 ml.). The reaction mixture warmed spontaneously and, as the suspended solid began to dissolve, a yellow precipitate appeared. After boiling the mixture for 15 minutes and cooling to room temperature, the yellow solid (1.94 g., 95%), m.p. 269.5–270°, was collected by filtration. Without further purification, it did not depress the m.p. of the sample from A and the infrared spectra of the two samples were identical. Application of this procedure to a portion (600 g. out of 1879 g.) of the crude, wet product from the large scale nitration of 4-methylumbelliferone gave 189 g. (40% yield from 4-methylumbelliferone), of pure 8-amino-4-methyl-

(11) All melting points in this section are corrected and were determined in soft glass capillary tubes.

(12) A. Russell and J. R. Frye, *Org. Syntheses*, **21**, 25 (1941).

umbelliferone, m.p. 269.5–270°, after one recrystallization from 95% ethanol. Mixed melting points and comparison of infrared spectra showed this material to be identical with the samples reported above.

8-Acetamido-4-methylumbelliferone (Id). Acetic anhydride (74.1 ml., 0.785 mole) was added rapidly to a boiling solution of 8-amino-4-methylumbelliferone (100 g., 0.523 mole) in glacial acetic acid (3 l.). After 5 minutes, the solution was allowed to cool to room temperature and it deposited off-white prisms (106.5 g., 87%), m.p. 276.8–277.2°. A small sample dissolved completely in 5% aq. sodium hydroxide giving a yellow solution, which exhibited intense blue fluorescence. A warm alcohol solution gave no color with aq. ferric chloride. Recrystallization from glacial acetic acid did not change the m.p. but gave an analytical sample.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.79; H, 4.76; N, 5.98. Found: C, 62.08; H, 4.94; N, 5.89.

8-Acetamido-7-allyloxy-4-methylcoumarin (IIb). A. A solution of 8-acetamido-4-methylumbelliferone (233 g., 1 mole) and allyl bromide (260 ml., 3 moles) in 0.33*M* methanolic sodium methoxide (3.5 l.) stood at room temperature for one week, during which 66 g. (0.28 mole) of starting material crystallized from the solution. After filtration, the clear solution was poured into a stirred mixture (*ca.* 20 l.) of ice and 1% hydrochloric acid and the product was collected by filtration, dissolved in chloroform, and washed thoroughly with 5% aq. sodium hydroxide, 1% hydrochloric acid, and water. After drying (magnesium sulfate), the chloroform solution was concentrated on a steam bath to 137.9 g. (70.5%, based on recovered starting material) of off-white prisms, m.p. 171.3–172.3°. Recrystallization from 95% ethanol did not change the m.p. but gave an analytical sample of colorless prisms.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.05; H, 5.45; N, 5.20.

8-Acetamido-6-allyl-4-methylumbelliferone (IIIb). 8-Acetamido-7-allyloxy-4-methylcoumarin (156.5 g.) was refluxed in *N,N*-diethylamine (450 ml.) for 1.5 hr. After standing for several hours, the solid which had crystallized from the cooled solution, was triturated with petroleum ether (b.p. 30–60°) to remove traces of diethylaniline and dried to obtain light yellow prisms (124.1 g., 79.3%), m.p. 162.5–166°. This material was completely soluble in 5% aq. sodium hydroxide and was suitable for use in the next step, but a portion of it was recrystallized from benzene to give colorless prisms, m.p. 167–168°.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.11; H, 5.46; N, 4.99.

4-Allyl-2,6-dimethyl-8H-pyrano[2,3-e]benzoxazole-8-one (VII). 8-Acetamido-7-allyloxy-4-methylcoumarin (5.00 g., 0.0183 mole) was heated in an oil bath to 210° (temp. of reaction mixture) for 2 hr. and poured into boiling 95% ethanol (25 ml.). The cool ethanol solution deposited a crystalline solid, which was collected and washed thoroughly with 5% aq. sodium hydroxide. An alkali insoluble residue (1.03 g.) was collected by filtration. An additional 0.17 g. of alkali insoluble material was obtained by diluting the ethanol mother liquor with water (500 ml.) and washing the precipitate with 5% aq. sodium hydroxide. The combined solids (1.20 g., 26%) were recrystallized from 95% ethanol to give pale yellow needles, m.p. 134–135°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.06; H, 5.16; N, 5.49. Found: C, 69.91; H, 5.44; N, 5.20.

Acidification of the combined aq. sodium hydroxide washes with conc. hydrochloric acid gave 2.51 g. (50%) of crude 8-acetamido-6-allyl-4-methylumbelliferone (IIIb), which was recrystallized from benzene to give colorless prisms, m.p. 167–168°.

8-Acetamido-7-acetoxy-6-allyl-4-methylcoumarin (IVa). Acetic anhydride (1.89 ml., 0.020 mole) was added dropwise to a stirred solution of crude 8-acetamido-6-allyl-4-methylumbelliferone (m.p. 162.5–166°, 5.47 g., 0.020 moles) in pyridine (30 ml.), which was being chilled in an ice bath. After standing overnight at room temperature, the solution was poured into a mixture (*ca.* 350 ml.) of ice and water and acidified with conc. hydrochloric acid. A white precipitate was collected by filtration and recrystallized from 95% ethanol to obtain colorless prisms (3.52 g., 56%), m.p. 198°.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.44; N, 4.44. Found: C, 64.80; H, 5.51; N, 4.35.

7-Acetoxy-6-allyl-8-(N,N-diacetylamino)-4-methylcoumarin (IVb). Acetic anhydride (44.7 ml., 0.472 mole) was added rapidly to a stirred solution of crude 8-acetamido-6-allyl-4-methylumbelliferone (25.82 g., 0.0945 mole) in pyridine (300 ml.). The next day, the solution was poured into a mixture of ice and water (*ca.* 3 l.) and a white precipitate was collected by filtration. Two recrystallizations from 95% ethanol gave colorless needles (12.47 g., 37%), m.p. 163.5°.

Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.93. Found: C, 64.15; H, 5.53; N, 3.91.

8-Acetamido-7-acetoxy-6-(2',3'-dibromopropyl)-4-methylcoumarin (V). A solution of bromine (1.32 g., 0.00825 mole) in chloroform (5 ml.) was added to a stirred solution of 8-acetamido-7-acetoxy-6-allyl-4-methylcoumarin (2.61 g., 0.00828 mole) in chloroform (50 ml.) at such a rate as to insure instant decolorization of the bromine. Evaporation of the chloroform on a steam bath left an off-white solid which crystallized from glacial acetic acid as a tan solid (3.22 g., 82%), m.p. 206.5° (dec.). Recrystallization of a small amount from *n*-butyl alcohol gave colorless prisms, m.p. 221° (dec.). The decomposition point varied with the rate of heating and was of little significance.

Anal. Calcd. for $C_{17}H_{17}Br_2NO_5$: C, 42.97; H, 3.61; Br, 33.64; N, 2.95. Found: C, 43.33; H, 3.64; Br, 33.33; N, 3.09.

8-Acetamido-4,5'-dimethylpsoralene (VIb). A solution of bromine (70.5 g., 0.441 mole) in chloroform (60 ml.) was added to a stirred solution of 8-acetamido-7-acetoxy-6-allyl-4-methylcoumarin (IVa. 26.92 g., 0.0854 mole) and 7-acetoxy-6-allyl-8-(*N,N*-diacetylamino)-4-methylcoumarin (IVb, 127 g., 0.355 mole) in chloroform (1 l.) at such a rate as to insure instantaneous decolorization of the bromine. The solution was concentrated to dryness under a stream of air and the white, powdery residue was added to a hot, stirred solution of sodium (54.0 g., 2.35 moles) in dry, absolute ethanol (3 l.). A yellow precipitate separated immediately and the suspension was refluxed for two hours. The hot reaction mixture was poured into a stirred mixture of conc. hydrochloric acid (3 l.), water (10 l.), and ice (15 kg.). Filtration gave a clear filtrate, which contained 8-amino-4,5'-dimethylpsoralene hydrochloride, and a tan solid which was washed with four portions (300 ml.) of 5% aq. sodium hydroxide, using a large centrifuge to avoid the slow filtration encountered during a preliminary run. The light yellow, alkali-insoluble, residue was washed free of alkali and recrystallized from glacial acetic acid, using Norit-A, to obtain colorless prisms (29.1 g., 24.3%), m.p. 304–305°.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.71; H, 5.00; N, 4.90.

8-Amino-4,5'-dimethylpsoralene (VIa). The clear filtrate from above, containing 8-amino-4,5'-dimethylpsoralene hydrochloride, was made alkaline (*p*H>10) by the addition of 5% aq. sodium hydroxide and a yellow precipitate was collected by filtration and washed with water. Recrystallization from 95% ethanol gave yellow, felted needles (17.2 g., 17%), m.p. 193–193.5°.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.59; H, 4.98; N, 5.93.

8-Dimethylamino-4,5'-dimethylpsoralene (VIc). A mixture of 8-amino-4,5'-dimethylpsoralene (400 mg., 1.75 mmoles), methyl iodide (2.48 g., 17.5 mmoles), anhydrous potassium carbonate (242 mg., 1.75 mmoles), and acetone (60 ml.) was refluxed overnight and concentrated to dryness on a steam bath. The yellow residue was washed thoroughly with water and dried to give a solid which did not melt

sharply. Benzenesulfonyl chloride (1 ml.) was added to a solution of the solid in pyridine (5 ml.) and, after stirring overnight, the solution was poured into water (100 ml.). The resulting suspension was warmed on a steam bath, to hydrolyze excess benzenesulfonyl chloride, until a brown granular precipitate could be collected by filtration. Sublimation of this material at 120°/0.27 mm. gave a yellow solid (208 mg., 46%), m.p. 142–142.5°. Recrystallization from ligroin (b.p. 90–120°) did not change the m.p., but gave an analytical sample of yellow needles.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 6.25; N, 5.44. Found: C, 70.35; H, 6.20; N, 5.61.

8-Chloro-4,5′-dimethylpsoralene (VId). A solution of sodium nitrite (140 mg., 2.0 mmoles) in water (*ca.* 3 ml.) was added slowly to a suspension of 8-amino-4,5′-dimethylpsoralene (400 mg., 1.75 mmoles) in conc. hydrochloric acid (10 ml.) that was cooled in an ice-salt bath to 0°. At no time during the addition did the temperature rise above 5°. After standing for 5 min., the clear solution was poured slowly into a boiling solution of cuprous chloride (396 mg.) in 6*M* hydrochloric acid (20 ml.). A gas was evolved and an orange precipitate was collected after allowing the solution to cool and diluting with an additional 60 ml. of water. After washing with 5% aq. sodium hydroxide, 5% hydrochloric acid, and water, the orange solid was recrystallized from 95% ethanol and then from benzene. Vacuum sublimation gave a colorless product (63 mg., 14.5%), m.p. 260.5–261°.

Anal. Calcd. for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65; Cl, 14.26. Found: C, 62.49; H, 3.26; Cl, 14.42.

8-Cyano-4,5′-dimethylpsoralene (VIe). Diazotization of 10.80 g. (0.0471 mole) of 8-amino-4,5′-dimethylpsoralene in conc. hydrochloric acid (675 ml.) with sodium nitrite (3.27 g., 0.0474 mole) as described above gave a clear solution, which was neutralized with excess 15% aq. sodium carbonate, keeping the temperature below 5° and occasionally adding a drop of *n*-heptyl alcohol to eliminate foaming. The neutral solution was added slowly to an aq. cuprous cyanide[13] solution at 0–5° and the brown reaction mixture was stirred with ice bath cooling for 30 min., kept at room temperature for one hour, and quickly warmed to 60°. The next day, a brown solid (14.54 g.) was collected and 2.00 g. was twice sublimed at 250°/0.30 mm. to give a white solid (0.578 g., 37%), m.p. 287–289°. Recrystallization from glacial acetic acid gave a sample of m.p. 290.5–291.5°.

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.33; H, 3.57; N, 5.95.

8-Bromo-4,5′-dimethylpsoralene (VIf). A suspension of 8-amino-4,5′-dimethylpsoralene (2.29 g., 0.0100 mole) in 48% hydrobromic acid (50 ml.) was diazotized with sodium nitrite (0.69 g., 0.0100 mole) and the clear solution was poured slowly into a boiling solution of cuprous bromide (2.0 g.) in 6% hydrobromic acid (100 ml.). After cooling to room temperature and diluting with water (200 ml.), a brown solid was collected and recrystallized twice from glacial acetic acid using Norit-A to obtain off-white needles (1.005 g., 34%), m.p. 261–261.5°.

Anal. Calcd. for $C_{13}H_9BrO_3$: C, 53.27; H, 3.09; Br, 27.26. Found: C, 53.26; H, 3.12; Br, 27.19.

4,5′-Dimethylpsoralene (VIg). Diazotization of 1.00 g. (4.37 mmoles) of 8-amino-4,5′-dimethylpsoralene in conc. hydrochloric acid (75 ml.) with sodium nitrite (301 mg., 4.36 mmoles) gave a clear solution, which was added slowly to a 30% aq. hypophosphorus acid solution containing powdered cupric sulfate (ca. 250 mg.) as a catalyst[14] at 0–5°. After refrigerating for several hours and standing overnight at room temperature, a light brown solid was collected, washed with 5% aq. sodium hydroxide, 5% hydrochloric acid, and sublimed at 150°/0.28 mm. Recrystallization from ethanol gave colorless, felted needles (367 mg., 39%), m.p. 165–165.5° (reported[3]: 161–162°).

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(13) Prepared from cupric sulfate pentahydrate (15.4 g.) by the method of H. T. Clarke and R. R. Read, *Org. Syntheses*, **Coll. Vol. I**, 514 (1941).

(14) A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 583 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY COLLEGE AT ALBANY[1]]

The Preparation and Properties of Some 1,2-Dihydrophthalazine Derivatives

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The reduction of 2-methyl- and 2-ethylphthalazinium iodide with aqueous sodium borohydride yielded the corresponding 2-alkyl-1,2-dihydrophthalazines. Reduction of 2-benzylphthalazinium chloride was accompanied by debenzylation to give 1,2-dihydrophthalazine. Quaternization of 2-methyl-1,2-dihydrophthalazine resulted in the formation of 2,2-dimethyl-1,2-dihydrophthalazinium iodide (V) as evidenced by the facile conversion of the salt to *α*-*N*,*N*-dimethylamino-*o*-toluonitrile.

As part of a continuing investigation[2] of reduced diazaheterocycles, we now wish to report the results of our investigation of reduced phthalazines.

In 1895, Gabriel and Müller[3] reported that 2-methylphthalazinium iodide (I) could be converted to a mixture of 2-methyl-1,2-dihydrophthalazine (III) and 2-methyl-1(2*H*)-phthalazinone (IV) on treatment with one equivalent of aqueous potassium hydroxide. The volatile base (III) was separated by steam distillation in an inert atmosphere. Elderfield and Wythe[4] have suggested that the

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(2) R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.*, **24**, 205 (1959).

(3) S. Gabriel and F. Müller, *Ber.*, **28**, 1830 (1895).

(4) R. C. Elderfield and S. L. Wythe in *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, ed., John Wiley and Sons, New York, 1957, p. 190.