[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Selective Alkylation of Polyphenols. I. The Use of Diphenylmethylene as a Protective Grouping for *o*-Dihydroxyflavones

LEONARD JURD

Received May 8, 1961

Rhamnetin reacts with α,α'-dichlorodiphenylmethane to form 3,5-dihydroxy-7-methoxy-3',4'-diphenylmethylenedioxyflavone. This may be methylated and hydrolyzed to yield either 3,7-di-*O*-methyl- or 3,5,7-tri-*O*-methylquercetin. The diphenylmethylenedioxyflavone may also be monobenzoylated and hydrolyzed with dilute acids to yield rhamnetin 3-benzoate. From this 5,7,3',4'-tetra-*O*-methylquercetin may be obtained. Gallacetophenone similarly reacts with α,α'-dichlorodiphenylmethane to form 2-hydroxy-3,4-diphenylmethylenedioxyacetophenone, an intermediate from which 7,8-dihydroxyflavones may be readily prepared. Thus the 2-*O*-anisoyl derivative rearranges to yield 2-hydroxy-3,4-diphenylmethylenedioxy-ω-anisoylacetophenone. With dilute acid this is simultaneously cyclized and hydrolyzed to give 7,8-dihydroxy-4'-methoxyflavone.

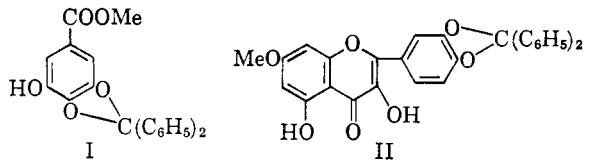
Partially alkylated flavonoid compounds frequently occur in plants. Difficulties have been experienced, however, in the selective partial alkylation of polyhydroxyflavones in the laboratory. The pronounced relative acidity of a hydroxyl in the 7-position of isoflavones, flavanones, and coumarins allows selective methylation of this hydroxyl by means of dimethyl sulfate and sodium bicarbonate.[1-4] Simple flavones which contain only the acidic 7-hydroxyl and less acidic 3- or 3'-hydroxyl groups may also be preferentially methylated in the 7-position by reaction with one equivalent of dimethyl sulfate. The methylation rates of 7- and 4'-hydroxyl groups and 3- and 4'-hydroxyl groups, however, do not differ sufficiently for the satisfactory partial methylation of flavones containing hydroxyls in these positions.[5] The direct alkylation of most of the naturally occurring, highly hydroxylated flavones with the usual reagents, therefore, usually results in complete *O*-alkylation, alkylation of all phenolic groups except the chelated 5-hydroxyl or nuclear alkylation.[6-14] *o*-Dihydroxyl groups may be protected during methylation by chelation with borax.[15] However, Wender and his associates[16] recently reported that methylation of quercetin under these conditions gives a complex mixture containing at least three unidentified quercetin partial methyl ethers, 3-*O*-methylquercetin, and the desired 3,7-di-*O*-methylquercetin.

In recent years quantities of partially methylated polyhydroxyflavones were required in this laboratory for comparison with natural products, for studies on their metabolic fates in animal bodies and for evaluation as antioxidants. Working primarily with quercetin three general procedures for selective alkylation have now been developed. By these methods, which are described in this and the succeeding papers, sixteen partially methylated derivatives have been prepared from quercetin, including eight of the nine partial ethers known to occur in nature. It is clear that these methods should be generally applicable to other polyhydroxyflavones.

α,α' - Dichlorodiphenylmethane[17] reacts with catechol, methyl gallate, and ellagic acid, relatively simple phenols containing a limited number of dissimilar hydroxyl groups, to form derivatives of the type (I).[18-20] From the reaction of this reagent

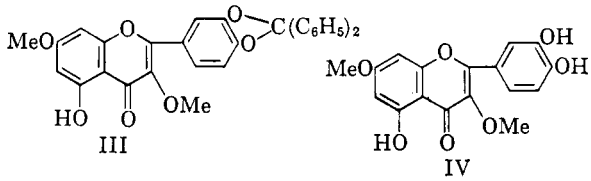
(1) M. L. Dhar and T. R. Seshadri, *J. Sci. Ind. Research (India)*, 14B, 423 (1955).
(2) M. L. Dhar and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 43A, 79 (1956).
(3) L. H. Briggs, and T. P. Cebalo, *Tetrahedron*, **6**, 145 (1959).
(4) P. L. Sawhney and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 37A, 592 (1953).
(5) T. H. Simpson and J. L. Beton, *J. Chem. Soc.*, 4065 (1954).
(6) P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 9A, 177 (1939).
(7) A. C. Jain and T. R. Seshadri, *J. Sci. Ind. Research (India)*, 13B, 539 (1954).
(8) A. G. Perkin, *J. Chem. Soc.*, **103**, 1632 (1913).
(9) S. Rajagopalan, P. R. Rao, K. V. Rao, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 29A, 9 (1949).
(10) W. Baker and R. Robinson, *J. Chem. Soc.*, 3115 (1928).
(11) A. C. Jain and T. R. Seshadri, *Quart. Reviews Chem. Soc.*, 10, 169 (1956).
(12) L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 22A, 215 (1945).
(13) P. S. Rao, P. R. Reddy, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 12A, 495 (1940).
(14) V. B. Mahesh, S. Neelakantan, and T. R. Seshadri, *J. Sci. Ind. Research (India)*, 15B, 287 (1956).
(15) A. C. Jain, K. S. Pankajamani, and T. R. Seshadri, *J. Sci. Ind. Research (India)*, 12B, 127 (1953).
(16) C. H. Yang, H. D. Braymer, E. L. Murphy, W. Chorney, N. Scully, and S. H. Wender, *J. Org. Chem.*, 25, 2063 (1960).
(17) This reagent is conveniently prepared by distilling equimolecular quantities of benzophenone and phosphorus pentachloride [J. F. Norris, R. Thomas, and B. M. Brown, *Ber.*, **43**, 2940 (1910)].
(18) W. Bradley, R. Robinson, and G. Schwarzenbach, *J. Chem. Soc.*, 793 (1930).
(19) O. T. Schmidt, H. Voight, W. Puff, and R. Koster, *Ann.*, **586**, 165 (1954).
(20) L. Jurd, *J. Am. Chem. Soc.*, **81**, 4606 (1959).

with quercetin identifiable products could not be isolated. However, when the 7-hydroxyl is protected, the reagent reacts almost exclusively with the 3′,4′-dihydroxyl grouping to give high yields of the 3′,4′-diphenylmethylenedioxy derivative. Thus rhamnetin, readily available by the methylation of quercetin pentaacetate,[21] heated alone with an equimolecular quantity of α,α'-dichlorodiphenylmethane for only a few minutes gives 85% yields of the highly crystalline 3,5-dihydroxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone (II). This, on methylation with one molecular equivalent of dimethyl sulphate, gives the 3,7-dimethoxyflavone derivative (III) which is rapidly hydrolyzed on warming with dilute acids to 3,7-di-*O*-methylquercetin (IV). Methylation of (II) with excess



I

II

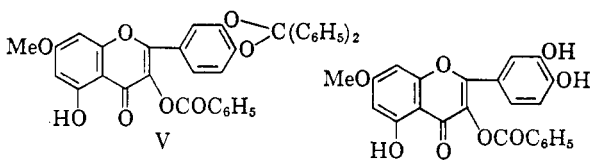


III

IV

of reagent and subsequent acid hydrolysis gives 3,5,7-tri-*O*-methylquercetin. 3-*O*-Methyl- and 3,5-di-*O*-methylquercetin have been prepared from 7-*O*-benzylquercetin by a similar series of reactions.[22]

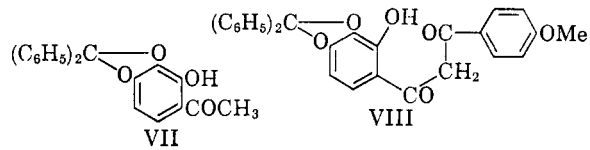
The 3-(and the 5) hydroxyl of II may be aroylated and the diphenylmethylene grouping removed without hydrolysis of the ester linkage. This approach may be used to prepare other quercetin derivatives. Thus monobenzoylation of II gives the 3-benzoate (V) which is hydrolyzed by dilute acids to rhamnetin 3-benzoate (VI). Methylation and subsequent alkaline hydrolysis of this then gives 5,7,3′,4′-tetra-*O*-methylquercetin.



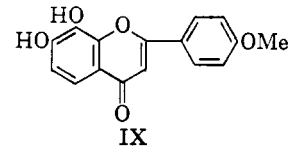
V

VI

It is noteworthy that α,α'-dichlorodiphenylmethane provides a particularly elegant protective grouping in the synthesis of 7,8-dihydroxyflavones by the Baker - Venkataraman rearrangement. A number of these flavones have now been synthesized in good yield by this method. Gallacetophenone reacts with α,α'-dichlorodiphenylmethane to yield VII. The 2-*O*-anisoyl derivative of this, for example, rearranges when heated with acetone and potassium carbonate[23,24] to give the β-diketone (VIII). Treated briefly with dilute acid VIII is simultaneously cyclized and hydrolyzed to 7,8-dihydroxy-4′-methoxyflavone (IX).



VII VIII



IX

EXPERIMENTAL

3,5-Dihydroxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone (II). A mixture of finely powdered rhamnetin (5.7 g.) and α,α'-dichlorodiphenylmethane (4.80 g; 1.1 mole equiv.) was heated in an oil bath to 230° during 5 min. A vigorous evolution of hydrogen chloride gas occurred when the temperature of the bath reached 210°. The cooled reaction mixture was dissolved in warm acetone (50 ml.) and the solution concentrated until crystallization began. Methanol was added and the product was collected (m.p. 188°; 7.4 g.; 85.5%). Recrystallized from benzene-hexane (a small quantity of unreacted rhamnetin begin removed by filtration) and acetone-methanol, 3,5-dihydroxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone separated as yellow needles, m.p. 191°.

Anal. Calcd. for $C_{29}H_{20}O_7$: C, 72.5; H, 4.20; 1 MeO—, 6.46. Found: C, 72.6; H, 4.16; MeO—, 6.23.

5-Hydroxy-3,7-dimethoxy-3′,4′-diphenylmethylenedioxyflavone (III). A mixture of the above product (4.3 g.), dimethyl sulfate (1.24 g.; 1.1. mol. equiv.), anhydrous potassium carbonate (5.0 g.), and dry acetone (150 ml.) was heated under reflux for 1.5 hr. The filtered acetone solution was concentrated until a heavy, crystalline product had separated. Recrystallized from methanol 5-hydroxy-3,7-dimethoxy-3′,4′-diphenylmethylenedioxyflavone separated as slightly yellow, granular crystals, m.p. 150° (3.5 g). It gave an olive green-brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{30}H_{22}O_7$: C, 72.85; H, 4.49; 2 MeO—, 12.6. Found: C, 72.9; H, 4.40; MeO—, 12.5.

The *acetate* of the product crystallized from acetone-methanol as colorless needles, m.p. 148–149°.

Anal. Calcd. for $C_{32}H_{24}O_8$: C, 71.6; H, 4.51; 2 MeO—, 11.6. Found: C, 71.8; H, 4.42; MeO—, 11.7.

3,7-Di-O-methylquercetin (IV). A solution of the above dimethoxy compound (2.8 g.) in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (2.0 ml.) was heated on a steam bath for 2 min. Water (10.0 ml.) was added and heating was continued for 10 minutes when yellow needles began to separate. Excess of water was added, the product was collected, washed with benzene (to remove benzophenone), and recrystallized from acetone-methanol. 3,7-Di-*O*-methylquercetin was obtained as yellow needles, m.p. 235° (lit.[25] m.p. 234–235°) (1.7 g.). Chromatographic comparison of this product and authentic 3,7-di-*O*-methylquercetin, kindly carried out by Dr. S. H. Wender, confirmed its identity.

(21) L. Jurd, *J. Am. Chem. Soc.*, 80, 5531 (1958).

(22) Part III, in preparation.

(23) D. S. Bapat and K. Venkataraman, *Proc. Indian Acad. Sci.*, 42 A, 336 (1955); R. Mani, V. Ramanathan, and K. Venkataraman, *J. Sci. Ind. Res. (India)*, 15 B, 490 (1956).

(24) L. Jurd, *Chem. & Ind.*, 965 (1960).

Anal. Calcd. for $C_{17}H_{14}O_7$: C, 61.8; H, 4.28; 2 MeO—, 18.8. Found: C, 62.0; H, 4.28; MeO— 18.6.

The *triacetate* of the product separated from acetone-methanol as colorless needles, m.p. 169° (lit.[25] m.p. 163–164.5°).

Anal. Calcd. for $C_{23}H_{20}O_{10}$: C, 60.5; H, 4.42; 2 MeO—, 13.6. Found: C, 60.7; H, 4.37; MeO—, 13.5.

3,5,7-Trimethoxy-3′,4′-diphenylmethylenedioxyflavone. 3,5-Dihydroxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone (2.0 g.) was heated under reflux with methyl iodide (16.0 ml.), anhydrous potassium carbonate (5.0 g.), and acetone (150 ml.) for 4 hr. The product gave a faint ferric chloride reaction. Methylation was completed, therefore, by refluxing it with dimethyl sulfate (2.0 ml.), potassium carbonate, and acetone for 2 hr. The product crystallized from acetone-methanol. 3,5,7-Trimethoxy-3′,4′-diphenylmethylenedioxyflavone separated as slightly yellow needles, m.p. 185° (2.0 g.). It did not give a color with alcoholic ferric chloride.

Anal. Calcd. for $C_{31}H_{24}O_7$: C, 73.2; H, 4.76; 3 MeO—, 18.3. Found: C, 73.2; H, 4.64; MeO—, 18.0.

3,5,7-Tri-O-methylquercetin. A solution of the above compound (1.5 g.) in glacial acetic acid (30 ml.) and hydrochloric acid (5.0 ml.) was heated on a steam bath for 10 min. The product obtained on adding water (200 ml.) was recrystallized from acetone-methanol. 3,5,7-Tri-*O*-methylquercetin separated as glistening, slightly yellow prisms, m.p. 270°.

Anal. Calcd. for $C_{18}H_{16}O_7$: C, 62.8; H, 4.69; 3 MeO—, 27.0. Found: C, 62.8; H, 4.77; MeO—, 26.7.

The product formed a *diacetate* which separated from acetone-methanol as colorless prisms, m.p. 219°.

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61.7; H, 4.71; 2 CH_3CO—, 20.1. Found: C, 61.6; H, 4.72; CH_3CO—, 20.2.

The *dibenzoate*, prepared by warming the trimethyl ether with benzoyl chloride and pyridine, crystallized from acetone-methanol as colorless needles, m.p. 204°.

Anal. Calcd. for $C_{32}H_{24}O_9$: C, 69.56; H, 4.38; 3 MeO—, 16.85. Found: C, 69.5; H, 4.45; MeO—, 16.3.

For 3,5,7-tri-*O*-methylquercetin Seshadri and his associates[26] have reported m.p. 282–284° dec. They did not further characterize the compound.

5-Hydroxy-3-benzoyloxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone (V). A mixture of 3,5-dihydroxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone (2.0 g.), benzoyl chloride (3.0 ml.), and pyridine (6.0 ml.) was warmed briefly on a steam bath and allowed to stand at room temperature for 5 min. Methanol (20 ml.) and water (20 ml.) were then added. The crystalline product was recrystallized from acetone-methanol and from benzene-hexane. 5-Hydroxy-4-benzoyloxy-7-methoxy-3′,4′-diphenylmethylenedioxyflavone separated as yellow needles, m.p. 243° (2.7 g.). In benzene-methanol it gave a brown color with ferric chloride.

Anal. Calcd. for $C_{36}H_{24}O_8$: C, 74.0; H, 4.14. Found: C, 73.9; H, 4.17.

Rhamnetin 3-benzoate (VI). Concentrated hydrochloric acid (4.0 ml.) was added to a suspension of the above benzoate (2.0 g.) in glacial acetic acid (50 ml.). The mixture was heated on a steam bath for 5 min. and the clear solution thus obtained was diluted with water (250 ml.). The solid product was recrystallized from methanol (norite). Rhamnetin 3-benzoate separated in yellow needles, m.p. 217°, (1.1 g.) which gave a deep brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{23}H_{16}O_8$: C, 65.7; H, 3.84; 1 MeO—, 7.38. Found: C, 65.8; H, 3.92; MeO—, 7.22.

Methylation of benzoate in the usual way gave 5,7,3′,4′-tetra-*O*-methylquercetin benzoate, m.p. 179°, which, on hydrolysis with aqueous methanolic alkali, gave 5,7,3′,4′-tetra-*O*-methylquercetin. This separated from methanol as slightly yellow needles, m.p. 191° (lit.[27] m.p. 193–195°).

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.7; H, 5.06; 4 MeO—, 34.6. Found: C, 63.6; H, 5.16; MeO—, 34.0.

2-Hydroxy-3,4-diphenylmethylenedioxyacetophenone. A mixture of gallacetophenone (8.4 g.) and α,α'-dichlorodiphenylmethane (13.0 g.; 1.1 mol. equiv.) was immersed in an oil bath at 170°. The temperature of the bath was raised to 185° during 5 min. by which time the evolution of hydrogen chloride had ceased. The red oil was dissolved in boiling methanol (40 ml.). Crystallization of a white solid began almost at once. After cooling the solid was collected, washed well with cold methanol, and recrystallized from acetone-methanol (norite). 2-Hydroxy-3,4-diphenylmethylene-dioxyacetophenone separated in colorless felted needles, m.p. 150–151° (11.5 g.).

Anal. Calcd. for $C_{21}H_{16}O_4$: C, 75.9; H, 4.86. Found: C, 75.9; H, 4.72.

The acetate and benzoate of this compound formed oils which could not be crystallized. The highly crystalline methyl ether was prepared by heating a mixture of the product (2.0 g.), anhydrous potassium carbonate (5.0 g.), methyl iodide (15 ml.), and acetone (50 ml.) for 4 hr. The acetone solution was evaporated to an oil which was treated with water. The solid thus obtained crystallized from methanol as colorless brittle prisms, m.p. 97° (1.8 g.).

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.3; H, 5.24; 1 MeO—, 8.96. Found: C, 76.3; H, 5.16; MeO—, 9.04.

2-Hydroxy-3,4-diphenylmethylenedioxy-ω-anisoylacetophenone (VIII). A mixture of 2-hydroxy-3,4-diphenylmethylenedioxyacetophenone (3.32 g.), anisoyl chloride (2.31 g.), and pyridine (10 ml.) was heated on a steam bath for 30 min. and added to excess of dilute aqueous ammonia. After 1 hr. the oily precipitate was separated by decantation, washed with water, and dissolved in ether. The ethereal solution was dried (sodium sulfate) and evaporated to give the 2-anisoyloxy-3,4-diphenylmethylenedioxyacetophenone as a pale yellow oil.

The oil was dissolved in dry acetone (200 ml.). Anhydrous potassium carbonate (10 g.) was added and the mixture refluxed for 20 hr. The undissolved potassium salts were filtered and suspended in dilute aqueous acetic acid. The acetone filtrate was concentrated and added to the aqueous acetic acid mixture. The yellow solid thus obtained was collected and recrystallized from acetone-methanol. 2-Hydroxy-3,4-diphenylmethylenedioxy-ω-anisoylacetophenone separated in glistening yellow plates, m.p. 174° (3.4 g., 73%).

Anal. Calcd. for $C_{29}H_{22}O_6$: C, 74.65; H, 4.76; 1 MeO—, 6.65. Found: C, 74.7; H, 4.73; MeO—, 6.71.

7,8-Dihydroxy-4′-methoxyflavone (IX). A solution of the above ω-anisoyl compound (2.9 g.) in glacial acetic acid (10 ml.) was treated with concentrated hydrochloric acid (1.0 ml.), heated briefly to boiling, and then on a steam bath for 2 minutes. The clear solution suddenly set solid with a crystalline mass. Water was added and the product was recrystallized from acetone-methanol. 7,8-Dihydroxy-4′-methoxyflavone separated in yellow needles, m.p. 288–290° (dec.) which gave a green color with alcoholic ferric chloride (1.5 g).

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.26; 1 MeO—, 10.92. Found: C, 67.7; H, 4.53; MeO—, 10.8.

It formed a *diacetate* which crystallized from methanol in colorless, fluffy needles, m.p. 173°.

Anal. Calcd. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.38; 1 MeO—, 8.43. Found: C, 65.6, H, 4.44; MeO—, 8.23.

Methylation of the dihydroxyflavone with dimethyl sulfate, potassium carbonate, and acetone gave the known

(25) M. Shimizu and G. Ohta, *J. Pharm. Soc. Japan*, **71**, 1485 (1951); *Chem. Abstr.* **46**, 7099 (1952).

(26) N. Narasimhachari, S. Narayanaswami, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **37A**, 104 (1953).

(27) B. L. Williams and S. H. Wender, *J. Am. Chem. Soc.*, **74**, 4372 (1952).

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

KURT D. KAUFMAN, WILLIAM E. RUSSEY, AND LEONARD R. WORDEN

Received September 5, 1961

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).