CHEMISTRY OF THE 9-METHOXYPSORALENES

by

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CHEMISTRY OF THE 9-METHOXYPSORALENES

INTRODUCTION

The significance of the study of the chemical properties of 9-methoxypsoralene has been outlined (1, p. 589-590) and will be briefly reviewed here.

Xanthotoxin (9-methoxypsoralene) is a furocoumarin that occurs in a number of plants indigenous to the Eastern Hemisphere. As its name implies, xanthotoxin is a fish poison and is, in general, toxic to cold-blooded animals, while it is relatively nontoxic to mammals. Current interest in this material is due to its photodynamic activity, which causes the skin to "tan" as opposed to "burn" if the drug is administered orally prior to exposure to the sunlight.

This investigation was undertaken to complete the study of the chemical behaviour of xanthotoxin and to prepare a series of new furocoumarins to be tested both for toxicity to fish and for photodynamic activity.

HISTORY

Discovery and Structure Proof

9-Methoxypsoralene was first isolated from Fagara zanthoxyloides Lam by Priess in 1911 (17, p. 94). He also noted that it was an active fish poison. This property apparently inspired him to borrow from the Greek and invent the trivial name "zanthotoxin" or, later, "xanthotoxin".[1]

The structure of xanthotoxin was elucidated by Thoms (30, p. 3325-3332; 31, p. 3705-3712) primarily on the basis of: 1) its relationship to bergaptene (4-methoxypsoralene) and 2) the fact that fusion with potassium hydroxide converted xanthotoxin into 2,3,4-trihydroxybenzoic acid.

Synthesis

There are a number of papers in the literature which describe the synthesis of the furocoumarin nucleus. Späth, in the original synthesis of 9-methoxypsoralene,

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[1] European and medical literature also employ the name "8-methoxypsoralene", which arises by beginning the numbering system at the hetero oxygen in the coumarin ring and continuing clockwise around the entire coumarin moiety. The furan ring then receives prime numbers. Most American chemical literature begins numbering counterclockwise at the furan oxygen and designates the nucleus as either "furo(3,2-g)coumarin" (6, p. 3619-3620) or "psoralene" (1, p. 589-596).

employed the reaction between malic acid and the appropriate hydroxydihydrobenzofuran (26, p. 767-770). This same general method has been used by several groups of workers (6, p. 3619-3620; 7, p. 1514-1518; 11, p. 647-654) to prepare variously substituted psoralenes. The method is, however, most useful for preparing 5- and 6-substituted psoralenes because beta-keto esters give better yields than does malic acid.

A new synthesis of xanthotoxin, which avoids the difficult ring closure with malic acid, has recently been published. This procedure made use of 7-hydroxy-8-methoxycoumarin, which was subsequently formylated with hexamine. The furan ring was then closed with bromoethyl acetate (19, p. 960-967).

Natural Sources, Isolation and Biological Assay

Psoralenes have been observed in a number of plant sources, for example: in Ammi majus (24, p. 4826-4828), in Ruta graveoleus, Ficus carica and Citrus limonum (20, p. 14116) and in Angelica archangelica (27, p. 179-189).

It seems likely that these furocoumarins may occur as the coumaric acid glucoside in their natural state. This was found to be the case for psoralene in a Coronnela species, where the compound was present as the glucoside, which was cleaved by acid; and spontaneous lactonization

occurred (29, p. 1637-1647).

Several methods have been developed for the chromatographic separation of coumarins and psoralenes from natural sources. One method made use of paper which was treated with glycol; ligroin was employed as solvent (18, p. 1083-1087). Rodighiero (20, p. 125-131) found that a methanol-pyridine-water system was useful on paper. Column separation of furocoumarins has also been reported (28, p. 3488-3491).

As previously stated, current interest in 9-methoxypsoralene is due largely to its photodynamic activity. For this reason, mention should be made of a bacterial assay that has recently been reported to relate bacterial growth to this activity (24, p. 571-572).

General Chemistry of the Psoralene Nucleus

9-Methoxypsoralene has been observed to nitrate in the 4-position (31, p. 3705-3712). Psoralene also yielded a mononitro-derivative (8, p. 434-438), but no information could be found in the literature to indicate which position was attacked.

Upon treatment with sulfuric acid, 9-methoxypsoralene formed a yellow solution (17, p. 94). Apparently no sulfonated derivative was isolated, however.

Halogenation of coumarins and furocoumarins has

been reported to cause a variety of different reactions. Perkin, for example, found that coumarin added two atoms of bromine (16, p. 37-55). A number of authors, however, have reported that the 3-position of coumarins is substituted using bromine (28, p. 7840; 29, p. 4034-4035) or N-bromosuccinimide (12, p. 937-939). Horning and Risner (7, p. 1514-1518) postulated that bromination of a 2,3-dihydropsoralene occurred at the 4- or 6-position since the product resisted dehydrohalogenation. On the other hand, a 2,3-dihydrobenzofuran was converted to the corresponding benzofuran by bromination with this reagent followed by dehydrohalogenation (5, p. 4326).

Priess (17, p. 94) reported that bromination of xanthotoxin yielded a dibromo-addition product. In this laboratory, however, only the 4-bromo- and 2,3-dihydro-2,3,4-tribromo-9-methoxypsoralene could be prepared by direct bromination (1, p. 591).

Oxidation of furocoumarins with hydrogen peroxide produced furan-2,3-dicarboxylic acid (1, p. 592; 25, p. 1146-1150; 15, p. 2513). Dichromate, however, produced psoralene quinone if negative substitutents were present in both the 4- and 9-positions (31, p. 3711; 15, p. 2513). On the other hand, this reagent has been reported to attack the furan double bond in 4-methoxypsoralene (22, p. 1019).

Much of the chemistry of the psoralenes is similar to that of the coumarins; and a number of reactions involving ring openings with base, bisulfite (24, p. 4826-4828), hydrazine, lithium aluminum hydride and dimethyl sulfate (1, p. 589-596) have been described. Reactions with ozone and phosphorus pentasulfide are also known (1, p. 589-596).

An interesting reaction of xanthotoxin has been reported by Schönberg (23, p. 1364-1368) in which one mole of phenanthraquinone added across a double bond in a photo-chemical reaction. Addition was assumed to be in the 2,3- position because the reaction did not occur with coumarin.

Demethylation of 9-methoxypsoralene has caused some controversy in the literature. The usual reagent, hydroiodic acid, is not useful because rearrangements involving the furan ring may occur (2, p. 2260-2265). Cleavages have been described using magnesium iodide (24, p. 4826-4828) and aniline hydrochloride (21, p. 3265-3266). The latter reaction could not be duplicated, however (1, p. 590). Further work along these lines will be described in the experimental section.

EXPERIMENTAL

Psoralene quinone (II)

9-Methoxypsoralene (1.0 gram, 0.0046 mole) was dissolved in 30 ml. glacial acetic acid. To this solution was added 30 ml. of a 15% aqueous chromium trioxide solution. The resulting solution was heated just to boiling on the hot plate and then poured immediately into 250 ml. water and cooled. The product was filtered and crystallized from ethanol; yield 0.16-0.25 gram, 16-25%; m.p. 275-277°C., dec.

Anal. Calcd. for $C_{11}H_4O_5$: C, 61.2; H, 1.85. Found: C, 60.8; H, 1.97.

The infrared spectrum of this compound was identical with that of psoralene quinone which was obtained from the previously described (31, p. 3711) oxidation of 4-amino-9-methoxypsoralene.

4,9-Dihydroxypsoralene (III)

Psoralene quinone (0.2 gram, 0.00093 mole), obtained by oxidation of 9-methoxypsoralene, was suspended in 50 ml. water and heated on the steam bath. This suspension was saturated with sulfur dioxide by bubbling the gas through the hot liquid for ten minutes. At the end of this time, all of the material was in solution; this solution was now a light green color. Upon cooling, green crystals formed;

yield 0.2 gram, 99%; m.p. 270°C. dec. The infrared spectrum of this compound was identical with that of 4,9-dihydroxypsoralene, which was obtained by a similar reduction of psoralene quinone prepared from 4-amino-9-methoxypsoralene.

4,9-Dimethoxypsoralene (isopimpinellin, IV)

4,9-Dihydroxypsoralene (0.35 gram, 0.0016 mole), obtained by oxidation and subsequent reduction of xanthotoxin, was dissolved in 50 ml. acetone containing 0.5 gram potassium carbonate and 1 ml. (0.011 mole) dimethyl sulfate. This mixture was refluxed two hours. At the end of this time, two more grams of potassium carbonate were added; and heating was continued for three hours. The mixture was cooled, acidified with dilute hydrochloric acid and diluted with water. The insoluble product was filtered and crystallized from ethanol using activated charcoal as a decolorizing agent; yield 0.10 gram, 25%; m.p. 152-153°C. A mixed melting point with an authentic sample of isopimpinellin was not depressed. The infrared spectra of the two samples were identical.

9-Hydroxypsoralene (xanthotoxol)

9-Methoxypsoralene (1.0 gram, 0.0046 mole) was mixed intimately with 4.0 grams of anhydrous aluminum chloride. The mixture was placed in a flask, protected with a calcium

chloride drying tube and heated ten hours at 140°C. (bath temperature). After cooling, the mixture was treated with hydrochloric acid (100 ml., 6N). The insoluble product was filtered and washed with a small amount of water. The product was crystallized successively from dilute acetic acid and water; yield 0.4 gram, 43%; m.p. 238-240°C. A mixed melting point with an authentic sample of xanthotoxol (m.p. 242-244°C.) was found to be 238-240°C. The infrared spectra of these two samples were identical.

2,3-Dihydro-9-methoxy-2,3,4-trichloropsoralene (VII)

A. 9-Methoxypsoralene (1.0 gram, 0.0046 mole) was dissolved in 50 ml. chloroform. Chlorine was passed slowly through this solution for fifteen minutes at room temperature. The chloroform was then removed on the steam bath. At this point, it was possible to isolate the product by repeated crystallizations from ethanol. It was subsequently found, however, that the product was stable in the presence of sodium iodide; and since treatment with this reagent greatly improved the isolation, it was desirable to use the following procedure. The residue after evaporation of the chloroform was dissolved in 50 ml. acetone, and 0.5 gram sodium iodide was added with shaking. The resulting solution was kept at room temperature for three hours and then filtered. Water was added to the point

of cloudiness, and the solution was cooled in the deep freeze. Upon cooling, 1.0 gram, 68%, of product was collected; m.p. 202-203°C.

Anal. Calcd. for $C_{12}H_7O_4Cl_3$: C, 44.8; H, 2.17. Found: C, 44.6; H, 2.28. λ max. 240, 270, 315 mμ.

B. 4-Chloro-9-methoxypsoralene (0.2 gram, 0.0008 mole) was chlorinated under the same conditions as above in 25 ml. of chloroform. In this case, a pure product could be easily obtained by crystallization from ethanol; yield 0.1 gram, 15%. The melting point and infrared spectrum were identical with those of the product from procedure "A".

4-Chloro-9-methoxypsoralene (VIII)

9-Methoxypsoralene (0.5 gram, 0.0023 mole) was suspended in 25 ml. ethanol and 25 ml. "Chlorox". Hydrochloric acid (1.0 ml., 6N) was added, and the mixture was heated gently on the steam bath for one hour. The reaction mixture was diluted with water, and the insoluble product was collected. Crystallization was effected from ethanol; yield 0.31 gram, 54%; m.p. 194-195°C.

Anal. Calcd. for $C_{12}H_7O_4Cl$: C, 57.5; H, 2.79. Found: C, 57.2; H, 2.87.

A mixed melting point determination with 4-chloro-9-methoxypsoralene prepared from the amine, m.p. 187-188°C.

(1, p. 593-594), was found to be 187-188°C. The infrared spectra of these two samples were identical with the exception of a peak at 1510 wave numbers in the sample from the Sandmeyer reaction. This peak was shown to be caused by a trace of 9-methoxy-4-nitropsoralene. It was therefore concluded that these materials were identical except for this impurity.

4-Chloro-2,3-dihydro-9-methoxypsoralene (X)

4-Amino-2,3-dihydro-9-methoxypsoralene (1, p. 594), (0.65 gram, 0.0028 mole) was suspended in 20 ml. concentrated hydrochloric acid and cooled in an ice-salt mixture. Sodium nitrite (0.19 gram, 0.0028 mole), dissolved in a little water, was added slowly. The mixture was allowed to stand in the cooling bath for five minutes and was then poured slowly into a boiling solution containing 30 ml. 6N hydrochloric acid and 0.75 gram cuprous chloride. The insoluble product was filtered and crystallized from ethanol; yield 0.36 gram, 44%; m.p. 193-194°C.

Anal. Calcd. for $C_{12}H_9O_4Cl$: C, 57.0; H, 3.54. Found: C, 56.6; H, 3.44.

9-Methoxypsoralene-4-sulfonyl chloride (XI) and 9-Methoxypsoralene-4-sulfonic acid (XII)

Two procedures were employed for the sulfonation of 9-methoxypsoralene. The first yielded largely the acid chloride; the second yielded predominantly the free sulfonic acid.

A. 9-Methoxypsoralene (0.5 gram, 0.0023 mole) was treated slowly at room temperature with 5 ml. chlorosulfonic acid. The resulting solution was allowed to stand for five minutes and then poured over 75 ml. ice. The insoluble acid chloride was collected and crystallized from a chloroform-petroleum ether mixture; yield 0.58-0.63 gram, 80-87%; m.p. 154-155°C.

Anal. Calcd. for $C_{12}H_7O_6SCl$: C, 46.0; H, 2.23. Found: C, 46.1; H, 2.43.

The filtrate from above yielded a trace of the free sulfonic acid upon evaporation before a fan.

B. 9-Methoxypsoralene (1.0 gram, 0.0046 mole) was dissolved in 15 ml. chloroform and cooled in an ice bath. Chlorosulfonic acid (3 ml.) was added dropwise with stirring. After standing for five minutes in the ice bath, the temperature was allowed to rise to 20°C. The chloroform solution was then poured over 75 ml. ice. After the ice had melted, more chloroform was added; and the layers were separated. The aqueous layer was extracted once more

with chloroform. The combined chloroform extracts were taken to dryness and yielded from 0.15 to 0.25 gram, 10-16%, 9-methoxypsoralene-4-sulfonyl chloride. This product was identical with that described in procedure "A".

The aqueous layer upon evaporation yielded 1.3 gram, 89%, of the sulfonic acid. This product was crystallized from acetic acid and dried by an azeotropic distillation of a benzene suspension. The melting point was 205°C.

Anal. Calcd. for $C_{12}H_8O_7S \cdot H_2O$: C, 46.1; H, 3.18. Found: C, 46.7; H, 3.30.

9-Methoxypsoralene-4-sulfonic acid (XII)

9-Methoxypsoralene-4-sulfonyl chloride (0.2 gram) was suspended in 25 ml. water and refluxed 45 minutes. The resulting solution was evaporated before the fan and yielded 0.17 gram, 85%, of product after crystallization from acetic acid. This material was shown by infrared data to be identical with the sulfonic acid obtained by the direct sulfonation described above.

4-Bromo-9-methoxypsoralene (XIII)

9-Methoxypsoralene-4-sulfonic acid (0.25 gram, 0.00079 mole) was suspended in 50 ml. chloroform, and 0.09 ml., 0.019 mole, of bromine was added. This mixture was heated on the steam bath with stirring until most of the chloroform was gone, and solution was effected. Petroleum ether

was then added to precipitate the product. The product was dissolved in 50 ml. acetone and treated with 0.5 gram sodium iodide for four hours at room temperature to remove any tribromo-derivative which might have been formed (1, p. 591). The acetone solution was filtered and diluted with water. The insoluble product was collected and crystallized from ethanol; yield 0.15 gram, 64%. A mixed melting point determination and infrared comparison indicated that this material was identical to 4-bromo-9-methoxypsoralene obtained by direct bromination (1, p. 591).

9-Methoxy-4-nitropsoralene (V)

9-Methoxypsoralene-4-sulfonic acid (0.25 gram) was dissolved in 10 ml. glacial acetic acid and 10 ml. concentrated nitric acid. The resulting solution was heated five minutes on the steam bath. It was then poured onto 50 grams ice, and the insoluble product was collected and crystallized from ethanol; yield 0.15 gram, 72%. A mixed melting point determination and a comparison of infrared spectra showed that this product was identical to 9-methoxy-4-nitropsoralene obtained by direct nitration (31, p. 3705-3712).

DISCUSSION

The behaviour of 9-methoxypsoralene under nitration (31, p. 3705-3712), bromination (1, p. 591; 17, p. 94), hydrogenation, ozonation, thionation and various ring opening procedures (1, p. 589-596) has been previously published. This paper will therefore be concerned with oxidation, ether cleavage, chlorination and sulfonation.

Oxidation

Schönberg (22, p. 1019) had reported that oxidation of 4-methoxypsoralene (bergaptene) with sodium dichromate attacked the furan double bond and formed 6-formyl-7-hydroxy-5-methoxycoumarin. His work was confirmed in this laboratory.

It seemed unusual, therefore, that the isomer of bergaptene, 9-methoxypsoralene, was unaffected by sodium dichromate under identical conditions. Treatment with chromium trioxide in acetic acid, however, did cause oxidation of 9-methoxypsoralene. Analysis of the product indicated that it might be psoralene quinone; and this was indeed shown to be the case when the product was found to be identical with psoralene quinone obtained by the previously reported (31, p. 3711) oxidation of 4-amino-9-methoxypsoralene.

That the oxidation product of 9-methoxypsoralene was psoralene quinone was further proved by reduction of the quinone with sulfur dioxide to the hydroquinone and subsequent methylation to yield isopimpinellin. The isopimpinellin obtained by this means was identical in melting point and infrared spectrum to an authentic sample.[1] This series of reactions is shown in Figure 1.

Ether Cleavage

Demethylation of 9-methoxypsoralene has been reported using magnesium iodide (24, p. 4828) and aniline hydrochloride (21, p. 3265-3266). The former reaction results in small yields, and the latter could not be duplicated in this laboratory (1, p. 590).

It had been previously observed (1, p. 593; 9, p. 437-440; 10, p. 151-156) that treatment of furocoumarins and chromones with aluminum chloride in benzene resulted in cleavage of the methoxyl groups in addition to the opening of the furan ring. Attempts were made to modify this reaction using an inactive aromatic compound to replace the benzene as solvent. It was hoped by this means to cleave the methoxyl and leave the furan ring intact as had been reported for furochromones (9, p. 439). In no

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[1] A sample of isopimpinellin was kindly supplied by Dr. W. L. Fowlks of the University of Oregon Medical School.

case, however, was the reaction successful. Nitrobenzene, chlorobenzene and bromobenzene were tested at various temperatures and heating times, but in each case the product was charred, or the starting material was recovered intact.

Using a procedure of Merchant and Shah (14, p. 886) for the cleavage of methoxyl groups with aluminum chloride in the absence of solvent, the conversion of 9-methoxypsoralene to 9-hydroxypsoralene (xanthotoxol) was accomplished in yields of 40-45%. The xanthotoxol obtained by this means had an identical melting point and infrared spectrum with that of an authentic sample.[1]

Chlorination

Bromination of 9-methoxypsoralene has been reported to yield a dibromo- (17, p. 94), monobromo- and a tribromo-derivative (1, p. 591). The preparation of the dibromo-compound, however, could not be duplicated in this laboratory (1, p. 591).

Direct chlorination of 9-methoxypsoralene with chlorine, on the other hand, yielded only a trichloro-derivative. In contrast to the tribromo-derivative (1, p. 591), none of these chlorine atoms was removed by treatment

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[1] A sample of xanthotoxol was supplied by Dr. W. L. Fowlks of the University of Oregon Medical School.

with sodium iodide in acetone. A comparison of the ultraviolet spectrum of this compound with that of other furocoumarins (1, p. 591) clearly indicated that the conjugation of the lactone carbonyl to the aromatic nucleus remained intact and that addition of two chlorines had occurred in the 2,3-position. This conjugation was shown by a peak above 300 mμ. (It was 315 mμ. in this case.)

Chlorination of 9-methoxypsoralene with sodium hypochlorite yielded a monochloro-derivative which melted at 195-196°C. 4-Chloro-9-methoxypsoralene had been synthesized from 4-amino-9-methoxypsoralene and was reported to melt at 187-188°C. (1, p. 593-594). A mixed melting point of these two compounds was found to be 187-188°C. The infrared spectra were identical between 2000-600 wave numbers with the exception of a peak at 1510 wave numbers in the sample obtained from the amine. It seemed possible that the impurity in this sample might be 4-chloro-2,3-dihydro-9-methoxypsoralene. This compound was prepared, but the infrared spectrum showed no absorption at 1510 wave numbers. Sublimation of the sample of 4-chloro-9-methoxypsoralene from the amine left behind a small residue which had an infrared spectrum identical with that of 4-nitro-9-methoxypsoralene and showed a strong absorbance at 1510 wave numbers. It was therefore concluded that

the two monochloro-derivatives were identical with the exception that the compound from the Sandmeyer reaction was contaminated with a little of the 4-nitro-derivative.

Direct chlorination of 4-chloro-9-methoxypsoralene with chlorine yielded the same trichloro-derivative as was obtained from the chlorination of 9-methoxypsoralene. It may therefore be concluded that the three chlorine atoms in this molecule are located in the 2,3,4-positions. As in the tribromo-compound, one halogen replaced a hydrogen in the 4-position; and the two other halogens were added across the 2,3-double bond. The above series of reactions is shown in Figure 2.

Sulfonation

Sulfonation of 9-methoxypsoralene with chlorosulfonic acid yielded either the free sulfonic acid or the acid chloride. The ratio between these two products was determined by the conditions of the reaction as described in the experimental section. The acid chloride was readily hydrolyzed to the free acid by boiling water.

That sulfonation had occurred in the 4-position was established by bromination and nitration of the sulfonic acid to form the previously described (1, p. 590-591) 4-bromo- and 4-nitro-9-methoxypsoralenes. This type of structural proof finds precedent in the work of

Merchant and Shah (14, p. 884-887). These reactions are shown in Figure 3.

General Conclusions

A few obvious generalizations may be made concerning the chemical activity of the 9-methoxypsoralenes on the basis of this and previous work which has already been mentioned.

There are five essentially aromatic hydrogens in 9-methoxypsoralene. Of these positions it would seem that only three would be reasonably attacked by electrophilic reagents. These are: the 2-position which is activated by the furan oxygen, the 4-position which is para to the methoxyl group, and the 6-position which is alpha to the lactone carbonyl.

Experimental evidence showed, however, that of these three positions only the 4- was attacked under the conditions tested. It may therefore be concluded that the 4-position is the most active center for electrophilic substitution.

9-Methoxypsoralene contains double bonds in the 2,3- and 5,6-positions both of which are conjugated with the benzene nucleus. Since the 2,3-double bond is more readily attacked by reagents such as hydrogen or halogen, it may be concluded that it has more the character of an

isolated double bond than does that of the coumarin ring. Conversely, since the coumarin double bond is not easily attacked, it must be more aromatic in character. This observation might be explained by the fact that the 5,6-double bond is conjugated both with the lactone carbonyl and with the aromatic nucleus.

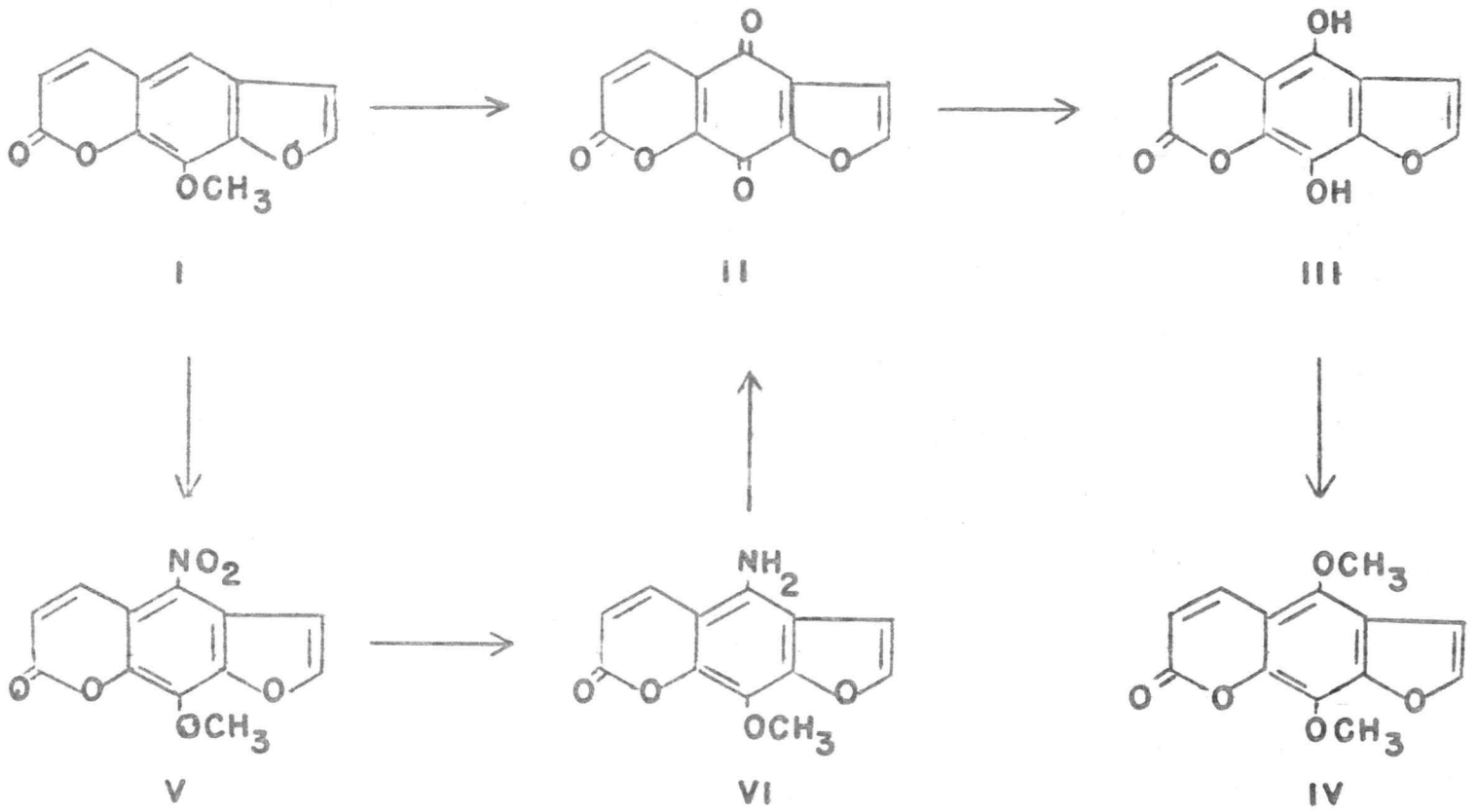

FIGURE 1

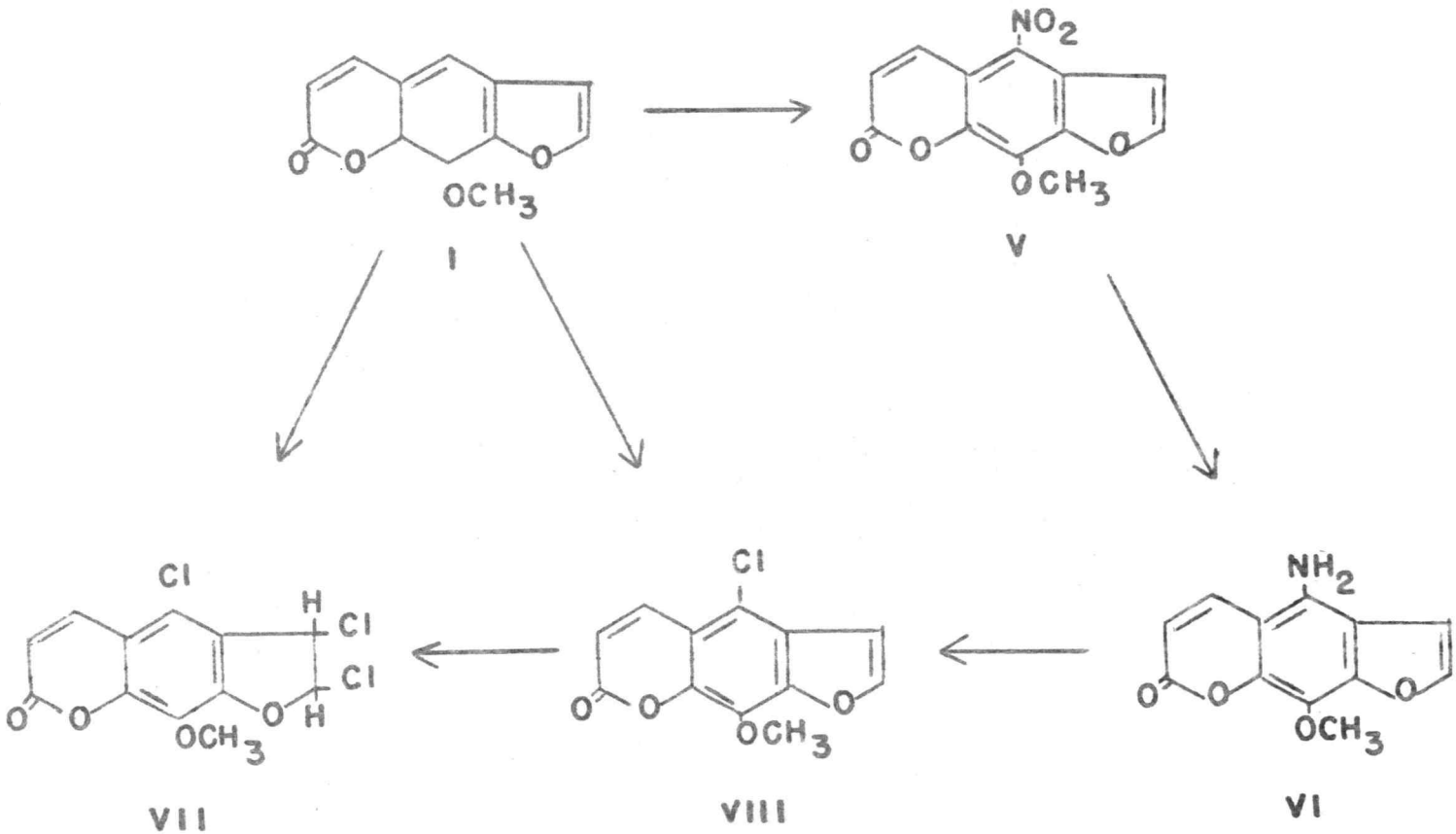

FIGURE 2

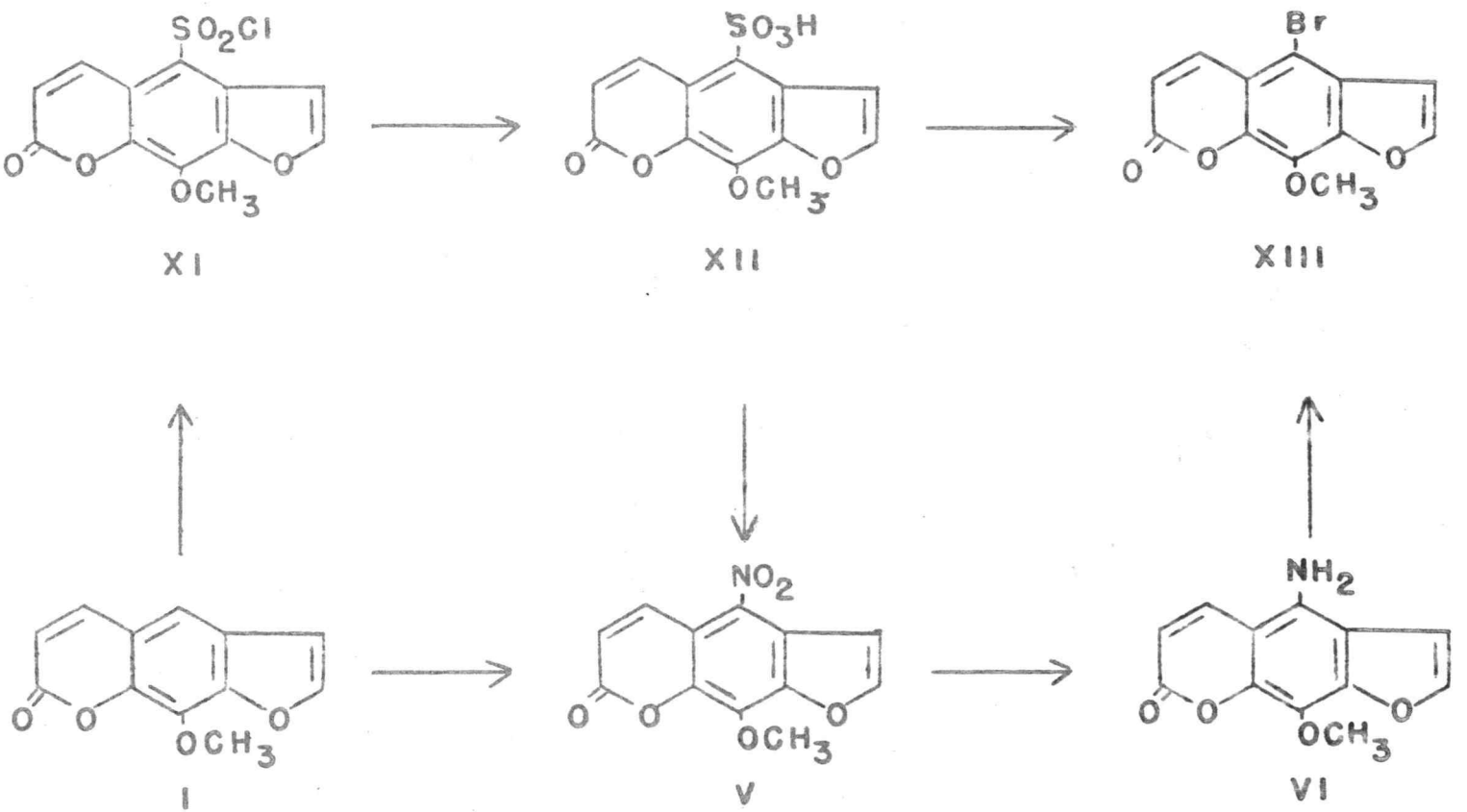

FIGURE 3

SUMMARY

The chemical reactions of 9-methoxypsoralene which had been previously published were described. These included nitration, bromination, ozonitation, thionation, photochemical reactions and various degradation procedures. A brief outline of the methods of synthesis and the general chemistry of the furocoumarins was included.

The experimental work described here was concerned with oxidation, chlorination, sulfonation and ether cleavage. Chromium trioxide converted 9-methoxypsoralene to psoralene quinone. This product was verified by infrared analysis and by the preparation of derivatives. Chlorination and sulfonation were both found to occur at the 4- position. Chlorine also added across the 2,3-double bond. 9-Methoxypsoralene was demethylated in good yield by heating with anhydrous aluminum chloride.

A few general statements were made concerning the relative reactivity of various positions in 9-methoxypsoralene.

BIBLIOGRAPHY

1. Brokke, Mervin E. and Bert E. Christensen. Psoralene. I. Certain reactions of xanthotoxin. Journal of Organic Chemistry 23:589-596. 1958.

2. Clarke, J. R., George Glaser and Alexander Robertson. Furano-compounds. Part VIII. The synthesis of isovisnagin and a partial synthesis of visnagin. Journal of the Chemical Society 2260-2265. 1948.

3. Dalvi, Vijay and Suresh Sethna. Bromination of coumarins. II. Bromination of 6-hydroxy-4-methylcoumarin and its methyl ether. Journal of the Indian Chemical Society 26:467-470. 1949. (Abstracted in Chemical Abstracts 44:7840a. 1950.)

4. Fowlks, W. L., D. G. Griffith and Evelyn L. Oginsky. Photosensitization of bacteria by furocoumarins and related compounds. Nature 181:571-572. 1958.

5. Geissman, T. A., T. G. Halsall and Elly Hinreiner. Coumarone dehydrogenation with N-bromosuccinimide. Journal of the American Chemical Society 72:4326. 1950.

6. Horning, E. C. and D. B. Reisner. Furocoumarins. Synthesis of 2,3-dihydropsoralene. Journal of the American Chemical Society 70:3619-3620. 1948.

7. Horning, E. C. and D. B. Reisner. Furocoumarin studies. Synthesis of psoralene and related furocoumarins. Journal of the American Chemical Society 72:1514-1518. 1950.

8. Jois, H. S. and B. L. Manjunath. Über einige Derivate des Psoralenes. Berichte der Deutschen Chemischen Gesellschaft 70:434-438. 1937.

9. Krishnaswamy, B. and T. R. Seshadri. Synthetic experiments in the benzo-pyrone series. Part V. Action of aluminum chloride on karanjin. Proceedings of the Indian Academy of Sciences 15:437-440. 1942.

10. Krishnaswamy, B. and T. R. Seshadri. Synthetic experiments in the benzo-pyrone series. Part VI. Action of aluminum chloride on angelicine, psoralene and

related compounds. Proceedings of the Indian Academy of Sciences 16:151-156. 1942.

11. Lagercrantz, Carl. Dihydrofurocoumarins. Synthesis of some long chain 4-n-alkyl substituted dihydroxanthotoxins, 4-phenyl-dihydroxanthotoxins and methyl 8-(dihydroxanthotoxin-4)-n-octanoate. Acta Chemica Scandinavica 10:647-654. 1956.

12. Lecocq, Jean and Buu-Hoi. Action de la N-bromosuccinimide sur des homologues de la coumarine. Comptes Rendus Hebdomadaries des Séances de l' Académie des Sciences 224:937-939. 1947.

13. Limaye, Dattatray Balkrishna and Narayana Vithal Bhide. Anwendung der Fittig- und Ebertreaktion auf die Methyl-äther des 4-Methylumbelliferons und der Umbelliferon-4-essigsäure. Rasayanam 1:136-140. 1938. (Abstracted in Chemisches Zentralblatt 110 (II):4034-4035. 1939.)

14. Merchant, J. R. and R. C. Shah. Substitution in the benzopyrone series. IV. Sulfonation of coumarin derivatives. Journal of Organic Chemistry 22: 884-887. 1957.

15. Noguti, Takami and Minoru Kawakami. Constituents of umbelliferene. VII. Constituents of the spice of Angelica clabra Makino. Journal of the Pharmaceutical Society (Japan) 58:1052-1061. 1938. (Abstracted in Chemical Abstracts 33:2513(9). 1939.)

16. Perkin, W. H. On some new derivatives of coumarin. Journal of the Chemical Society 24:37-55. 1871.

17. Priess, Hans. The constituents of Fagara zanthoxyloides Lam. Berichte der Deutschen Pharmazeutischen Gesellschaft 21:227-267. 1911. (Abstracted in Chemisches Zentralblatt 82(II):94-95. 1911.)

18. Riedl, K. and L. Neugebauer. Über die papier chromatographische Trennung von Cumarinen. Monatshefte für Chemie 83:1083-1087. 1952.

19. Rodighiero, Giovanni and Cipriano Antonello. New synthesis of xanthotoxin. Annali di Chimica (Rome) 46:960-967. 1956. (Abstracted in Chemical Abstracts 56:6616g. 1957.)

20. Rodighiero, Giovanni, G. Coprarale and E. Ragazz. The coumarins present in Ruta graveolens, in the leaves of Ficus carica and in the essence of Citrus limonum. Atti dell' istituto veneto di scienze, lettere ed arti. Classe di scienze matenmatiche e naturali 3:125-131. 1952-1953. (Abstracted in Chemical Abstracts 48:14116h. 1954.)

21. Schönberg, Alexander and Gamil Aziz. Furochromones and coumarins. VI. Demethylation of xanthotoxin, khellin and khellol with aniline hydrochloride and magnesium iodide. Journal of the American Chemical Society 75:3265-3266. 1953.

22. Schönberg, Alexander, Nasry Badran and Nicolas Starkowsky. Furochromones and coumarins. IX. Reactions of khellol glucoside, visnagin and bergaptene. Journal of the American Chemical Society 75:1019-1021. 1955.

23. Schönberg, Alexander, Nazih Latif, Radwan Mou Basher and Aly Sina. Photochemical reactions in sunlight. Part XVI. (a) Photo-reduction of phenylglyoxylic acid. (b) Photo-reactions between aldehydes and o-quinones. (c) Reactions between o-quinones and ethylenes in the dark and in the light. Journal of the Chemical Society 1364-1368. 1951.

24. Schönberg, Alexander and Aly Sina. Experiments with xanthotoxin and imperatorin obtained from the fruits of Ammi majus (L.). Journal of the American Chemical Society 72:4826-4828. 1950.

25. Späth, Ernst and Ludwig Kahovec. Über pflanzliche Fischgifte. VI. Mitteil: Die Konstitution des Isoimperatorins (aus Imperatoria Ostruthium). Berichte der Deutschen Chemischen Gesellschaft 66: 1146-1150. 1933.

26. Späth, Ernst and Matthias Pailer. Synthese des Xanthotoxins (XVII Mitteil. Über naturliche Cumarine.). Berichte der Deutschen Chemischen Gesellschaft 69:767-770. 1936.

27. Späth, Ernst and F. Vierhapper. Natural coumarins. XL. Coumarins of the drug semen angelicae. Monatshefte fur Chemie 72:179-189. 1938. (Abstracted in Chemical Abstracts 33:2505(5). 1939.)

28. Stanley, W. L. and S. H. Vannier. Chemical composition of lemon oil. I. Isolation of a series of substituted coumarins. Journal of the American Chemical Society 79:3488-3491. 1957.

29. Stoll, A., A. Pereira and J. Renz. Das Furocumarin und die β-D-Glucosido-furocumarin Säure aus den Samen von Coronilla-Arten. Helvetica Chimica Acta 33: 1637-1647. 1950.

30. Thoms, H. Über die Konstitution des Xanthotoxins und seine Beziehungen zum Bergaptene. Berichte der Deutschen Chemischen Gesellschaft 44:3325-3332. 1911.

31. Thoms, H. and E. Baetcke. Die Konstitution des Bergaptenes. Berichte der Deutschen Chemischen Gesellschaft 45:3705-3712. 1912.