

TABLE I (Cont'd)  
 SUBSTITUTED HIPURIC ANILIDES FROM HIPURIC ACID AND SUBSTITUTED ANILINES

tion in Hours		Solvent for Recrystallization	Nitrogen Analyses		Total Yield, Grams	Percentage Yield	Color of Product
138-162 hr.	162-380 hr.		% Calcd.	% Found			
0.0982	0.4076	Ethanol	15.51	See Ref. 4	4.9539	36.75	White
0.0850	0.5430	Ethanol	15.51	15.56	6.1500	45.62	White
0.161	0.725	Ethanol	10.37	10.45	3.7900	28.00	White
0.0026	0.0000	Ethanol or Methanol	10.37	10.26	6.9844	51.69	Cream
0.177	0.653	Ethanol	10.37	10.38	9.4690	70.09	White
acid, and <i>p</i> -nitroaniline <sup>a</sup>							
0.0791	0.3305	Glacial HOAc; then addition of water	9.39	9.29	5.4380	36.47	Cream
0.0120	0.153	Glacial HOAc; then addition of water	9.39	9.32	1.9330	14.34	White
0.091	0.3162	Ethanol or acetophenone	9.46	9.40	10.8702	73.35	Cream
0.2111	1.1169	Ethanol	9.46	9.34	3.7810	25.51	White
0.2266	1.1611	Ethanol	9.86	9.87	5.2347	36.81	Cream
0.2437	1.0495	Ethanol	9.86	9.99	11.2409	79.05	White
0.0941	0.3942	Ethanol	8.97	8.96	1.7703	11.71	White

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

### Psoralene I: Certain Reactions of Xanthotoxin\*

MERVIN E. BROKKE AND BERT E. CHRISTENSEN

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A number of the chemical reactions of 9-methoxypsoralene and its derivatives are described. These include nitration, halogenation, reduction, thionation, demethylation, ozonation, and other degradation procedures. Degradation studies and unequivocal synthesis show that bromination occurs at the four position. The structures of the 2,3-dihydropsoalene derivatives were established by a comparison of the ultraviolet absorption spectra of psoralene and coumarin derivatives. Thionation of the 9-methoxypsoralenes proceeds in a manner analogous to that reported for coumarins.

In 1911, Priess<sup>1</sup> discovered a new piscicide in an alcoholic extract of *fagara zanthoxyloides* Lam. to which he gave the name xanthotoxin. Later Thoms<sup>2</sup> after determining the structure of this compound renamed it xanthotoxin and in 1936 Spath reproduced it synthetically.<sup>3</sup>

In addition to its toxic action on fish<sup>4</sup> xanthotoxin (9-methoxypsoralene or 9-methoxyfuro[3,2-*g*]coumarin I) has since been shown to possess a mollusci-

cidal activity.<sup>5</sup> When administered in large doses to mammals it was found to produce fatty degeneration of the liver and adrenal hemorrhage,<sup>6</sup> while in humans the compound has found medical acceptance for the treatment of leukoderma.<sup>7</sup> The most recent applications have made use of the fact that I alters the erythral response to ultraviolet light,<sup>8a,b,c</sup> a property which has been used clinically to prevent sunburn.<sup>8a</sup> There is some evidence that

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(1) H. Priess, *Ber. Pharm. Ges.*, **21**, 227 (1911).

(2) H. Thoms, *Ber.*, **44**, 3325 (1911).

(3) E. Spath and M. Pailer, *Ber.*, **69**, 767 (1936).

(4) E. Spath and F. Kuffner, *Monatsh.*, **69**, 75 (1936).

(5) A. Schönberg and N. Latif, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(6) A. Elwi, *J. Roy. Egypt. Med. Assoc.*, **33**, 773 (1950).

(7) I. Fahmy and H. Abu-Shady, *Quart. J. Pharm. and Pharmacol.*, **21**, 499 (1948).

(8) (a) A. Lerner, *J. Invest. Dermatol.*, **20**, 299 (1953).

(b) A. Griffin, M. O'Neal, and T. Fitzpatrick, *Congress of intern. biochem.*, Brussels 1955, 121. (c) L. Musajo, G. Rotighiero and G. Caporale, *Chimica e industria*, **35**, 13 (1953).

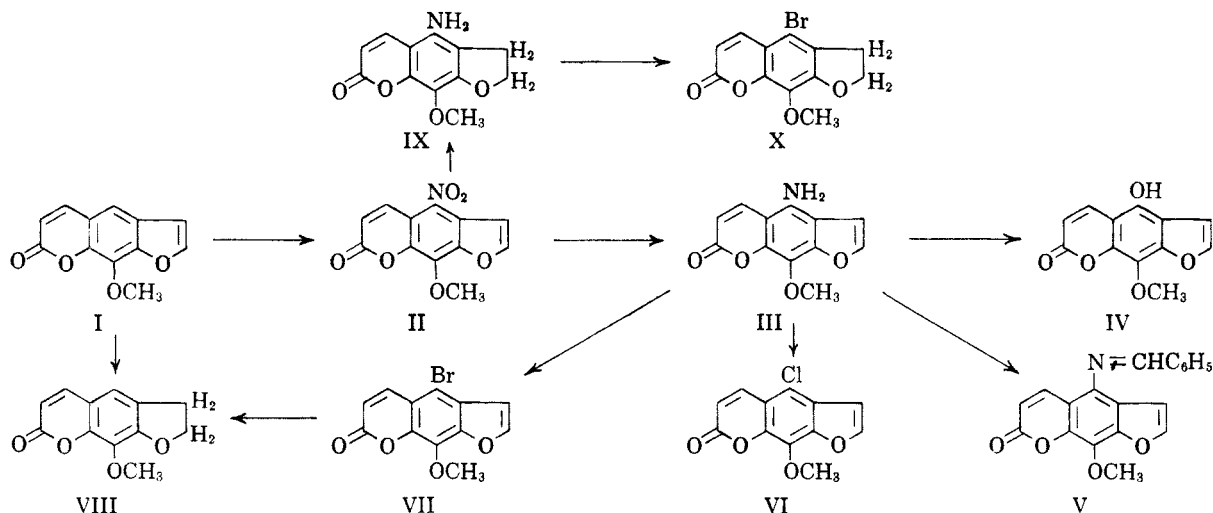


Figure 1

under certain conditions xanthotoxin may be carcinogenic.<sup>8b</sup>

Because of the wide-spread and increasing interest in xanthotoxin for its pharmacological action, this study was undertaken to investigate some of the chemical properties of the compound and to prepare new derivatives for biological testing.

Both Priess<sup>1</sup> and Thoms<sup>2</sup> prepared mononitro derivatives of I. Thoms and Baetcke<sup>9</sup> established that this nitro substituent was at the 4-position by reducing it to the corresponding amino compound, followed by oxidation to the quinone. This quinone was shown to be identical to that obtained from bergaptene (4-methoxypsoralene).

In the current study both the nitro and amino derivatives (see II and III, Fig. 1) were prepared in excellent yields. 4-Amino-9-methoxypsoralene III exhibited the normal behavior of an aromatic amine, for example, in the formation of an acetyl derivative and a Schiff's base.

Since III appeared to be a potential key compound for the preparation of other derivatives, it was subjected to a number of diazotization reactions. This type of reaction finds precedent in the work of Dey and Kutti<sup>10</sup> who diazotized and coupled a group of substituted coumarins; and in that of Noguchi and Kawanami<sup>11</sup> who prepared 9-hydroxy-4-methoxypsoralene from aminobergaptene. Analogous Sandmeyer reactions with III yielded the corresponding bromo and chloro derivatives while hydrolysis of the diazotized product yielded the phenol, 4-hydroxy-9-methoxypsoralene IV.

Spath has reported a phenol<sup>12</sup> which was shown to be either 4-hydroxy-9-methoxypsoralene or its isomer 9-hydroxy-4-methoxypsoralene. 9-Hydroxy-

4-methoxypsoralene was shown to have a melting point of 198°,<sup>11</sup> while IV prepared in this laboratory melted at 220–226°. Since Spath found the melting point of his phenol to be 224–226° his compound was probably IV.

Schönberg and Sina<sup>13</sup> demethylated 9-methoxypsoralene to form the corresponding phenol, by the use of magnesium iodide and sulfuric acid. Later, Schönberg and Ayiz<sup>14</sup> reported that aniline hydrochloride was a superior cleaving agent. The latter work however, could not be confirmed in this laboratory. Cleavage with aniline hydrochloride was attempted both with the refluxing technique of Schönberg and by fusion in sealed tubes at various temperatures and heating times. In no case could any reaction be observed. Cleavage with the magnesium iodide procedure, on the other hand, was accomplished in small yield. Although other workers have reported cleavage of a butylfurocoumarin ether by mild treatment with mineral acid,<sup>15</sup> this reagent as expected was ineffectual with 9-methoxypsoralene.

In the original synthesis of I, Spath<sup>3</sup> prepared 2,3-dihydro-9-methoxypsoralene VIII which was subsequently dehydrogenated. In this laboratory it was found that the reverse reaction readily occurred; VIII was formed in good yield in palladium-catalyzed hydrogenation reactions.

That the hydrogenation product of 9-methoxypsoralene and the 2,3-dihydro-9-methoxypsoralene reported by Spath were identical structures was deduced from a consideration of the fact that their melting points were identical and from a study of the ultraviolet data given in Table I.

(9) H. Thoms and E. Baetcke, *Ber.*, **45**, 3705 (1912).

(10) B. Dey and V. Kutti, *Proc. Nat. Inst. Sci. India*, **6**, 641 (1940).

(11) T. Noguchi and M. Kawanami, *Ber.*, **71**, 1428 (1938).

(12) E. Spath, *Monatsh.*, **72**, 179 (1938).

(13) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 4826–8 (1950).

(14) A. Schönberg and G. Ayiz, *J. Am. Chem. Soc.*, **75**, 3265–6 (1953).

(15) G. Pigulevskii and G. Kuznetrova, *Zhur. obshechei Khim.*, **23**, 1937 (1953).

TABLE I  
 ULTRAVIOLET ABSORPTION DATA OF CERTAIN COUMARIN AND PSORALENE DERIVATIVES

Compound	$\lambda_{\max.}$	Log $\epsilon$	$\lambda_{\max.}$	Log $\epsilon$	$\lambda_{\max.}$	Log $\epsilon$	$\lambda_{\max.}$	Log $\epsilon$	
A	<220	>4.04	...	...	275	4.04	315	3.76	
B	<220	>4.04	270	3.30	275	3.30	...	...	
C	225	4.11	255	3.70	295	3.76	350	4.07	
D	<220	>4.08	250	3.48	290	3.60	...	...	
E	245	4.08	275	3.45	282	3.48	...	...	
F	<220	>3.6	282	3.52	289	3.48	...	...	
G	243 <sup>a</sup>	4.13	265	3.96	289	3.90	300	4.04	
H	252 <sup>b</sup>	3.28	262	3.44	284	3.40	335	4.08	
I	240	4.30	246	4.29	290	3.98	>320	>3.90	
J	225	4.24	258	3.67	295	3.88	>320	>4.21	
A	Coumarin <sup>16</sup>					F	2,3-Dihydrobenzofuran <sup>17</sup>		
B	3,4-Dihydrocoumarin <sup>16</sup>					G	9-Methoxypsoralene		
C	6,7-Dihydroxycoumarin <sup>16</sup>					H	2,3-Dihydro-9-methoxypsoralene		
D	3,4-Dihydro-6,7-dihydroxycoumarin <sup>16</sup>					I	4,5-Dimethylpsoralene <sup>c</sup>		
E	Benzofuran <sup>17</sup>					J	2,3-Dihydro-4,5-dimethylpsoralene <sup>c</sup>		

<sup>a</sup> This compound has a split peak at 243 and 248 each with same extinction coefficient. It also has a peak below 220. <sup>b</sup>This compound has a peak below 220. <sup>c</sup> These two compounds were synthesized in this laboratory and will be published elsewhere.

It is evident from the data presented in Table I that reduction of coumarin and 6,7-dihydroxycoumarin resulted in a lower extension of the conjugation with elimination of peaks above 300  $m\mu$ ; this same observation has been made in numerous other instances.<sup>16</sup> Furthermore since neither benzofuran, nor 2,3-dihydrobenzofuran shows an absorption spectrum above 300  $m\mu$ , it is reasonable to assume the benzofuran portion of the furocoumarin molecules would not be responsible for absorption in this region.

Therefore the peaks observed above 300  $m\mu$ , in the cases of G, H, I, and J must arise from the conjugation of the lactone carbonyl with the aromatic nucleus. For this reason the hydrogenation of 9-methoxypsoralene must have occurred in the 2,3-positions rather than the 5,6. It is to be noted that hydrogenation of the furan ring results in formation of a saturated ether which causes a bathochromic effect, offsetting the effect of the loss of conjugation due to reduction of the furan ring.

Nitration of 2,3-dihydro-9-methoxypsoralene VIII proceeded similarly to that of 9-methoxypsoralene yielding a mononitro derivative. This nitro derivative resisted dehydrogenation. Although this compound was hydrogenated further by both catalytic and chemical reduction no pure products were isolated from the reaction mixture.

On the other hand, 9-methoxy-4-nitropsoralene II was readily reduced by catalytic procedures to the corresponding 4-amino-2,3-dihydro-9-methoxypsoralene (IX). The position of the additional hydrogen atoms (2,3) was ascertained by converting the 4-amino substituent to the 4-bromo analog X and then comparing ultraviolet spectra of X with that of the known 4-bromo-9-methoxypsoralene. See Table II.

The presence of the peak at 330  $m\mu$  in the spectrum of 4-bromo-2,3-dihydro-9-methoxypsoralene is indicative of unsaturation in the 5,6 position thus extending conjugation of the carbonyl moiety to the aromatic nucleus. Despite the loss of conjugation due to reduction of the furan ring, the effect of the formation of the aliphatic ether causes a slight bathochromic shift in this instance.

Priess<sup>18</sup> reported that direct bromination of 9-methoxypsoralene in chloroform yielded a dibromo addition product which melted at 164°. He postulated that the addition took place either in the 2,3- or 5,6-positions. In this laboratory, the bromination in chloroform yielded a monobromo derivative VII, m.p. 185–186°, and a tribromo derivative XVII, m.p. 165°. Bromination with *N*-bromosuccinimide yielded the same monobromo substitution product VII as before. Under the various conditions of brominations which were tried, these were the only products ever isolated from the reaction. The tribromo derivative XVII, was readily converted to the monobromo derivative by the conventional method (treating it with an acetone solution of sodium iodide).

Horning and Risner<sup>19</sup> have reported the bromination of 5-methyl-2,3-dihydrofuro[3,2-*g*]coumarin with *N*-bromosuccinimide. Since their product could not be dehydrohalogenated and did not react with silver nitrate, these workers concluded that the bromine must be either on the lactone ring or the benzene nucleus.

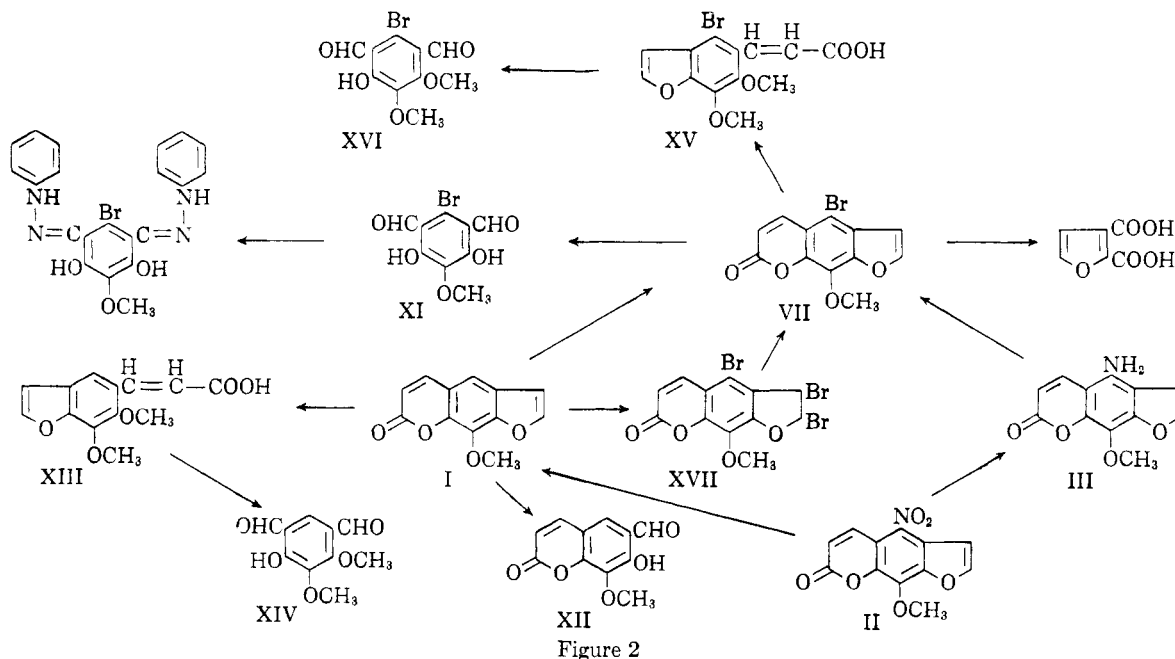
The monobromo derivative of 9-methoxypsoralene VII was inert to aqueous base, silver nitrate, and Grignard formation under all conditions tested. It was however very labile to catalytic hydrogenation

(16) R. Goodwin and B. Pollock, *Arch. Biochem.*, **49**, 1 (1954).

(17) J. Jones and A. Lindsey, *J. Chem. Soc.*, 1836 (1950).

(18) H. Priess, *Chem. Zentralblatt* II, 94 (1911).

(19) E. Horning, and D. Risner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).



yielding VIII in 15 minutes at 40 lbs. hydrogen pressure in presence of palladized charcoal.

In order to establish the position of the bromo substituent, the monobromo derivative was oxidized with hydrogen peroxide<sup>20</sup> yielding furan-2,3-dicarboxylic acid, thus eliminating from consideration the 2- and 3-positions. Comparative ozonizations were carried out using 9-methoxypsoralene and bromo-9-methoxypsoralene, the former yielding the known 6-formyl-7-hydroxy-8-methoxycoumarin.<sup>21</sup> Final confirmation of this product was made by the preparation of the dinitrophenyl hydrazone derivative.

Bromo-9-methoxypsoralene on the other hand was cleaved in both hetero-rings yielding a substituted isophthalaldehyde (XI). The presence of two formyl substituents in XI, was established by the preparation and analysis of the bisphenylhydrazone derivative.

Although only one hetero ring in 9-methoxypsoralene was cleaved by direct ozonolysis, the corresponding isophthalaldehyde was obtained by opening the lactone ring with dimethyl sulfate.<sup>3,22</sup> Upon ozonolysis of the resultant product the same reactions were observed as in the instance of the bromo-9-methoxypsoralene. These reactions all pointed to the fact that the monobromo substituent must be in the 4-position. This observation was confirmed when the 4-bromo-derivative was synthesized unequivocally by the Sandmeyer procedure from 4-amino-9-methoxypsoralene. These series of reactions are given in Fig. 2.

The position of the remaining two bromo substituents in the tribromo-9-methoxypsoralene was established by the ultraviolet spectral data shown in Table II.

TABLE II  
ULTRAVIOLET ABSORPTION DATA OF BROMINATED PSORALENE DERIVATIVES

	$\lambda_{\max.}$	Log $\epsilon$	$\lambda_{\max.}$	Log $\epsilon$	$\lambda_{\max.}$	Log $\epsilon$	$\lambda_{\max.}$	Log $\epsilon$
A	222	4.41	246 <sup>a</sup>	4.01	268	4.28	308	4.14
B	<220	>4.62	254	4.42	266	4.43	330	4.52
C	<220	>4.27	246	3.98	268	4.27	310	4.14

A 4-Bromo-9-methoxypsoralene  
B 4-Bromo-2,3-dihydro-9-methoxypsoralene  
C 2,3-dihydro-9-methoxy-2,3,4-tribromopsoralene

<sup>a</sup> This compound has a split peak at 346 and 256  $m\mu$

The fact that the two additional bromo substituents did not eliminate the adsorption above 300  $m\mu$  is indicative of addition in the 2,3-positions, for reasons mentioned previously.

2,3-Dihydro-9-methoxypsoralene was likewise observed to form a monobrominated product with bromine in chloroform solutions. *N*-bromosuccinimide however, gave a mixture which has not as yet been resolved. Although this bromo derivative resists dehydrohalogenation it was found to be labile in aqueous base yielding a hydroxy compound. A mixed melting point determination indicated that this monobrominated product was not identical with 4-bromo-2,3-dihydro-9-methoxypsoralene X.

Coumarin and its derivatives are known to react with phosphorus pentasulfide to produce thio-coumarins.<sup>23</sup> This reaction has been carried out

(20) E. Spath and L. Kahovec, *Ber.*, **66**, 1146 (1933).

(21) G. Rodighiero and C. Antonello, *Ann. Chim. (Rome)*, **46**, 960 (1956); *Chem. Abstr.*, **56**, 6616 (1957).

(22) N. Shah and R. Shah, *J. Univ. Bombay*, **7**, Pt. 3, 213 (1938); *Chem. Abstr.* **33**, 3779 (1939).

(23) A. Clayton and W. Godden, *J. Chem. Soc.* 210 (1912).

successfully with I, II, VII, and VIII to produce the corresponding furothiocoumarins (see Fig. 3).

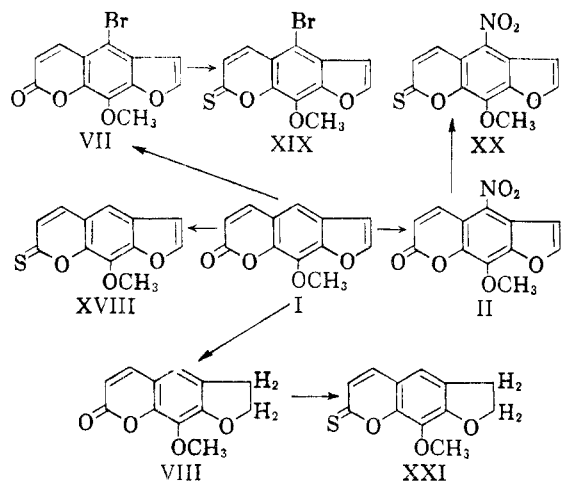


Figure 3

Under normal conditions coumarins are reduced by lithium aluminum hydride to give *o*-(3-hydroxy-1-propenyl)phenols.<sup>24</sup> This reaction proceeded in the same manner with I yielding 6-hydroxy-7-methoxy-5-(3-hydroxy-1-propenyl)benzofuran XXII. Furthermore, the lactone ring of I was also opened with hydrazine<sup>25</sup> to yield the corresponding hydrazide XXIII.

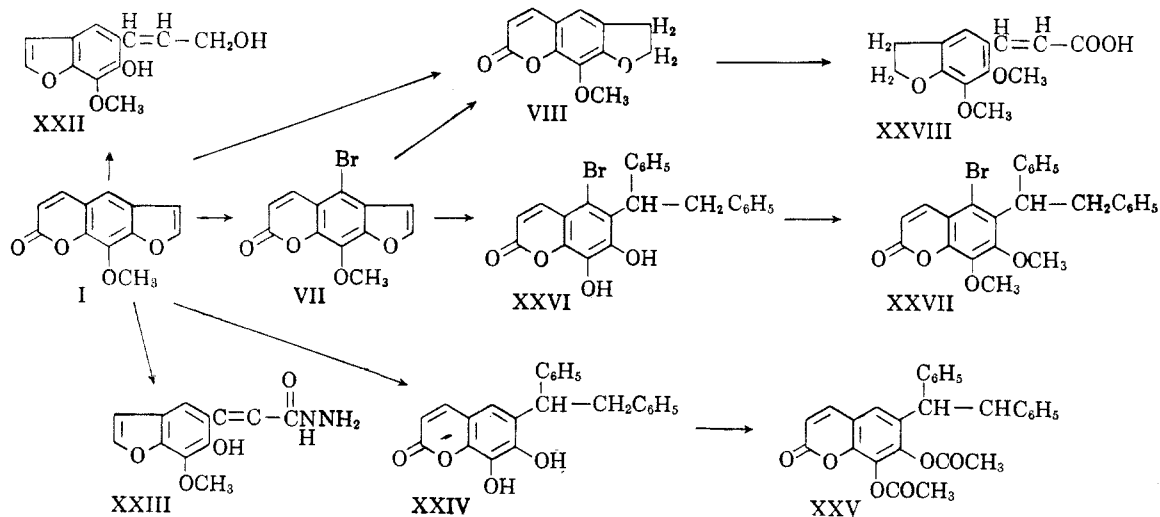


Figure 4

Angelicin and psoralene have been shown to add two moles of benzene in the presence of aluminum chloride to yield 1,2-diphenylethylhydroxycoumarins.<sup>26</sup> Aluminum chloride has also been found to act as an ether-cleaving agent in aromatic solvents.<sup>27</sup>

(24) P. Karrer and P. Banerjea, *Helv. Chim. Acta*, **32**, 1692 (1949).

(25) A. Darapsky, H. Berger and A. Neuhaus, *J. Prakt. Chem.* **147**, 145 (1936).

(26) B. Krishnaswamy and T. Seshadri, *Proc. Indian Acad. Sci.* **16A**, 151 (1942).

(27) B. Krishnaswamy and T. Seshadri, *Proc. Indian Acad.* **15A**, 437-40 (1942).

Both of these reactions occurred simultaneously with I and VII to produce 6-(1,2-diphenylethyl)-7,8-dihydroxycoumarin and 5-bromo-6-(1,2-diphenylethyl)-7,8-dihydroxycoumarin respectively (see Fig. 4).

## EXPERIMENTAL

*9-Methoxy-4-nitro-psoralene* (II). Ten g. of 9-methoxy-psoralene was dissolved in 100 ml. of glacial acetic acid; while maintaining the temperature at 20°, 80 ml. of concd. nitric acid was added slowly with stirring. In a few seconds the mixture turned a deep red and then began to solidify. The mass was then poured onto 200 g. of ice. After the ice had melted the solution was filtered to yield 12.0 g. of a product which melted at 235-238° after recrystallization from ethanol.

*4-Amino-9-methoxy-psoralene* (III). 9-Methoxy-4-nitro-psoralene (10 g.) stannous chloride (20 g.) and tin granules (20 g.) were stirred at room temperature in 40 ml. of alcohol and 120 ml. of concd. HCl for 24 hr. (cooling was necessary at first). The material was then filtered, washed with sodium bicarbonate solution, and recrystallized from 95% ethanol to yield 5.6 g. of 4-amino-9-methoxy-psoralene, m.p. 234-235°. Evaporation of the mother liquid yielded 2.3 g. of the product, raising the over-all yield to 89.3%. The identity of the product was confirmed by preparation of the acetyl derivative m.p. 244-245°.<sup>9</sup>

*9-Benzalamino-9-methoxy-psoralene* V. 4-Amino-9-methoxy-psoralene (0.10 g.) was warmed in 5 ml. of benzaldehyde and the mixture was poured into 25 cc. of 95% ethanol. After standing overnight in the refrigerator, pale yellow crystals, 0.079 g., m.p. 189-200° dec., were obtained.

*Anal.* Calcd. for C<sub>19</sub>H<sub>13</sub>O<sub>4</sub>N: C, 71.5; H, 4.07. Found: C, 71.5; H, 3.96.

*4-Hydroxy-9-methoxy-psoralene* IV. One gram of 4-amino-9-methoxy-psoralene, 0.3 g. sodium nitrite, and 10 ml. of concd. hydrochloric acid were mixed in 65 ml. 95% methanol at zero degrees and allowed to stand for 10 min. The mixture was then warmed to room temperature and 0.10 g. dark green material was removed at this point. This substance was found to melt at 220-226° after crystallization from 95% ethanol (reported m.p. 224-226°<sup>12</sup>).

*Anal.* Calcd. for C<sub>12</sub>H<sub>8</sub>O<sub>5</sub>: C, 62.2; H, 3.45. Found: C, 61.8; H, 3.50.

*4-Chloro-9-methoxy-psoralene* VI. 4-Amino-9-methoxy-psoralene (1.3 g.) was suspended in 30 ml. of concd. hydrochloric acid solution maintained in an ice-salt bath. An aqueous

solution containing 0.38 g. of sodium nitrite was then added slowly to the cooled solution. The mixture was permitted to stand in the cooling bath for 5 min. and then the reaction mixture was transferred to 50 ml. of boiling 6*N* hydrochloric acid which contained 1.5 g. of cuprous chloride. The product was collected, treated with Norite and recrystallized from ethanol, m.p. 187–188°, yield 0.35 g.

*Anal.* Calcd. for  $C_{12}H_7O_4Cl$ : C, 57.5; H, 2.79. Found: C, 57.5; H, 2.80.

*Attempted demethylation of 9-methoxypsoralene.* Three grams of 9-methoxypsoralene were mixed intimately with twice the molar quantity of aniline hydrochloride and heated with stirring in a carbon dioxide atmosphere. The bath temperature was started at 180° and raised to 205° in 40 min. After cooling the mixture was extracted with water and the insoluble residue was recrystallized from dilute acetic acid.<sup>14</sup> After one crystallization, 2.36 grams of material remained m.p. 143–145°; mixed m.p. with 9-methoxypsoralene showed no depression.

*4-Bromo-9-methoxypsoralene (VII).* A. Five grams of 9-methoxypsoralene were mixed with a one molar excess of bromine in chloroform solution. The solvent was then stripped off on the steam bath and the residue was crystallized from 95% ethanol to yield 5.76 g., m.p. 185–186°.

*Anal.* Calcd. for  $C_{12}H_7O_4Br$ : C, 48.8; H, 2.38. Found: C, 48.8; H, 2.46.

B. 9-Methoxypsoralene (1.47 g.) and *N*-bromosuccinimide (1.21 g.) were suspended in 100 ml. of carbon tetrachloride. After refluxing for 2 hr., the solvent was evaporated and the residue was washed with hot water and crystallized from 95% ethanol; yield 1.15 g., m.p. 183–184.5°. Mixed melting point with A showed no depression.

C. 2,3-Dihydro-9-methoxy-2,3,4-tribromopsoralene (100 mg.) was dissolved in 25 ml. acetone and potassium iodide (0.5 gram) was added with stirring. After 2.5 hr. the solution was filtered, diluted with water, and cooled. The insoluble product was collected and crystallized from ethanol to yield 40 mg., m.p. 185–186°. A mixed melting point with 4-bromo-9-methoxypsoralene showed no depression.

D. 4-Amino-9-methoxypsoralene (1.3 g.) was suspended in 25 ml. 48% hydrobromic acid and then cooled in an ice-salt mixture. Sodium nitrite (0.388 g.) dissolved in a little water was added with stirring and the mixture was allowed to stand for 5 min. The mixture was then poured slowly into a boiling solution composed of 1.61 g. of cuprous bromide and 50 ml. 24% hydrobromic acid. The product was collected, dried, and then sublimed at 170° and 15 mm. pressure. This in turn was crystallized from methanol to yield 0.6 g., m.p. 185–186°. A mixed melting point with 4-bromo-9-methoxypsoralene obtained by direct bromination showed no depression.

*4-Bromo-2,3-dihydro-9-methoxypsoralene (X).* 4-Amino-2,3-dihydro-9-methoxypsoralene (150 mg.) was suspended in 25 ml. 48% hydrobromic acid and cooled in an ice-salt mixture. Sodium nitrite (45 mg.) dissolved in a little water was added and the solution was allowed to stand 5 min.; it was then poured into 50 ml. boiling 6*N* hydrobromic acid which contained cuprous bromide (160 mg.). This mixture was diluted with 100 ml. of water and cooled. The product was collected, treated with Norite, and crystallized from ethanol; yield 90 mg., m.p. 201–203°.

*Anal.* Calcd. for  $C_{12}H_9O_4Br$ : C, 48.6; H, 3.03. Found: C, 48.6; H, 3.16.

*Furan-2,3-dicarboxylic acid.* 4-Bromo-9-methoxypsoralene (2.0 g.) was dissolved in 200 ml. 4% methanolic potassium hydroxide and allowed to stand at room temperature overnight. One hundred ml. of water was added and the volume was reduced *in vacuo* to 100 ml. Then 100 ml. of 8% hydrogen peroxide was added and the solution was allowed to stand for 2 days at room temperature, whereupon the temperature was raised to 60–70° and the mixture heated for an additional 6 hr. The oxalic acid formed was removed with ammoniacal calcium chloride. The solution was acidified and extracted with ether. The yield was 0.1 g. of ma-

terial, m.p. 217–220° dec. A mixed melting point with furan-2,3-dicarboxylic acid prepared by a similar oxidation of 9-methoxypsoralene showed no depression.

*Anal.* Calcd. for  $C_8H_4O_6$ : C, 46.2; H, 2.56; Found: C, 46.5; H, 2.86.

*2,3-Dihydro-9-methoxypsoralene (VIII).* A. One gram of 9-methoxypsoralene was dissolved in 100 ml. of ethanol and 0.5 g. 10% palladium on charcoal was added. This mixture was then shaken for 2 hr. at room temperature under 40 pounds hydrogen pressure. The catalyst was then removed and the solvent was evaporated. The residue after crystallization from ethanol yielded 0.31 g. white needles melting at 160–161°. 2,3-Dihydro-9-methoxypsoralene synthesized by another procedure has been reported by Spath to melt at 163°.

*Anal.* Calcd. for  $C_{12}H_{10}O_4$ : C, 66.1; H, 4.59. Found: C, 66.2; H, 4.85.

B. One gram of 4-bromo-9-methoxypsoralene was suspended with 0.5 g. 10% palladium on charcoal in 75 cc. of 95% ethanol. This mixture was shaken for 15 min. under 30 pounds hydrogen pressure, the catalyst was removed, and the solution was reduced in volume, chilled, and filtered to yield 0.65 g. of crystals, m.p. 130–140°. This material was recrystallized three times from ethanol raising the melting point to 158–160°. A mixed melting point with 2,3-dihydro-9-methoxypsoralene showed no depression.

*2,3-Dihydro-9-methoxy-*x*-nitropsoralene.* One gram of 2,3-dihydro-9-methoxypsoralene was stirred into 25 ml. of a 50% solution of concentrated nitric acid in glacial acetic acid. The solution became cloudy after standing about one minute at room temperature and was immediately poured into 200 ml. of ice water. The product was filtered, washed with water, and recrystallized from ethanol to yield 1.2 g. of material, m.p. 192–198° dec.

*Anal.* Calcd. for  $C_{12}H_9O_6N$ : C, 54.7; H, 3.54. Found: C, 54.6; H, 3.53.

*4-Amino-2,3-dihydro-9-methoxypsoralene (IX).* One gram of 9-methoxy-4-nitropsoralene was suspended with 0.5 g. 10% palladium on charcoal in 150 ml. of 95% ethanol and shaken 2 hr. under 40 pounds hydrogen pressure at room temperature. The mixture was then heated to boiling and the catalyst removed. Upon cooling to 5° the product crystallized and was collected; yield 0.55 g., m.p. 214–216°.

*Anal.* Calcd. for  $C_{12}H_{11}O_4N$ : C, 61.7; H, 4.72. Found: C, 61.6; H, 4.63.

*2-Bromo-4,6-dihydroxy-5-methoxy-*m*-phthalaldehyde (XI).* One gram 4-bromo-9-methoxypsoralene was dissolved in 50 ml. methylene chloride. This solution was cooled in an ice bath whereupon a stream of approximately 3% ozone in oxygen was bubbled through it at the rate of about 50 ml. per minute, for 2 hr. The solution was then poured into 75 ml. of 30% acetic acid containing 0.5 g. zinc dust. The methylene chloride was evaporated on the steam bath and the remaining liquid decanted from the zinc. Upon cooling 0.25 gram product separated. The product was recrystallized from dilute acetic acid, m.p. 169–171°.

*Anal.* Calcd. for  $C_9H_7O_5Br$ : C, 39.3; H, 2.54. Found: C, 39.3; H, 2.61. Bisphenylhydrazone; m.p. 263° dec.

*Anal.* Calcd. for  $C_{21}H_{19}O_5N_2Br$ : C, 55.4; H, 4.18. Found: C, 55.4; H, 4.34.

*6-Formyl-7-hydroxy-8-methoxycoumarin (XII).* One gram of 9-methoxypsoralene was dissolved in 50 ml. methylene chloride. The solution was cooled to zero degrees with an ice bath and approximately 3% ozonized oxygen was bubbled through for 3 hr. at the rate of about 50 ml. per minute. The solution was then added slowly to a suspension of 0.1 g. zinc dust in 75 ml. 30% acetic acid. After standing 1 hr. at room temperature, the methylene chloride was removed on the steam bath, the remaining solution was decanted and cooled. The product was collected and recrystallized from water to yield 0.41 g., m.p. 194–195.5°. Phenylhydrazone dec. 275°. Reported:<sup>21</sup> 195–196°, Phenylhydrazone derivative, 278–279° dec.

*Anal.* Calcd. for  $C_{11}H_8O_6$ : C, 60.1; H, 3.63. Found: C, 59.7; H, 3.76.

*3-[5-(6,7-Dimethoxybenzofuryl)]propenoic acid* (XIII). One gram of 9-methoxypsoralene was dissolved in 50 ml. of acetone and dimethyl sulfate (10 ml.) was added, followed by 50 ml. 20% potassium hydroxide. After refluxing for 15 min. another 10 ml. of dimethyl sulfate was added followed by 25 ml. of 20% potassium hydroxide. Reflux was continued for 2 hr. The solution was then cooled and acidified. The acetone was removed *in vacuo* and the product was collected. Recrystallization was effected from dilute acetic acid; yield 0.90 g., m.p. 112–114°.

*Anal.* Calcd. for  $C_{13}H_{12}O_6$ : C, 63.0; H, 4.84. Found: C, 63.4; H, 4.87.

*4,5-Dimethoxy-6-hydroxy-m-phthalaldehyde* (XIV). One gram of the foregoing unsaturated acid was dissolved in 50 ml. of methylene chloride. The solution was cooled in an ice bath and a stream of approximately 3% ozone in oxygen was bubbled through at the rate of about 50 ml. per minute for 2 hr. The solution was then poured slowly into 75 ml. of 30% acetic acid containing 0.5 g. of zinc dust. The methylene chloride was removed using a steam bath and the remaining liquid was decanted from the zinc. Upon cooling 0.25 g. product separated. This was crystallized from dilute acetic acid, treated with Norite and recrystallized from water, m.p. 133–134°.

*Anal.* Calcd. for  $C_{10}H_{10}O_6$ : C, 57.2; H, 4.77. Found: C, 57.3; H, 4.76.

*3-[5-(4-Bromo-6,7-dimethoxybenzofuryl)]propenoic acid* (XV). One gram of 4-bromo-9-methoxypsoralene was dissolved in 50 ml. acetone. Dimethyl sulfate (7 ml.) was added, followed by 50 ml. of 20% potassium hydroxide. The solution was refluxed for 2 hr., then acidified and the acetone removed *in vacuo*. The product was collected and crystallized from dilute methanol; yield 0.75 g., m.p. 143–145°.

*Anal.* Calcd. for  $C_{13}H_{11}O_6Br$ : C, 47.7; H, 3.37. Found: C, 48.0; H, 3.55.

*2-Bromo-5,6-dimethoxy-4-hydroxy-m-phthalaldehyde* (XVI). Two grams of the foregoing unsaturated acid was dissolved in 100 ml. of chloroform and the solution was cooled in an ice bath. A stream of approximately 3% ozonized oxygen was bubbled through this solution for 3 hr. at the rate of about 50 ml. per minute. The solvent was then removed *in vacuo* and 50 ml. water was added. This mixture was kept at room temperature overnight and then placed on the steam bath for 15 min. The water was decanted and the residue recrystallized from dilute methanol to yield 0.40 g., m.p. 89–91°.

*Anal.* Calcd. for  $C_{10}H_8O_6Br$ : C, 41.7; H, 3.10. Found: C, 42.0; H, 3.15.

*2,3-Dihydro-9-methoxy-2,3,4-tribromopsoralene* (XVII). One gram 9-methoxypsoralene (1 mole) was dissolved in 100 ml. chloroform and bromine (7.5 grams, 10 moles in 50 ml. of chloroform) was added. This solution was evaporated on the steam bath until 20–25 ml. of chloroform remained. The residue was then poured into 200 ml. of petroleum ether and cooled. The insoluble product was collected and crystallized from methanol. The yield was 1.5 g., m.p. 165–166°.

*Anal.* Calcd. for  $C_{12}H_7O_4Br_3$ : C, 31.7; H, 1.54. Found: C, 31.5; H, 1.63.

*x-Bromo-2,3-dihydro-9-methoxypsoralene*. Two grams of 2,3-dihydro-9-methoxypsoralene was dissolved in a small volume of chloroform to which had been added a one molar excess of bromine. This solution was placed on the steam bath and allowed to evaporate to dryness. The residue was recrystallized from 95% ethanol; yield 2.60 g., m.p. 202–203°.

*Anal.* Calcd. for  $C_{12}H_9O_4Br$ : C, 48.5; H, 3.02. Found: C, 48.3; H, 2.96.

*2,3-Dihydro-x-hydroxy-9-methoxypsoralene*. One-half gram of *x*-bromo-2,3-dihydro-9-methoxypsoralene was refluxed for 30 min. in 25 ml. of 6*N* sodium hydroxide. This solution

was then acidified with 6*N* sulfuric acid, and the product was filtered to yield 0.39 g. of material which melted at 264–268° after recrystallization from ethanol.

*Anal.* Calcd. for  $C_{12}H_{10}O_5$ : C, 61.6; H, 4.27. Found: C, 61.3; H, 4.21.

*9-Methoxyfuro[3,2-g]thiocoumarin* (XVIII). 9-Methoxypsoralene (1.75 g.) was mixed intimately with 3.5 g. phosphorus pentasulfide. This mixture was heated for 2 hr. in 75 ml. of xylene at the refluxing temperature. The mixture was then filtered and cooled. The product was collected and then recrystallized from glacial acetic acid; yield 1.85 g., m.p. 197–198°.

*Anal.* Calcd. for  $C_{12}H_8O_3S$ : C, 62.2; H, 3.44. Found: C, 62.2; H, 3.61.

*4-Bromo-9-methoxyfuro[3,2-g]thiocoumarin* (XIX). One gram of 4-bromo-9-methoxypsoralene and 2.5 g. of phosphorus pentasulfide were mixed intimately. The mixture was refluxed in 75 ml. xylene for 2 hr. The xylene solution was then filtered and cooled and the product was collected and recrystallized from ethanol; yield 0.80 g., m.p. 235–238°.

*Anal.* Calcd. for  $C_{12}H_7O_3BrS$ : C, 46.3; H, 2.25. Found: C, 46.2; H, 2.35.

*9-Methoxy-4-nitrofuro[3,2-g]thiocoumarin* (XX). One gram 9-methoxy-4-nitropsoralene and phosphorus pentasulfide (2.5 grams) were mixed intimately and then heated 3 hr. in 75 ml. of refluxing xylene. The xylene was decanted and cooled. The product was collected and crystallized from ethanol to yield 0.45 g., m.p. 205–206° (dec.).

*Anal.* Calcd. for  $C_{12}H_7O_5NS$ : C, 52.0; H, 2.53. Found: C, 51.9; H, 2.52.

*2,3-Dihydro-9-methoxyfuro[3,2-g]thiocoumarin* (XXI). 2,3-Dihydro-9-methoxypsoralene (0.7 gram) was mixed intimately with phosphorus pentasulfide (1.75 gram) and heated 3 hr. in 75 ml. of refluxing xylene. The xylene was decanted and taken to dryness and the residue was crystallized from ethanol; yield 0.25 gram, m.p. 165–167°.

*Anal.* Calcd. for  $C_{12}H_{10}O_3S$ : C, 61.6; H, 4.27. Found: C, 61.3; H, 4.47.

*5-(3-Hydroxy-1-propenyl)-6-hydroxy-7-methoxybenzofuran* (XXII). One gram of 9-methoxypsoralene and one gram of lithium aluminum hydride were refluxed in 300 ml. of dry ether for 8 hr. At the end of this time, water was added to destroy the excess reagent and the mixture was acidified with dilute sulfuric acid. Upon evaporation, the ether layer was found to contain 0.91 gram of a mixture which was shown to contain some inorganic material. This mixture was recrystallized from benzene yielding 300 mg. of a pure compound, m.p. 124–126°.

*Anal.* Calcd. for  $C_{12}H_{12}O_4$ : C, 65.6; H, 5.46. Found: C, 65.6; H, 5.49.

*3-[5-(6-Hydroxy-7-methoxybenzofuryl)]propenoic hydrazide* (XXIII). Two grams 9-methoxypsoralene (1 mole) and hydrazine hydrate (1.4 grams, 3 moles) were refluxed 24 hr. in 100 ml. of 95% ethanol. The solution was then diluted with water and cooled. The product was collected and recrystallized from ethanol, yield 1.7 grams, m.p. 183–185°.

*Anal.* Calcd. for  $C_{12}H_{12}O_4N_2$ : C, 58.2; H, 4.84. Found: C, 58.3; H, 5.02.

*6-(1,2-Diphenylethyl)-7,8-dihydroxycoumarin* (XXIV). One gram of 9-methoxypsoralene was refluxed with 2 g. of aluminum chloride in 100 ml. benzene for 30 min. The benzene was decanted and evaporated to dryness. The residue was acidified and crystallized from dilute ethanol; yield 0.8 g. m.p. 240–244°.

*Anal.* Calcd. for  $C_{23}H_{18}O_4$ : C, 75.2; H, 4.90. Found: C, 74.7; H, 5.17.

The *diacetyl derivative* (XXV) was prepared by refluxing 200 mg. in acetic anhydride and pyridine for 2 hr. The solution was poured into water and the product was collected and recrystallized from dilute ethanol; yield 200 mg., m.p. 138–140°.

*Anal.* Calcd. for  $C_{27}H_{22}O_6$ : C, 73.5; H, 4.98. Found: C, 73.5; H, 4.95.

*4-Bromo-6-(1,2-diphenylethyl)-7,8-dihydroxycoumarin* (XXVI). One gram of 4-bromo-9-methoxypsoralene and 2.0 g. aluminum chloride were mixed intimately and then covered with 75 ml. benzene. This mixture was refluxed 20 min.; the benzene was then decanted and evaporated. The resulting residue was acidified with dilute hydrochloric acid, washed with water, and recrystallized twice from dilute ethanol and finally from dilute isopropyl alcohol; yield 0.46 g., m.p. 230–233°.

Anal. Calcd. for  $C_{23}H_{17}O_4Br$ : C, 63.3; H, 3.90. Found: C, 63.0; H, 4.07.

*4-Bromo-7,8-dimethoxy-6-(1,2-diphenylethyl)coumarin* (XXVII). 4-Bromo-7,8-dihydroxy-6-(1,2-diphenylethyl)coumarin (250 mg.) was dissolved in 20 ml. acetone. Two ml. dimethyl sulfate and one gram potassium carbonate were added and the solution was refluxed 17 hr. It was then poured into 100 ml. of water and cooled. The insoluble product was collected and recrystallized from dilute ethanol to yield 140 mg., m.p. 127–130°.

Anal. Calcd. for  $C_{25}H_{21}O_4Br$ : C, 64.5; H, 4.53. Found C, 64.3; H, 4.65.

*3-[5-(2,3-Dihydro-6,7-dimethoxybenzofuryl)]propenoic acid* (XXVIII). 2,3-Dihydro-9-methoxypsoralene (0.5 gram) was dissolved in 25 ml. acetone and 5.0 ml. of dimethyl sulfate was added. The solution was heated to reflux and 25 ml. of 20% potassium hydroxide was added slowly. Reflux was continued for 2 hr. after addition of the alkali. The solution was then cooled, acidified with dilute hydrochloric acid, and the acetone removed *in vacuo*. The insoluble product was collected and crystallized from dilute methanol to yield 0.3 g., m.p. 100–102°.

Anal. Calcd. for  $C_{13}H_{14}O_5$ : C, 62.5; H, 5.61. Found: C, 62.4; H, 5.72.

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CORVALLIS, ORE.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

## The Functional Groups of Nomilin and Obacunone<sup>1</sup>

F. M. DEAN<sup>2</sup> AND T. A. GEISSMAN

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In conjunction with evidence derived from infrared spectra and including intensity measurements in the carbonyl-stretching region, the chemical properties of nomilin and obacunone indicate that these compounds are ketonic dilactones with a furan ring and but one carbocyclic system. One lactone ring of nomilin carries a  $\beta$ -acetoxy group whereas obacunone has the corresponding  $\alpha,\beta$ -unsaturated lactone ring; this ring is readily opened by hydrolysis. The second lactone ring is opened by hydrogenolysis generating a carboxyl group which is remarkably acidic, properties that permit tentative conclusions to be drawn as to the relative positions of some of the functional groups.

Of the three optically active, lactonic, bitter principles of citrus fruits, limonin<sup>3</sup> has been more thoroughly studied than nomilin and obacunone, knowledge of which is chiefly due to Emerson,<sup>4</sup> who showed that both nomilin,  $C_{28}H_{34}O_9$ , and obacunone,  $C_{26}H_{30}O_7$ , gave obacunoic acid,  $C_{26}H_{32}O_8$ , on hydrolysis, the former yielding acetic acid at the same time. Further evidence indicated the presence of two lactone rings, one carrying a  $\beta$ -acetoxy group, and one of a somewhat unreactive carbonyl group. The present investigation has confirmed and extended these results.

The absence of hydroxyl groups from obacunone was clear from the inertness of this compound to acetylation and from its transparency near  $3\mu$  in the infrared. Because the intense and ill-resolved absorption (Fig. 1) in the region 1700–1734  $cm^{-1}$  due to the lactonic system and carbonyl group made it difficult to detect individual functions, attention

TABLE I  
ULTRAVIOLET END-ABSORPTIONS

	$\epsilon \times 10^{-3}$	
	209 $m\mu$	218 $m\mu$
Nomilin	5.70	4.27
Obacunone	16.7	16.0
Methyl obacunoate	13.6	11.3
Obacunone oxime	15.4	13.1
$\alpha$ -Obacunol	18.3	14.4
Dihydroobacunone	10.0	6.4
Obacunone hydrochloride	5.5	4.0
Double bonds <sup>10</sup>		
(i) Disubstituted	$\sim 1$	$\sim 0$
(ii) Trisubstituted	3–4	$\sim 1.5$
(iii) Tetrasubstituted	4.5–10	4–6
Furan	$\lambda_{208}$ 5.6	$\lambda_{216}$ 5.0
Marrubin <sup>29</sup>	$\lambda_{210}$ 5.7	—

was directed to the spectrum of obacunone oxime, which, in paraffin mulls, had two bands of more or less equal intensity at 1749 and 1677  $cm^{-1}$ . Whilst the latter band was correctly placed for the C=N stretching frequency of an oxime, its intensity was unexpectedly high compared with the data given by Cross and Rolfe,<sup>5</sup> who quote oximes having extinction coefficients approximately one tenth those of ketones. In an attempt to minimize inter-

(5) L. H. Cross and A. C. Rolfe, *Trans. Faraday Soc.*, **47**, 354 (1951).

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(2) Department of Organic Chemistry, Liverpool University, Liverpool, England.

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(4) O. H. Emerson, *J. Am. Chem. Soc.*, **70**, 545 (1948); **73**, 2621 (1951).