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Synthetic Furocoumarins. Xanthotoxin and Methylxanthotoxins.

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The synthesis of 4-methylxanthotoxin (X), 4,5'-dimethylxanthotoxin (XXIV) and the hitherto unknown 5'-methylxanthotoxin (XXIII) are described, using 6-allyl-7-hydroxy-8-methoxycoumarin (XV) and its 4-methyl derivative (XVII) as intermediates.

The pharmacological activity of furocoumarins is varied. Not only are they active as dermal photosensitizing agents (2) but recently new properties have been reported for them, *viz.* their interaction with DNA and photoinactivation of DNA-containing viruses (3,4), their anti-cancer (5), cytological (4), radio-protecting (6), radiosensitizing (6), antibiotic (7), fungicidal (8) and molluscicidal (9) activities. In the course of our investigations on compounds potentially active in the treatment of vitiligo, also known as leucoderma, we became interested in the synthesis of furocoumarins by routes of commercial value.

Xanthotoxin.

Xanthotoxin or 8-methoxypsoralen (V) is a naturally occurring furocoumarin found in many plants (10,11). Recently it has been isolated from the dried leaves of *Heracleum Sosnowskyi* (12), the essential oils of the fruits of *Ruta Pinnata* (13) and the fruits of *Afraegle paniculata* (14) and of *Pastinaca Sativa* (15). Yields of xanthotoxin from natural sources range from 0.1-0.3%.

Spath and Pailer (16) reported a synthesis of xanthotoxin which was later slightly modified by Lagercrantz (17). Rodighiero and Antonello (10) synthesized xanthotoxin by a scheme depicted by structures I to V in Figure 1. The yields, however, were poor in both the above routes. Recently Seshadri and Sood (11) have obtained xanthotoxin in 5-8% overall yield starting from 7,8-dihydroxycoumarin or 8-acetyl-7-hydroxycoumarin. From both these compounds they prepared 7-allyloxy-8-methoxycoumarin (XIII) which they then converted to xanthotoxin by a route depicted by structures XIII → XV → XVIII → V in Figure 1.

In our initial efforts to improve the yields of the crucial stage in the synthesis by Rodighiero and Antonello (10), *viz.* the preparation of 6-formyl-7-hydroxy-8-methoxycoumarin (II) from 7-hydroxy-8-methoxycoumarin (I), we tried a modified Vilsmeier reaction (18) in the place of Duff's reaction used by them, but without any success.

We then adopted the route I → XIII → XV → XVIII → V and obtained xanthotoxin in 13% overall yield. When our work was in progress, Seshadri and Sood (11) reported the synthesis of xanthotoxin in about 15% overall yield from 7-allyloxy-8-methoxycoumarin (XIII) prepared from 7,8-dihydroxycoumarin or 8-acetyl-7-hydroxycoumarin. In our experiments the Claisen rearrangement of 7-allyloxy-8-methoxycoumarin (XIII) was effected with facility by heating in *N*,*N*-diethylaniline.

Methylxanthotoxins.

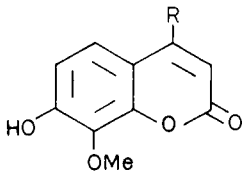
To our knowledge no methyl substituted xanthotoxins have been found in nature, but several have been synthetically prepared (19). 4-Methylxanthotoxin (X) and 4,5'-dimethylxanthotoxin (XXIV) have been synthesized by Antonello (19) through a route similar to that for xanthotoxin described by Rodighiero and Antonello (10). The sequence of steps for the two compounds is illustrated in Figure 1 by structures VI through X for 4-methylxanthotoxin and VI → VII → XI → XII → XXIV for 4,5'-dimethylxanthotoxin.

We have synthesized 4-methylxanthotoxin (X) by a route similar to the one we have used for the synthesis of xanthotoxin (Figure 1, VI → XIV → XVII → XIX → X). To synthesize 4,5'-dimethylxanthotoxin (XXIV) and the hitherto unknown 5'-methylxanthotoxin (XXIII), we have adopted the method of Kaufman (20) for the synthesis of methyl substituted psoralenes. The routes followed are illustrated in Figure 1 by structures I → XIV → XV → XVI → XXI → XXIII for 5'-methylxanthotoxin and by structures I → XIV → XVII → XXII → XXIV for 4,5'-dimethylxanthotoxin. Bromination of the free phenol (XV) instead of its acetate (XVI) resulted only in addition across the double bond in the allyl side-chain to give XX which was also readily converted to 5'-methylxanthotoxin (XXIII). In Table I, the yields obtained by us for the compounds described are compared with those reported by previous workers.

EXPERIMENTAL (21)

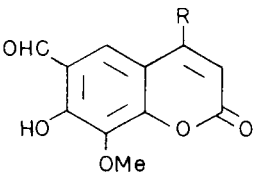
7-Allyloxy-8-methoxycoumarin (XIII).

A mixture of 19.2 g. (0.1 mole) of 7-hydroxy-8-methoxycoumarin (10), 55.2 g. (0.4 mole) of anhydrous potassium carbonate and 60.5 g. (0.5 mole) of allyl bromide in 500 ml. of acetone was heated under reflux for 16 hours. The acetone was distilled and the residue treated with water and cooled in ice. The solid product was filtered and recrystallized from aqueous ethanol to give 18.7 g. (81%) of white needles, m.p. 85° (lit. (11) m.p. 85-87°).



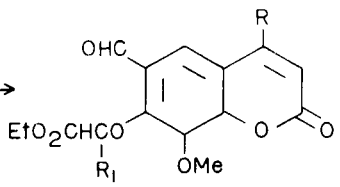
I, R = H

VI, R = Me



II, R = H

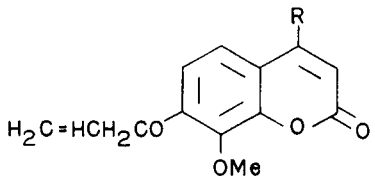
VII, R = Me



III, R = R_1 = H

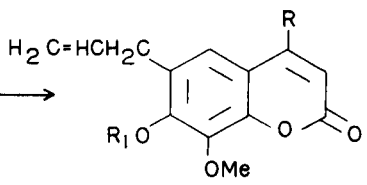
VIII, R = Me, R_1 = H

XI, R = R_1 = Me



XIII, R = H

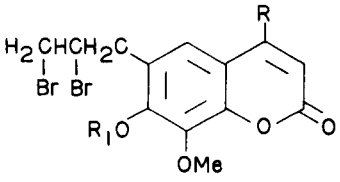
XIV, R = Me



XV, R = R_1 = H

XVI, R = H, R_1 = Ac

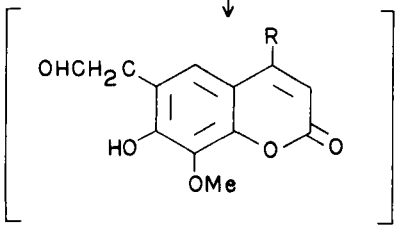
XVII, R = Me, R_1 = H



XX, R = R_1 = H

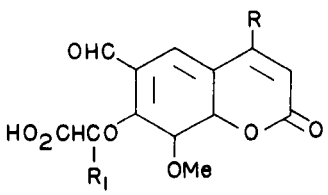
XXI, R = H, R_1 = Ac

XXII, R = Me, R_1 = H



XVIII, R = H

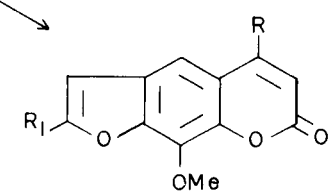
XIX, R = Me



IV, R = R_1 = H

IX, R = Me, R_1 = H

XII, R = R_1 = Me



V, R = R_1 = H

X, R = Me, R_1 = H

XXIII, R = H, R_1 = Me

XXIV, R = R_1 = Me

TABLE I

Furocoumarin	Reported yield (a) %	Present yield (a) %
Xanthotoxin	0.9 (b)	13
4-methylxanthotoxin	4.3	16.1
4,5'-dimethylxanthotoxin	3.7	25.5
5'-methylxanthotoxin	---	15.4

(a) Calculated on I or VI as starting material. (b) Seshadri and Sood (11) have reported nearly 15% yield starting from 7-allyloxy-8-hydroxycoumarin.

6-Allyl-7-hydroxy-8-methoxycoumarin (XV).

7-Allyloxy-8-methoxycoumarin (7.0 g., 0.03 mole) was refluxed in 10 ml. *N,N*-diethylaniline for 1 hour. The reaction mixture was allowed to stand overnight in a refrigerator and the solid that separated was filtered, triturated with petroleum ether (b.p. 40-60°), dried and recrystallized from 95% ethanol to give 4.1 g. (59%) of pale yellow needles, m.p. 122-123° (lit. (11) m.p. 121-122°). When recrystallized from glacial acetic acid, off-white needles were obtained, m.p. 125.5-126°.

Xanthotoxin (V).

6-Allyl-7-hydroxy-8-methoxycoumarin (0.2 g., 0.0009 mole) was converted to xanthotoxin by a slight modification of the method of Aneja and co-workers (22). Ozone was passed for 20 minutes. After heating the crude acetaldehydo-coumarin with orthophosphoric acid for five minutes at 100°, the mixture was poured into ice-cold water and then extracted with chloroform. The extract was shaken with ice-cold 1% solution of sodium hydroxide, washed with water and dried over anhydrous sodium sulphate. The chloroform was evaporated to give a pale yellow residue of xanthotoxin (0.05 g., 27%). It was recrystallized from benzene-petroleum ether (60-80°). White needles were obtained, m.p. and mixed m.p. with an authentic sample, 147-148°. U.V. (99% ethanol) max.: 219 mμ (log ε, 4.32); 249 mμ (log ε, 4.35); 300 mμ (log ε, 4.06); min.: 231 mμ (log ε, 4.12); 276 mμ (log ε, 3.81).

6-Allyl-7-acetoxy-8-methoxycoumarin (XVI).

A mixture of 2.3 g. (0.01 mole) of 6-allyl-7-hydroxy-8-methoxy-coumarin (XV) and a few crystals of fused sodium acetate in 20 ml. of acetic anhydride was heated under reflux for 7 hours. The reaction was poured into ice-cold water. The solid that separated was collected by filtration and was recrystallized from aqueous ethanol. Colorless, glistening needles were obtained, m.p. 101°, yield 2.5 g. (90%).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11. Found: C, 65.67; H, 5.20.

6-(2',3'-Dibromopropyl)-7-acetoxy-8-methoxycoumarin (XXI).

A solution of 1.28 g. (0.008 mole) bromine in 15 ml. of glacial acetic acid was added dropwise to a well-stirred solution of 2.2 g. (0.008 mole) 6-allyl-7-acetoxy-8-methoxycoumarin in 20 ml. of glacial acetic acid at 20°. After one hour at 20° the reaction mixture was diluted with 150 ml. of water and allowed to remain at room temperature overnight. A solid (3.1 g., 88.8%) was collected by filtration and used as such in the next step without further purification. An analytical sample was obtained by recrystallization from aqueous ethanol, m.p. 128°.

Anal. Calcd. for $C_{15}H_{14}O_5Br_2$: C, 41.50; H, 3.23; Br, 36.84. Found: C, 41.39; H, 3.29; Br, 36.77.

6-(2',3'-Dibromopropyl)-7-hydroxy-8-methoxycoumarin (XX).

This compound was obtained by brominating 6-allyl-7-hydroxy-8-methoxycoumarin (XV) (2.32 g., 0.01 mole) according to the foregoing procedure. A white solid was obtained which on crystallization from 95% ethanol produced white needles, m.p. 163°, yield, 3.0 g. (76%).

Anal. Calcd. for $C_{13}H_{12}Br_2O_4$: C, 39.82; H, 3.09; Br, 40.80. Found: C, 39.72; H, 3.21; Br, 40.67.

5'-Methylxanthotoxin (XXIII).

This compound was prepared from 2.17 g. (0.005 mole) of crude 6-(2',3'-dibromopropyl)-7-acetoxy-8-methoxycoumarin (XXI) or from 1.96 g. (0.005 mole) 6-(2',3'-dibromopropyl)-7-hydroxy-8-methoxy-coumarin (XX) by refluxing with potassium hydroxide in ethanol according to the method of Kaufman (19). A brown tar was obtained which was triturated with 95% ethanol to give a solid. Three crystallizations from 95% ethanol gave off-white needles, m.p. 151-152°, yield 45%; U.V. (99% ethanol) max.: 219 mμ (log ε, 4.35), 251 mμ (log ε, 4.42), 302 mμ (log ε, 4.05); min.: 232 mμ (log ε, 4.15), 278 mμ (log ε, 3.79).

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.37. Found: C, 67.74; H, 4.48.

7-Allyloxy-8-methoxy-4-methylcoumarin (XIV).

This was prepared from 7-hydroxy-8-methoxy-4-methylcoumarin (19) in a manner identical to that described for XIII. White needles were obtained from aqueous ethanol, m.p. 84-85°, yield 74%.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.43; H, 5.73.

6-Allyl-7-hydroxy-8-methoxy-4-methylcoumarin (XVII).

This was made by refluxing 7-allyloxy-8-methoxy-4-methylcoumarin in *N,N*-diethylaniline according to the method described for XV. Pale yellow needles from aqueous ethanol, m.p. 169-170°, yield 77.7%.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.38; H, 5.75.

4-Methylxanthotoxin (X).

A stream of 2% ozonized oxygen (50 ml./min.) was passed for 24 minutes through a cold solution of 6-allyl-7-hydroxy-8-methoxy-4-methylcoumarin (0.2 g.) in dry ethyl acetate. The solution was then hydrogenated in the presence of 1% palladized charcoal (0.5 g.) until the rapid absorption of hydrogen ceased. The catalyst was filtered off and the filtrate evaporated to dryness. The crude acetaldehydo-coumarin so obtained was then cyclized by heating to 100° for 2 minutes with ortho-phosphoric acid (2 ml.). The reaction mixture was poured into ice-cold water and 4-methylxanthotoxin was obtained by following the extraction procedure described above for V. White needles were obtained, m.p. 167-168° (lit. (19) m.p. 168°), yield 28%; U.V. (99% ethanol) max.: 222 mμ (log ε, 4.36); 248 mμ (log ε, 4.49); 300 mμ (log ε, 4.24); min.: 228 mμ (log ε, 4.31); 276 mμ (log ε, 4.00).

6-(2',3'-Dibromopropyl)-7-hydroxy-8-methoxy-4-methylcoumarin (XXII).

Bromination of 6-allyl-7-hydroxy-8-methoxy-4-methylcoumarin (XVII) was carried out according to the method described above for XXI. A light brown tar was obtained which solidified on standing overnight. Recrystallization from aqueous ethanol produced white needles, m.p. 155-156°, yield 82%.

Anal. Calcd. for $C_{14}H_{14}Br_2O_4$: C, 41.39; H, 3.45; Br, 39.38. Found: C, 41.45; H, 3.47; Br, 39.26.

4,5'-Dimethylxanthotoxin (XXIV).

6-(2',3'-Dibromopropyl)-7-hydroxy-8-methoxy-4-methylcoumarin (2.03 g.) was cyclized by refluxing with potassium hydroxide in 95% ethanol as described above for XXIII. The brown solid that was obtained was recrystallized from 90% ethanol (activated charcoal). White needles were obtained, m.p. 158-159° (lit. (19) m.p. 159°), yield 54%; U.V. (99% ethanol) max.: 214 mμ (log ε, 4.28), 250 mμ (log ε, 4.46), 301 mμ (log ε, 4.02); min.: 230 mμ (log ε, 4.14), 277 mμ (log ε, 3.80).

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