A New Synthesis of Methoxalen

Pentti Nore and Erkki Honkanen

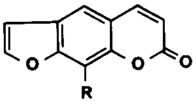
Orion Pharmaceutical Co, Research Laboratories, SF-00101 Helsinki 10, Finland

Received November 2, 1979

A new seven step synthesis of methoxalen, 9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one, starting from 2-chloro-2'-hydroxy-3',4'-dimethoxyacetophenone is described. The yields in every step are good (60-100%).

J. Heterocyclic Chem., **17**, 985 (1980).

Some naturally occuring furocoumarins, such as psoralen, 7*H*-furo[3,2-*g*][1]benzopyran-7-one (Ia) and especially methoxalen, 9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (Ib), have been used many years in medicine in the treatment of *vitiligo, psoriasis* and other dermal diseases. Currently the only commercial source is plant materials, mainly the seeds of *Ammi majus*, L. (1). A semisynthetic method based on the isolation of 9-geranoxypsoralen (Ic) from citrus oils and the cleavage of the geranyl group followed by the methylation of the 9-hydroxypsoralen formed with diazomethane has also been developed for the preparation of methoxalen (2). The low concentration (0.1-0.3%) of methoxalen in the plant materials and the tedious isolation and purification procedures make the compound costly.



Ia, R = H

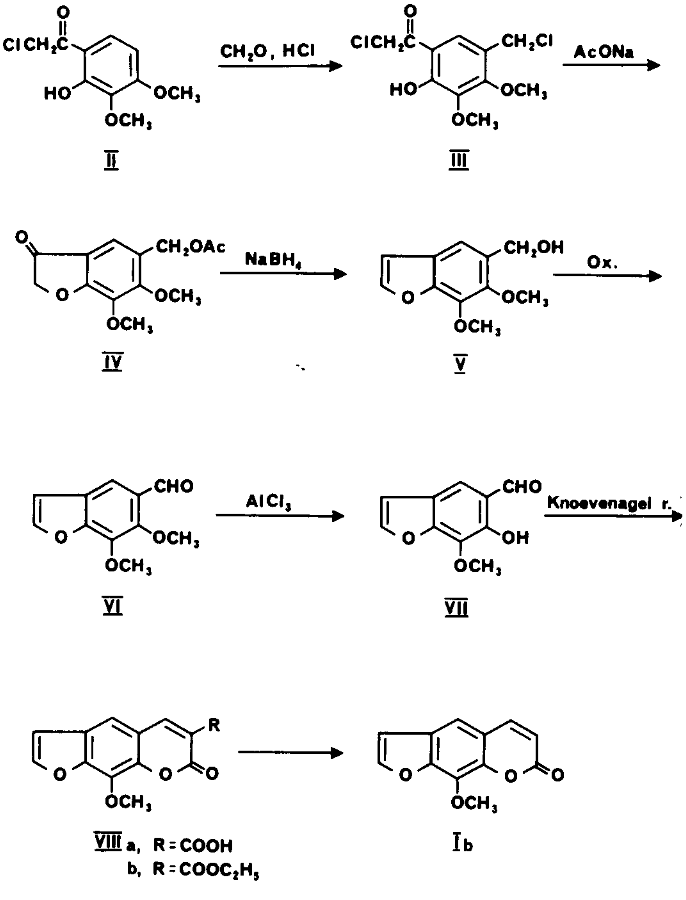
Ib, R = CH_3O

Ic, R = $C_{10}H_{17}O$

Several synthetic methods for the preparation of methoxalen have been described in the literature (3-7). However, none of these methods have practical value for the production of methoxalen in large scale. Hence, we have made a new practical synthesis of methoxalen, which avoids the above problems encountered with the syntheses of furocoumarins.

The key compound in this synthesis is 2-chloro-2'-hydroxy-3',4'-dimethoxyacetophenone (II). This is prepared in good yield from commercially available 1,2,3-trimethoxybenzene. On chloromethylation of II with paraformaldehyde and hydrogen chloride in acetic acid solution 2-chloro-2'-hydroxy-3',4'-dimethoxy-5'-chloromethylacetophenone (III) is obtained in 77% yield. Ring closure and substitution of chlorine with acetoxy group in position 5' occur on the treatment of III with sodium acetate in acetonitrile yielding 5-acetoxymethyl-6,7-dimethoxy-3-(2*H*)benzofuranone (IV) in almost quantitative yield. Reduction of IV with sodium borohydride and simultaneous loss of water and alcoholysis with methanol yields 6,7-dimethoxy-5-hydroxymethylbenzofuran (V) also in excellent yield. Oxidation of V with chromium trioxide-sulfuric acid in acetone, with chromium trioxide-pyridine complex in dichloromethane, with potassium permanganate in the presence of 18-crown-6 ether or with benzyltriethylammonium permanganate to 6,7-dimethoxy-5-benzofurancarboxaldehyde (VI) followed by selective demethylation with aluminium chloride yields 6-hydroxy-7-methoxy-5-benzofurancarboxaldehyde (VII). Knoevenagel reaction of VII with malonic acid (diethyl malonate or ethyl cyanoacetate) yields the 6-substituted methoxalen derivatives (VIIIa,b), from which methoxalen is obtained after hydrolysis and/or decarboxylation. The method of synthesis is illustrated in Scheme 1.

Scheme 1



0022-152X/80/050985-03$02.25

The total yield in this seven step synthesis is about 20%, which is much higher than the overall yields of the methods reported in the literature. This synthesis is easy to perform as the intermediates (II-VIII) do not need to be purified.

Interestingly the 6-carboxylic acid derivative of methoxalen (VIIIa) does not show photosensitizing activity in skin tests.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Elementary microanalyses were performed in Mikroanalytisches Laboratorium by Dr. Ilse Beetz, West Germany. The nmr spectra were measured on Perkin-Elmer R 12 A spectrometer using tetramethylsilane as an internal standard. The mass spectra were recorded by Dr. J. Taskinen on Jeol JMS-D 100 mass spectrometer at 75 eV electron energy using a direct inlet probe.

2-Chloro-2'-hydroxy-3',4'-dimethoxyacetophenone (II).

This compound has been made by Price and Bogert (8) in 16% yield. The synthesis was improved as follows: To a mixture of 300 g. (2.25 moles) of aluminium chloride in 450 ml. of 1,2-dichloroethane was gradually added under cooling (0-10°) a solution of 168 g. (1 mole) of 1,2,3-trimethoxybenzene and 226 g. (2 moles) of chloroacetylchloride in 300 ml. of 1,2-dichloroethane. The solution was stirred for 2 hours at 0° and for 3 hours at room temperature. Crushed ice (1.5 kg.) and concentrated hydrochloric acid (300 ml.) were added to the reaction mixture. The product was filtered, washed with acetone and dried. To increase the yield an additional amount of the desired product was obtained by separating the organic phase in the above filtrate, washing with water and evaporating to dryness *in vacuo*. The residue was triturated with ether and the crystallized product was filtered. The total yield of II was 162 g. (70%), m.p. 160-162° (from acetone). After evaporation of the ether 45 g. of 1,2,3-trimethoxybenzene was recovered. Calculated from the reacted 1,2,3-trimethoxybenzene the total yield of II was 96%; nmr (deuteriochloroform): δ 13.00 (s, 1H), 7.53 (d, 1H, J = 10 Hz), 6.58 (d, 1H, J = 10 Hz), 4.63 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H); ms: m/e (M^+), 232 (8%) and 230 (23%), 194 (7), 182 (12), 181 (100), 166 (9), 148 (13), 120 (9).

Anal. Calcd. for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4,81; Cl, 15.37. Found: C, 51.96; H, 4.94; Cl, 15.46.

2-Chloro-2'-hydroxy-3',4'-dimethoxy-5'-chloromethylacetophenone (III).

A stirred mixture of 161.4 g. (0.7 mole) of II and 56.0 g. of paraformaldehyde in 1.4 l. of acetic acid was saturated at room temperature with hydrogen chloride gas. The temperature was increased to 60-70° during which time hydrogen chloride gas was bubbled through the mixture. After stirring for 24 hours at room temperature the crystallized product was filtered, washed with ether and dried. The yield of III was 151 g. (77%), m.p. 130-131° (from acetone); nmr (deuteriochloroform): δ 12.22 (s, 1H), 7.50 (s, 1H), 4.66 (s, 2H), 4.59 (s, 2H), 4.14 (s, 3H), 3.91 (s, 3H); ms: m/e (M^+), 280 (2%) and 278 (3%), 243 (12), 229 (10), 208 (18), 207 (100), 192 (18), 165 (20).

Anal. Calcd. for $C_{11}H_{12}Cl_2O_4$: C, 47.33; H, 4.33; Cl, 25.41. Found: C, 47.18; H, 4.36; Cl, 25.57.

5-Acetoxymethyl-6,7-dimethoxy-3-(2*H*)benzofuranone (IV).

A mixture of 136.6 g. (0.5 mole) of III and 102.5 g. (1.25 moles) of anhydrous sodium acetate in 2.5 l. of acetonitrile was stirred and refluxed for 1.5 hours. Acetonitrile was distilled off and the residue was treated with 1 l. of water. After extraction with dichloromethane (3 × 500 ml.) the extract was washed with water and the solvent was removed *in vacuo*. The oily product was used without purification to the next step. The yield of IV was 132 g. (99%); nmr (deuteriochloroform): δ 7.42 (s, 1H), 5.10 (s, 2H), 4.68 (s, 2H), 4.04 (s, 3H), 4.01 (s, 3H), 2.11 (s, 3H); ms: m/e (M^+), 266 (72%), 224 (60), 223 (100), 208 (56), 192 (27), 179 (18), 177 (26).

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.92; H, 5.21.

6,7-Dimethoxy-5-hydroxymethylbenzofuran (V).

To a solution of 79.8 g. (0.3 mole) of IV in 1.8 l. of methanol was added gradually with cooling (below 20°) a solution of 17 g. (0.45 mole) of sodium borohydride in 45 ml. of water. After stirring for 1.5 hours at room temperature 600 ml. of water was added. The solution was made acid with 350 ml. of 20% hydrochloric acid and extracted three times with dichloromethane. The solvent was removed from the extract *in vacuo*. The oily residue of V, which was used without purification in the next step, weighed 62 g. (99%); nmr (deuteriochloroform): δ 7.49 (d, 1H, J = 2.5 Hz), 7.10 (s, 1H), 6.59 (d, 1H, J = 2.5 Hz), 4.66 (s, 2H), 4.10 (s, 3H), 3.88 (s, 3H); ms: m/e (M^+), 208 (100%), 193 (58), 150 (17), 133 (74).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.52; H, 5.79.

6,7-Dimethoxy-5-benzofurancarboxaldehyde (VI).

a) By Oxidation with Chromic Oxide-Sulfuric Acid in Acetone.

To a cooled (0°) solution of 20.8 g. (0.1 mole) of V in 350 ml. of acetone was added with stirring a solution of 6.7 g. of chromic oxide (0.067 mole) and 5.8 ml. of sulfuric acid in 14 ml. of water. The mixture was diluted with 700 ml. of water and then was extracted with dichloromethane (3 × 100 ml). The extract was washed with water, sodium bicarbonate solution and once more with water. After evaporation of the solvent *in vacuo* the residue crystallized on standing. The yield of VI was 12.6 g. (61%), m.p. 32-34°; nmr (deuteriochloroform): δ 10.60 (s, 1H), 7.79 (s, 1H), 7.67 (d, 1H, J = 2.5 Hz), 6.80 (d, 1H, J = 2.5 Hz), 4.20 (s, 3H), 4.02 (s, 3H); ms: m/e (M^+), 206 (100%), 191 (47), 176 (27), 163 (17), 160 (18), 107 (21), 77 (16).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.99; H, 5.17.

b) By Oxidation with Chromic Oxide-Pyridine Complex in Dichloromethane.

To a solution of 31.7 g. (0.4 mole) of pyridine in 750 ml. of dichloromethane was added gradually with cooling (0-10°) 20.6 g. (0.2 mole) of chromic oxide. After stirring for 15 minutes a solution of 10.4 g. (0.05 mole) of V in 50 ml. of dichloromethane was added. The mixture was stirred for 1.75 hours at room temperature. The reaction mixture was filtered and the precipitate washed with dichloromethane. To the filtrate 100 ml. of water was added and the organic phase was separated, washed first with 2 *N* sodium hydroxide solution, then with 2 *N* hydrochloric acid and lastly with water. The solvent was evaporated *in vacuo* and the yield of VI was 6.3 g. (61%).

c) By Oxidation with Potassium Permanganate in the Presence of 18-Crown-6 Ether in Dichloromethane.

A solution of 10.4 g. (0.05 mole) of V in 50 ml. of dichloromethane was added during 25 minutes to a stirred mixture of 9.1 g. (0.058 mole) of potassium permanganate, 0.75 g. of 18-crown-6 ether and 200 ml. of dichloromethane at room temperature. After stirring for 6 hours at room temperature charcoal and Celite were added and the mixture was filtered. The precipitate was washed several times with dichloromethane. The filtrate was washed with water and the solvent removed *in vacuo*. The yield of VI was 6.5 g. (63%).

d) By Oxidation with Benzyltriethylammonium Permanganate in Dichloromethane.

To a solution of 16.0 g. (0.05 mole) of benzyltriethylammonium permanganate (9) in 250 ml. of dichloromethane was added gradually with stirring at room temperature 10.4 g. (0.05 mole) of V in 30 ml. of dichloromethane. The solution was stirred for 5 hours at 20°. The isolation of the product was performed as described in example c). The yield of VI was 7.5 g. (73%).

6-Hydroxy-7-methoxy-5-benzofurancarboxaldehyde (VII).

A mixture of 8.0 g. (0.06 mole) of anhydrous aluminium chloride in 500 ml. of 1,2-dichloroethane was stirred at room temperature until dissolved. A solution of 10.3 g. (0.05 mole) of VI in 20 ml. of 1,2-dichloroethane was then added and the mixture was refluxed for 1.5 hours. After cooling 400 g. of crushed ice and 100 ml. of 20% hydrochloric acid were added.

The organic phase was separated, charcoal was added and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue dissolved in 1 *N* sodium hydroxide solution and filtered. The filtrate was acidified with conc. hydrochloric acid and the precipitate filtered, washed with water and dried *in vacuo*. The yield of VII was 5.9 g. (61%), m.p. 71-72°; nmr (deuteriochloroform): δ 11.15 (s, 1H), 10.02 (s, 1H), 7.64 (d, 1H, J = 2.5 Hz), 7.52 (s, 1H), 6.79 (d, 1H, J = 2.5 Hz), 4.16 (s, 3H).

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.61; H, 4.31.

9-Methoxy-7-oxo-7*H*-furo[3,2-*g*][1]benzopyran-6-carboxylic Acid (VIIIa).

A solution of 9.6 g. (0.05 mole) of VII, 12.5 g. (0.12 mole) of malonic acid, 0.3 ml. of aniline in 33 ml. of pyridine was heated with stirring for 2 hours at 60°. To the cooled mixture 250 ml. of 1 *N* hydrochloric acid was added. The product was filtered, washed with water and ethanol, after which it was dried. The yield of VIIIa was 9.2 g. (71%), m.p. 236-237°; nmr (deuteriochloroform-DMSO-d_6): δ 8-10 (1H), 8.83 (s, 1H), 8.06 (d, 1H, J = 2.5 Hz), 7.82 (s, 1H), 7.03 (d, 1H, J = 2.5 Hz), 4.22 (s, 3H); ms: m/e (M^+), 260 (100%), 216 (23), 201 (24), 173 (33), 145 (13).

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.01; H, 3.10. Found: C, 59.85; H, 3.25.

Ethyl 9-Methoxy-7-oxo-7*H*-furo[3,2-*g*][1]benzopyran-6-carboxylate (VIIIb).

To a warm solution of 9.6 g. (0.05 mole) of VII in 100 ml. of 99.5% ethanol 9.6 g. (0.06 mole) of diethyl malonate and 0.15 ml. of piperidine were added. The solution was refluxed for 15 minutes. After cooling the crystallized product was filtered, washed with cold ethanol and dried. The yield of VIIIb was 11.0 g. (77%), m.p. 139-141°; nmr (deuteriochloroform): δ 8.62 (s, 1H), 7.77 (d, 1H, J = 2.5 Hz), 7.54 (s, 1H), 6.91 (d, 1H, J = 2.5), 4.45 (q, 2H, J = 7 Hz), 4.31 (s, 3H), 1.43 (t, 3H, J = 7 Hz); ms: m/e (M^+), 288 (100%), 243 (32), 217 (15), 216 (40), 201 (20), 173 (17), 159 (13), 145 (11), 129 (15).

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.49; H, 4.20. Found: C, 62.71; H, 4.28.

The ethyl ester (VIIIb) (14.4 g.) was hydrolyzed to the acid (VIIIa) by refluxing for 0.5 hour with a mixture of acetic acid (10 ml.) and conc. hyrochloric acid (45 ml.). The mixture was diluted with water and the precipitate filtered, washed with cold ethanol and dried. The yield of VIIIa was 12.1 g. (93%), m.p. 236-237°.

9-Methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (Ib), (Methoxalen).

A mixture of 13.0 g. of VIIIa, 1.3 g. of copper powder and 200 ml. of quinoline was refluxed for 1 hour. After cooling 200 ml. of dichloromethane and charcoal were added and the mixture was filtered. The filtrate was washed several times with diluted hydrochloric acid and then with water. The solvent was removed *in vacuo* and the residue crystallized from a mixture of benzene and petroleum ether (b.p. 60-80°). The yield of methoxalen (Ib) was 7.8 g. (72%), m.p. 148-149°; nmr (deuteriochloroform): δ 7.76 (d, 1H, J = 10 Hz), 7.71 (d, 1H, J = 2.5 Hz), 7.38 (s, 1H), 6.84 (d, 1H, J = 2.5 Hz), 6.39 (d, 1H, J = 10 Hz), 4.28 (s, 3H); ms: m/e (M^+), 216 (100%), 201 (28), 188 (9), 173 (41), 145 (16), 89 (20).

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.66; H, 3.72. Found: C, 66.48; H, 3.66.

REFERENCES AND NOTES

(1) J. R. Fahmy and H. Abu-Shady, *Quart. J. Pharm.*, **20**, 281 (1947) and **21**, 499 (1948).

(2) W. L. Stanky and S. H. Vannier, U. S. Patent 2,889,337 (1959).

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

(4) G. Rodighiero and C. Antonelli, *Ann. Chim.*, **46**, 960 (1956).

(5) C. Lagergranz, *Acta Chem. Scand.*, **10**, 647 (1956).

(6) T. R. Seshadri and M. S. Sood, *Indian J. Chem.*, **1**, 292 (1963).

(7) N. J. de Souza, P. V. Noyak and E. Secco, *J. Heterocyclic Chem.*, **3**, 42 (1966).

(8) D. Price and M. T. Bogert, *J. Am. Chem. Soc.*, **56**, 2442 (1943).

(9) H-J. Schmidt and H. J. Schäfer, *Angew. Chem.*, **91**, 77 (1979).