Synthesis of a Rotenone-Like Benzopyranobenzopyranone

Norton P. Peet and Shyam Sunder*

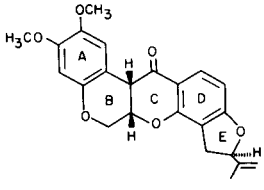
Pharmaceutical Research and Development-Medicinal Chemistry, The Dow Chemical Company, Building 219, 9550 Zionsville Road, Indianapolis, Indiana 46268

Received March 27, 1981

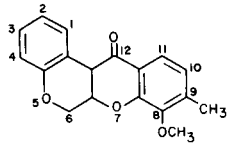
The synthesis of a novel rotenone-like molecule, 9-methoxy-8-methyl-6,6a,12,12a-tetrahydro[1]benzopyrano-[3,4-*b*][1]benzopyran-12-one (**2**) is described. Efficient syntheses of 3,4-dihydro-2*H*-[1]benzopyran-3-one (**9**) from ethyl 3-hydroxy-2*H*-[1]benzopyran-4-carboxylate (**6**), an intermediate in the synthesis of **2**, were developed. Thermolysis of **6** and **9** in decalin yielded 6,8-dihydro-14*H*-bis[1]benzopyrano[3,4-*b*:4′,3′-*e*]pyran-14-one (**8**), which has previously been described. Also produced in the thermolysis was the isomeric 1*H*-bis[1]-benzopyrano[3,4-*b*:3′,4′-*d*]pyran-7-(9*H*)one (**10**), the first member of a novel, pentacyclic ring system.

J. Heterocyclic Chem., **18**, 1123 (1981).

In connection with a study designed to evaluate rotenone (**1**) and rotenone-like compounds as SRS-A antagonists (1,2), we wished to prepare compounds of lesser complexity than rotenone. One target was a simplified rotenone-like molecule which contained the same four six-membered rings (rings A-D), but which only approximated the E ring by a simple pair of substituents on the D ring. Accordingly, we chose novel compound **2** as our specific target.



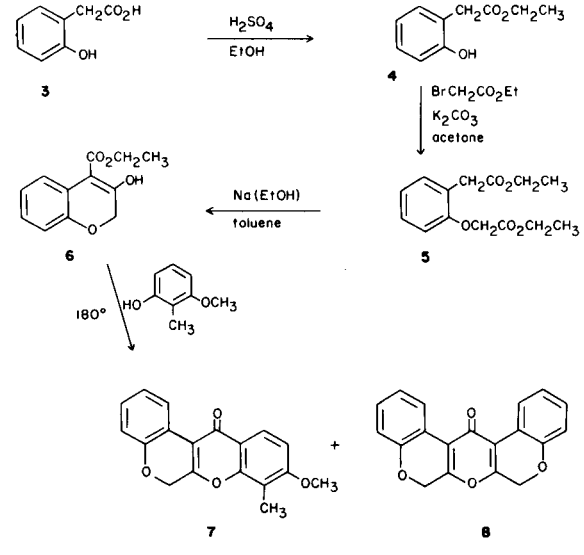
1



2

Several approaches to the synthesis of rotenone-like molecules have been employed (3). For our approach to **2**, we chose the general procedure of Verhe and Schamp (4,5), in which they condensed 4-carbethoxychroman-3-ones with phenols to yield 6a,12a-didehydrorotenoids. They then generated rotenoids from the didehydro compounds by catalytic hydrogenation.

Scheme I



An earlier report by Verhe and Schamp (6) describes three methods for the preparation of 4-carbethoxychroman-3-ones. Employing one of these methods, we prepared **6** as shown in Scheme I. Thus, (2-hydroxyphenyl)acetic acid (**3**) was treated with ethanol and sulfuric acid to give the corresponding ester **4** (92% yield), which was subsequently alkylated with ethyl bromoacetate to afford diester **5** (66% yield). Dieckmann cyclization of **5** with sodium (and a catalytic amount of ethanol) in toluene gave 4-carbethoxychroman-3-one (**6**, 92% yield).

When equimolar amounts of **6** and 3-methoxy-2-methylphenol were heated together neat at 180° for six hours, we were able to isolate didehydro-**2** (**7**) in 21% yield. In one experiment, **7** was purified by thick-layer chromatography (silica gel) and a small amount of pyranone **8** was also isolated. Compound **8** was also encountered as a minor by-product by Verhe and co-workers (7) in their synthesis of rotenoids. These authors then synthesized **8** more efficiently by the thermolysis of **6**. They suggested that **8** was formed by transesterification of **6** with the ketone derived from thermal deethoxycarbonylation of **6** (**9**), followed by Fries rearrangement and dehydration.

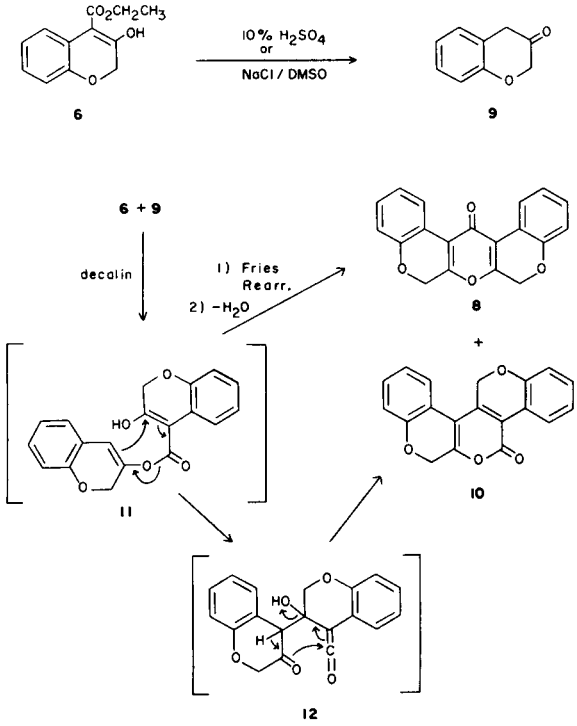
We chose to pursue the preparation of pyranone **8** from **6** and **9**. Chroman-3-one (**9**) has previously been prepared in four steps from 3-carboxy-2*H*-benzopyran, which, in turn, is prepared from salicylaldehyde in two steps (6,8). We felt that **9** should be more easily accessible from **6**. Indeed, Verhe and co-workers (4) have prepared analogs of **9** from the corresponding analogs of **6** by simple distillation. However, these conversions were not complete, and the ketones were separated by preparative vpc. We found that **9** could be produced cleanly and efficiently by treatment of **6** with either 10% sulfuric acid at reflux or sodium chloride in dimethyl sulfoxide at reflux (Scheme II).

After heating equimolar quantities of **6** and **9** in decalin at reflux, we were able to isolate a modest amount of pyranone **8**. We also obtained from this reaction a small

0022-152X/81/061123-03$02.25

© *HeteroCorporation*

Scheme II



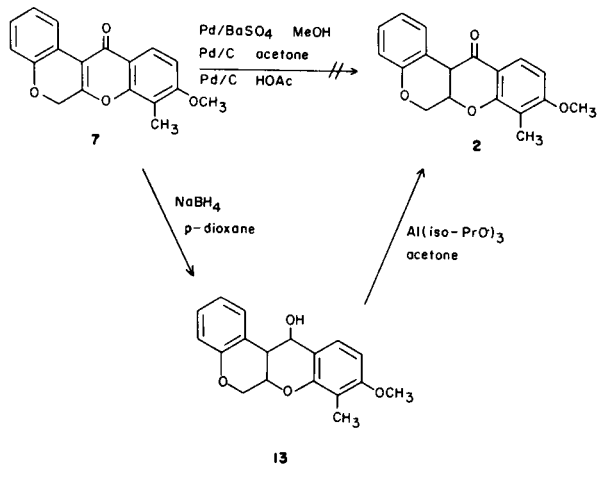
quantity of an isomeric compound, 1*H*-bis[*b*]benzopyrano-[3,4-*b*:3′,4′-*d*]pyran-7-(9*H*)one (**10**), which we fully characterized. Compound **10** is the first member of a novel, pentacyclic ring system. The nmr spectrum of **10** showed two different methylene groups, and one aromatic proton at low field due to deshielding by the carbonyl group. In contrast, symmetrical pyranone **8** displayed only one signal for the methylene groups and showed a 2-proton aromatic multiplet at low field due to carbonyl deshielding. Additional spectral data which we gathered for **10** was also structurally diagnostic.

Although compounds **8** and **10** are the two predicted condensation products of **6** and **9**, it seems unlikely that they are so produced under the conditions of the reaction. In Scheme II is shown a potential thermal mechanism for the formation of **10** from **6** and **9**. Intermediate **11** is the initially formed transesterification intermediate, suggested by Verhe and co-workers (7), in the formation of **8** from **6** (and **9**). If intermediate **11** undergoes a Claisen rearrangement, rather than a Fries rearrangement, intermediate **12** would result. Dehydration and electrocyclic ring closure of **12** would produce **10**. There is literature precedence for thermal Fries rearrangement of systems related to intermediate **11**. For example, Skraup and Beng (9) thermalized the phenyl ester of 2,2-dimethylacrylic acid and obtained, as one of the products, 2-(2,2-dimethylacryloyl)phenol. Precedent also exists for compounds related to intermediate **11** undergoing both Fries and Claisen rearrangements. Colonge and Chambard (10,11) obtained both dihydrocoumarins and 4-chromanones by treating phenyl esters of 2,2-dialkylacrylic acids with aluminum chloride in carbon disulfide.

Turning back to our main objective, the synthesis of **2**, we were unable to hydrogenate **7** (to **2**) using conditions (palladium on barium sulfate in methanol) described by Verhe and Schamp (4,5) for a similar reduction. In fact, we were unable to hydrogenate **7** under more vigorous conditions, *i.e.*, using palladium on carbon as the catalyst in either acetone or acetic acid.

Since we could not produce **2** directly from **7**, we chose to employ the two-step procedure of reduction with sodium borohydride followed by Oppenauer oxidation (12) to effect this transformation. Thus, treatment of **7** with sodium borohydride in *p*-dioxane gave carbinol **13** (69% yield), which appeared to be a single epimer. Subsequent oxidation of **9** with aluminum isopropoxide gave the desired 9-methoxy-8-methyl-6,6a,12,12a-tetrahydro[1]-benzopyrano[3,4-*b*][1]benzopyran-12-one (**2**). The latter transformations which afforded our target compound are illustrated in Scheme III.

Scheme III



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727 Spectrophotometer, nmr spectra with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 3000D (electron impact and chemical ionization) spectrometer at 70 eV. Combustion analyses for C, H, and N were performed by Dow Analytical Laboratories.

Materials.

Ethyl (2-hydroxyphenyl)acetic acid (**4**), [lit (13) bp 149° (18 mm)], ethyl 2-(ethoxycarbonylmethoxy)phenylacetate (**5**), mp 46-47.5° [lit (6) mp 48-49°, lit. (14) mp 46°], and ethyl 3-hydroxy-2*H*-[1]benzopyran-4-carboxylate (**6**), bp 124-134° (1.0 mm) [lit (6) mp 43°; lit (15) mp 43.5-44.5°] were prepared as described by Verhe and Schamp (6).

3,4-Dihydro-2*H*-1-benzopyran-3-one (**9**).

A. From **6** and Sulfuric Acid.

A mixture of 7.00 g (34.3 mmoles) of **6** and 120 ml of 10% sulfuric acid was heated at reflux for 5 hours. The mixture was cooled, extracted with methylene chloride and the extracts were dried (sodium sulfate) and concentrated to leave 4.95 g of red oil. Purification by Kugelrohr distillation gave 4.65 g (92%) of **9** [lit (8) bp 80° (1 mm)]; ir (neat): 1730 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 7.40-6.90 (m, 4H, aromatic), 4.32 (s, 2H, OCH_2), 3.51 (s, 2H, CH_2CO); ms: (70 eV, chemical ionization, methane) m/e 149 ($M^+ + 1$), 177 ($M^+ + 29$), 189 ($M^+ + 41$).

B. From **6** and Sodium Chloride in Dimethyl Sulfoxide.

A solution of 2.45 g (12.0 mmoles) of **6** and 0.5 g of sodium chloride in 10 ml of dimethyl sulfoxide and 0.5 ml of water was heated at reflux for 2 hours. The solution was cooled, diluted with water and extracted with ether. The ether extracts were dried (sodium sulfate) and concentrated to leave 1.30 g (73%) of **6**, which was purified by Kugelrohr distillation. An infrared spectrum of this sample was identical to that prepared as in Part A.

Thermolysis of **6** and **9** in Decalin.

A solution of 1.79 g (8.13 mmoles) of **6** and 1.30 g (8.77 mmoles) of **9** in 15 ml of decalin was heated at reflux for 2.5 hours. The solution was cooled, diluted with 50 ml of ether and stored in the refrigerator for 3 days. The resulting crystals were collected to yield 200 mg of 1*H*-bis[1]benzopyrano[3,4-*b*:3',4'-*d*]pyran-7-(9*H*)one (**10**), mp 235-240°, mp 239-241° (ethanol); ir (Nujol): 1675 (C=O), 1635, 1590 cm^{-1}; nmr (detueriochloroform): δ 8.90-8.64 (m, 1H, H at 6-position), 7.33-6.77 (m, 7H, remaining aromatic), 4.94 (s, 2H, CH_2), 4.00 (s, 2H, CH_2); ms: (70 eV, electron impact) m/e 304 (molecular ion).

Anal. Calcd. for $C_{19}H_{12}O_4$: C, 74.99; H, 3.97. Found: C, 74.90; H, 4.07.

The filtrate from above was concentrated and the residue was triturated with a small volume of ether to produce 80.0 mg of **8**, mp 223-224.5° (ethanol) [lit (7) mp 214-216°]; ir (Nujol): 1650 (C=O), 1620 (C=C) cm^{-1}; nmr (deuteriochloroform): δ 8.87-8.62 (m, 2H, aromatic), 7.28-6.75 (m, 2H, aromatic), 4.90 (s, 4H, both CH_2 groups); ms: (70 eV, electron impact) m/e 304 (molecular ion).

Anal. Calcd. for $C_{19}H_{12}O_4$: C, 74.99; H, 3.97. Found: C, 75.00; H, 4.10.

9-Methoxy-8-methyl[1]benzopyrano[3,4-*b*][1]benzopyran-12-(6*H*)one (**7**).

A 10.0 g (49.0 mmoles) quantity of **6** and 6.77 g (49.0 mmoles) of 2-methyl-3-methoxyphenol (Aldrich) were heated at 180° for 6 hours with evacuation. The oil was cooled, partitioned between aqueous sodium hydroxide and methylene chloride and the layers were separated. The aqueous layer was extracted with ether and the combined organic phases were dried (sodium sulfate) and concentrated to leave 5.20 g of red oil which solidified. Trituration with ether gave two crops of white solid, totaling 3.00 g (21%) of **7**, mp 183-184° (methylene chloride-methanol); ir (Nujol): 1630 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.87-8.53 (m, 1H, H at 1-position), 8.04 (d, J = 9 Hz, 1H, H at 11-position), 7.34-6.71 (m, 4H, remaining aromatic), 4.97 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 2.24 (s, 3H, CCH_3); ms: (70 eV, electron impact) m/e 294 (molecular ion).

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.32; H, 4.82.

In another preparation, **7** was purified by thick-layer chromatography (Silica Gel 60 F-254, 2 mm, EM Reagents), eluting with 9:1 benzene: acetone. A small quantity of 6,8-dihydro-14*H*-bis[1]benzopyrano-[3,4-*b*:4',3'-*e*]pyran-14-one (**8**), which moved faster than **7**, was isolated, mp 229-230°. The infrared spectrum of this sample was superimposable with that of the sample of **8** obtained from the thermolysis of **6** and **9** in decalin.

6,6a,12,12a-Tetrahydro-9-methoxy-8-methyl[1]benzopyrano[3,4-*b*][1]benzopyran-12-ol (**13**).

To a 0.700-g (2.38 mmoles) quantity of **7** in 60 ml of *p*-dioxane was added 450 mg (11.9 mmoles) of sodium borohydride, followed by 30 ml of 95% ethanol. After stirring at 60-70° for 2 hours, the solution was cooled and 7 ml of acetone was added. After 5 minutes, the solution was poured into 400 ml of cold water, and the resulting white solid, after 2 hours, was collected and air-dried to yield 0.490 g (69%) of **13**, mp 181-187°, mp 193-194° (ethanol); ir (Nujol): 3360 (OH), 1605 (C=C) cm^{-1}; nmr (deuteriochloroform and DMSO-d_6): δ 7.53-7.35 (m, 1H, aromatic), 7.26-6.74 (m, 4H, aromatic), 6.47 (d, J = 8 Hz, 1H, aromatic), 5.13-4.95 (m, 1H, C*H*OH), 4.92-4.13 (m, 4H, OCH_2CH and OH; OH was deuterium oxide-exchangeable, with C*H*OH signal collapsing to a d, J = 5 Hz), 3.78 (s, 3, OCH_3), 3.53-3.33 (m, 1H, C*H*CHOH), 2.03 (s, 3H, $ArCH_3$); ms: (70 eV, chemical ionization, methane) m/e 299 ($M^+ + 1$).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.20; H, 6.16.

9-Methoxy-8-methyl-6,6a,12,12a-tetrahydro[1]benzopyrano[3,4-*b*][1]benzopyran-12-one (**2**).

A mixture of 200 mg (0.670 mole) of **13** and 2.00 g (9.79 mmoles) of aluminum isopropoxide (Alfa) in 20 ml of acetone and 30 ml of benzene was heated at reflux for 2 hours. The solvents were evaporated and the residue was treaed with dilute hydrochloric acid with icebath cooling. The mixture was extracted with ethyl acetate and the organic extracts were washed with water, dried (sodium sulfate) and concentrated to yield an oil which solidified. Recrystallization from ethyl acetate-ether afforded 40 mg of **2** as white needles. The filtrate was concentrated and recrystallized from methanol to yield an additional 80 mg of **2**, mp 180°. Total yield of **2** was 120 mg (60%); ir (Nujol): 1690 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 7.75 (d, J = 9 Hz, 1H, H at 11-position), 7.30-6.58 (m, 4H, aromatic), 6.47 (d, J = 9 Hz, 1H, H at 10-position), 4.97-3.67 (m, 7H, CH_2CHCH and OCH_3, with OCH_3 s at 3.78), 2.04 (s, 3H, $ArCH_3$); ms: (70 eV, electron impact) m/e 296 (molecular ion).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.00; H, 5.51.

Acknowledgement.

The authors thank Dr. Wayne Harris for helpful suggestions during the course of this work.

REFERENCES AND NOTES

(1a) P. B. Anzeveno, *J. Org. Chem.*, **44**, 2578 (1979); (b) P. B. Anzeveno, *J. Heterocyclic Chem.*, **16**, 1643 (1979).

(2) R. J. Ashack, L. P. McCarty, R. S. Malek, F. R. Goodman and N. P. Peet, *J. Med. Chem.*, **23**, 1022 (1980).

(3) For a recent summary of the different procedures which have been employed for rotenoid synthesis, see Reference 4.

(4) R. Verhe, N. De Kimpe, L. De Buyck, W. Steurbaut, M. Sadones, R. Willaert, J. P. Verbeek and N. Schamp, *Bull. Soc. Chim. Belg.*, **89**, 459 (1980).

(5) R. Verhe and N. Schamp, *Experientia*, **31**, 759 (1975).

(6) R. Verhe and N. Schamp, *Bull. Soc. Chim. Belg.*, **82**, 283 (1973).

(7) R. Verhe, L. De Buyck, N. De Kimpe and N. Schamp, *ibid.*, **87**, 83 (1978).

(8) J. N. Chatterjea, B. K. Banerjee and K. Achari, *J. Ind. Chem. Soc.*, **46**, 867 (1969).

(9) S. Skraup and E. Beng, *Ber.*, **60B**, 942 (1927); *Chem. Abstr.*, **21**, 2125 (1927).

(10) J. Colonge and R. Chambard, *Compt. Rend.*, **233**, 1464 (1951); *Chem. Abstr.*, **46**, 7569e (1952).

(11) J. Colonge and R. Chambard, *Bull. Soc. Chim. France*, 573 (1953); *Chem. Abstr.*, **48**, 5862i (1954).

(12) H. Omokawa and K. Yamashita, *Agr. Biol. Chem.*, **37**, 1717 (1973).

(13) H. A. Offe and H. Jatzkewitz, *Chem. Ber.*, **80**, 469 (1947); *Chem. Abstr.*, **42**, 7771h (1948).

(14) S. Czaplincki, S. Kostanecki and V. Lampe, *Ber.*, **42**, 827 (1909).

(15) N. S. Vul'fson and T. N. Podrozova, *J. Gen. Chem. USSR*, **32**, 2968 (1962).