

SYNTHESIS AND STRUCTURE OF 5-METHOXY-6,7-METHYLENEDIOXYFLAVONE

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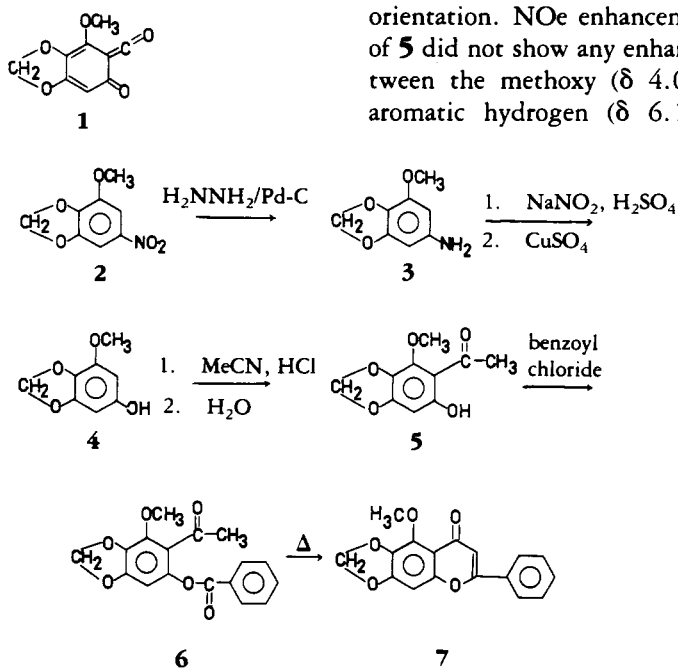
ABSTRACT.—Synthesis of 5-methoxy-6,7-methylenedioxyflavone [7] was achieved. This supported the structure of the compound that was initially established by spectroscopic methods.

5-Methoxy-6,7-methylenedioxyflavone [7] was first isolated from an extract of *Physalis minima* L. (Solanaceae) (1). The structure of the compound was established mainly by using ^{13}C -nmr, ^1H -nmr, and mass spectrometric methods, and no degradation work was carried out.

The presence of the methylenedioxy group in 5-methoxy-6,7-methylenedioxyflavone was established by ^1H -nmr and ^{13}C -nmr spectrometry (1) and the Hansen (2) color reaction. The attachment of the group to ring A of the flavone molecule was proposed on the observation of the m/z 194 ion [1] in its mass spectrum.

The position of the methylenedioxy group was established by comparing the ^1H -nmr spectrum of the compound with that of 2,5-dimethoxy-6,7-methylenedioxyisoflavone (3,4). In order to confirm the structure assignment, the synthesis of 5-methoxy-6,7-methylenedioxyflavone was carried out according to Scheme 1.

Compound 2 was prepared by a literature method (3). NOe enhancement studies showed that one of its aromatic protons (δ 7.55) was ortho to the methoxy group, and meta coupling ($J = 1.9$ Hz) between the two aromatic hydrogen signals was also observed in its ^1H -nmr spectrum, showing that the nitro group introduced was in the proper orientation. NOe enhancement studies of 5 did not show any enhancement between the methoxy (δ 4.08) and the aromatic hydrogen (δ 6.18) signals,



SCHEME 1

suggesting that the acetyl function was attached to the position ortho to the methoxy group. Compound **5** was converted to 2-acetyl-3-methoxy-4,5-methylenedioxyphenylbenzoate [**6**], which gave 5-methoxy-6,7-methylenedioxyflavone [**7**] on thermal cyclization (5,6). The product had mp 207–208°, and no depression of mp was observed when it was mixed with authentic natural sample. The similarity of the uv, ir, ¹H-nmr, ¹³C-nmr, and mass spectra of the synthetic compound with those of the natural product showed that the assignment of the methylenedioxy group at the 6 and 7 positions of ring A was beyond doubt.

EXPERIMENTAL

Mp's were uncorrected, uv spectra were recorded in MeOH, ¹H-nmr and ¹³C-nmr spectra were recorded in CDCl₃ using TMS as internal standard, and mass spectra were recorded by direct inlet at 70 eV with VG Micromass 7035. 3-Methoxycatechol was obtained from TCI (Tokyo Chemical Industry Co.). Kieselgel 60 (Merck) was used for cc and Kieselgel 60 F₂₅₄ for tlc.

Compound **2** was prepared as previously described (3): light yellow solid, mp 145° [lit. (3) 145–146°]; eims *m/z* (rel. abundance) [M]⁺ 197 (100); ¹H nmr (CDCl₃) δ 3.97 (s, 3H, -OMe), 6.14 (s, 2H, O-CH₂-O), 7.55 (d, meta-coupling *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 1.9 Hz, 1H). Strong nOe enhancement was observed between the aromatic proton (δ 7.55) and the methoxy group, indicating that the hydrogen was ortho to it.

5-AMINO-2,3-METHYLENEDIOXYANISOLE [**3**].—2,3-Methylenedioxy-5-nitro-anisole (24 g) was placed in a 1-liter three-necked round bottom flask equipped with a reflux condenser and a mechanical stirrer, and 400 ml of 95% EtOH was added. The solution was warmed until the solid partially dissolved, and 1 g of 10% Pd/C (pre-moistened with EtOH) was added. Finally, 22 ml of hydrazine (95%) was added from the dropping funnel and the mixture was refluxed until the yellowish color disappeared (about 30 min). The warm solution was filtered over celite to remove the catalyst, and the excess hydrazine and the solvent were distilled off. The concentrated solution was then cooled in the refrigerator. 5-Amino-2,3-methylenedioxyanisole crystallized out as a colorless solid (15.8 g, 75.4% yield): mp 84° [lit. (3) 81–84°]; eims *m/z* (rel. abundance) [M]⁺ 167 (100); ¹H nmr (CDCl₃) δ 3.84 (s, 3H, -OMe),

5.83 (s, 2H, O-CH₂-O), 5.95 (d, meta-coupling *J* = 1.9 Hz, 1H), 5.84 (d, *J* = 1.9 Hz, 1H), 3.5 (b, 2H, -NH₂).

3-METHOXY-4,5-METHYLENEDIOXYPHENOL [**4**].—A suspension of 13.3 g of 5-amino-2,3-methylenedioxyanisole in 400 ml of water was cooled to 0° in an ice-salt-H₂O bath. The mixture was acidified with 68 ml of 5 N H₂SO₄, and a solution of 6 g of NaNO₂ in 50 ml of H₂O was added slowly to the stirred mixture. The unreacted nitrous acid was decomposed by the addition of 0.34 g of urea. A 3-liter three-necked flask equipped with a dropping funnel (with cooling jacket), a mechanical stirrer, and a reflux condenser was set up. A CuSO₄ solution of 818 g of CuSO₄ and 900 ml of H₂O in the flask was brought to boiling with constant stirring, and the diazonium sulfate solution was added slowly to the boiling solution. After the addition was complete, the solution was cooled to room temperature and extracted several times with Et₂O. The Et₂O solution was dried with anhydrous Na₂SO₄. After distilling off the Et₂O, a dark-colored oily residue was obtained. Distillation of the oily residue at 130°/0.3 mm gave 3.6 g (27% yield) of 3-methoxy-4,5-methylenedioxyphenol: light orange yellow solid, mp 89.8° [lit. (3) 87–90°]; eims *m/z* (rel. abundance) [M]⁺ 168 (100); ¹H nmr (CDCl₃) δ 3.85 (s, 3H, -OMe), 5.55 (s, broad, 1H, -OH), 5.89 (s, 2H, O-CH₂-O), 6.03 (d, meta-coupling *J* = 2.2 Hz), 6.10 (d, *J* = 2.2 Hz).

6-HYDROXY-2-METHOXY-3,4-METHYLENEDIOXYACETOPHENONE [**5**].—3-Methoxy-4,5-methylenedioxyphenol (1.26 g) and MeCN (2.5 g) were placed in a 100-ml two-necked round bottom flask containing 50 ml of dry Et₂O, and anhydrous ZnCl₂ (2.6 g) was then added. The flask was equipped with a gas inlet tube, a cold finger filled with dry ice, and a magnetic stirrer. Dry HCl gas was bubbled through the stirred mixture in an ice-H₂O bath for about 1 h. After the reaction mixture was kept in the refrigerator for 2 days, the Et₂O layer was decanted off and the oily residue was hydrolyzed by refluxing with 100 ml of H₂O. The aqueous solution was then extracted overnight with CHCl₃ in a liquid-liquid extractor. The CHCl₃ extract was evaporated to dryness, and the residue obtained was purified by cc using hexane, hexane/CHCl₃, and CHCl₃ solvents as eluents. A yellow band was eluted in CHCl₃. Upon evaporation of the CHCl₃, 6-hydroxy-2-methoxy-3,4-methylenedioxyacetophenone (327 mg, 21% yield) was obtained as a yellow solid: mp 117–119°; uv λ max (MeOH) nm 213, 243, 285.6, 350.8; ¹H nmr (CDCl₃) δ 13.79 (s, 1H, -OH ortho to carbonyl), 6.18 (s, 1H, Ar-H), 5.91 (s, 2H, O-CH₂-O), 4.08 (s, 3H, -OMe), 2.61 (s, 3H, -Ac). NOe studies did not show any enhancement between the methoxy group signal and the aromatic hydrogen, indicat-

ing that the hydrogen must be para to the methoxy group. High resolution eims m/z (rel. abundance) $[M]^+$ 210.0528 (80) ($C_{10}H_{10}O_5$ required 210.0528), $[M - Me]^+$ 195 (100), $[M - 2Me]^+$ 180 (50).

2-ACETYL-3-METHOXY-4,5-METHYLENEDIOXYPHENYLBENZOATE [6].—6-Hydroxy-2-methoxy-3,4-methylenedioxyacetophenone (326 mg) was dissolved in 1 ml of pyridine in a 50 ml round-bottom flask chilled in an ice bath. Benzoyl chloride (1 ml) was added, the mixture was stirred, and the reaction was monitored by tlc. After the reaction was complete, the mixture was poured into crushed ice containing 2 ml of concentrated HCl with stirring. After all the ice had melted, the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with dilute HCl to ensure the removal of pyridine, followed by Na_2CO_3 solution and H_2O . Evaporation of the solvent after drying with anhydrous Na_2SO_4 gave 395 mg (81% yield) of 2-acetyl-3-methoxy-4,5-methylenedioxyphenylbenzoate: mp 107–108°; uv λ max (MeOH) nm 236, 206; 1H nmr ($CDCl_3$) δ 8.16–8.05 (m, 2H), 7.7–7.4 (m, 3H), 6.47 (s, 1H, H para to -OMe), 6.01 (s, 2H, O- CH_2 -O), 4.05 (s, 3H, O-Me), 2.45 (s, 3H, -Ac); high resolution eims m/z (rel. abundance) $[M]^+$ 314.0790 (50) ($C_{17}H_{14}O_6$ required 314.0790), $[\text{O} - C=O]^+$ 105 (100), $[\text{O}]^+$ 77 (70).

5-METHOXY-6,7-METHYLENEDIOXYFLAVONE [7].—2-Acetyl-3-methoxy-4,5-methylenedioxyphenylbenzoate (100 mg) was heated in a 25-ml round-bottom flask with 10 ml of anhydrous glycerol with constant stirring in an oil bath at 190°. The reaction was monitored with tlc. After the reaction was complete, the mixture was cooled down to room temperature and diluted

with H_2O . The aqueous solution was extracted with $CHCl_3$, and the organic layer was washed with H_2O . The residue obtained, after evaporation of the $CHCl_3$ solvent, was separated with cc. Hexane, hexane/ $CHCl_3$, and $CHCl_3$ were used as eluents. After the separation, 10 mg (11% yield) of crystalline 5-methoxy-6,7-methylenedioxyflavone was obtained, mp 207–208°. No depression was observed in the mmp determination with the authentic natural sample. The natural product sample was recrystallized with MeOH, and its mp, 207–208°, was re-determined. Uv, 1H -nmr, ^{13}C -nmr, and mass spectra were similar to those of the natural compound.

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LITERATURE CITED

1. A.S. Ng, *Phytochemistry*, **27**, 3078 (1988).
2. O.R. Hansen, *Acta Chem. Scand.*, **7**, 1125 (1953).
3. J. Geigert, F.R. Stermitz, G. Johnson, D.D. Maag, and D.K. Johnson, *Tetrahedron*, **29**, 2703 (1973).
4. H. Chiji, Y. Arakawa, S. Ueda, M. Kuroda, and M. Igawa, *Phytochemistry*, **25**, 281 (1986).
5. A.T.M. Dunne, J.E. Gowan, J. Keane, B.M. O'Kelly, D. O'Sullivan, M.M. Roche, P.M. Ryan, and T.S. Wheeler, *J. Chem. Soc.*, 1252 (1950).
6. H.M. Lynch, T.M. O'Toole, and T.S. Wheeler, *J. Chem. Soc.*, 2063 (1952).

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