Synthesis of Ceratiolin, a Constituent of *Ceratiola ericoides*

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(Received April 22, 1989)

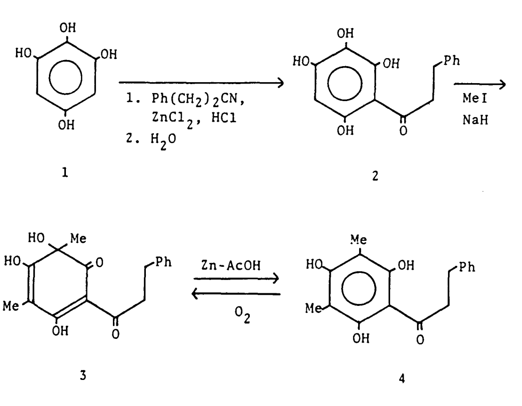
Synopsis. Ceratiolin, a constituent of *Ceratiola ericoides* was synthesized by the methylation of 2′,3′,4′,6′-tetrahydroxydihydrochalcone, prepared by the Hoesch reaction of 1,2,3,5-benzenetetrol with 3-phenylpropionitrile. Furthermore, it was proved that ceratiolin easily forms by the oxidation of 2′,4′,6′-trihydroxy-3′,5′-dimethyldihydrochalcone.

Recently, Fischer et al.1) isolated a new constituent, ceratiolin, from the water-soluble extracts of the fresh leaves of *Ceratiola ericoides,* one of only three genera in the Empetraceae, and proposed the racemic structure **3** for this new compound from its spectral and CD data.

A novel structure of **3** and its characteristic allelopathic property1,2) have prompted us to attempt the synthesis of **3**.

In this paper, we wish to report on the convenient synthesis of **3** by the di-*C*-methylation of 2′,3′,4′,6′-tetrahydroxydihydrochalcone (**2**). Dihydrochalcone **2** was obtained from 1,2,3,5-benzenetetrol (**1**)3) and 3-phenylpropionitrile by the Hoesch reaction in 63% yield. Ceratiolin (**3**) was prepared by the methylation of **2** with methyl iodide in the presence of sodium hydride in dimethyl sulfoxide in 48% yield. The structure of synthetic **3** was identified by a comparison of IR, ^{1}H NMR, and ^{13}C NMR spectra with those of a natural sample.

Furthermore, Fischer et al.1) reported that ceratiolin biogenetically appears to be an oxidative derivative of dihydrochalcone **4**. This speculation was experimentally proved by the formation of **3** through the oxidation of 2′,4′,6′-trihydroxy-3′,5′-dimethyldihydrochalcone (**4**).



Experimental

All the melting points were uncorrected. The IR and UV spectra were recorded with a Hitachi 100-50 spectrophotometer and Hitachi 215 spectrophotometer, respectively. The ^{1}H NMR and ^{13}C NMR spectra were measured with a Hitachi R-600 spectrometer and a Hitachi R-90H spectrometer, using tetramethylsilane as an internal standard, respectively. The mass spectra were obtained on a Hitachi RMU-6M mass spectrometer.

2′,3′,4′,6′-Tetrahydroxydihydrochalcone (2). To a mixture of 1,2,3,5-benzenetetrol (**1**)3) (10.0 g), 3-phenylpropionitrile (15.0 g), and anhydrous zinc chloride (3.5 g) in dry ether (100 ml), dry hydrogen chloride gas was passed for 3 h under cooling with an ice-salt bath. The reaction mixture was allowed to stand overnight at 0 °C, and the resulting dark-brown precipitate was heated with water (600 ml) on a water bath for 2 h. The hydrolysis product was extracted with ethyl acetate and chromatographed on a column of silica gel using benzene-ethyl acetate-acetic acid (6 : 1 : 1) as an eluent to afford **2** (12.1 g, 63%) as yellow crystals. Mp 138—139 °C (recrystallized from chloroform). MS *m/z* 274 (M^+). IR (KBr) ν 3420, 3030, 1640, 1424, 1200, and 718 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=2.85—3.48 (4H, m, H_α and H_β), 5.92 (1H, s, 5′-H), 7.26 (5H, s, Ar-H), 11.29 and 12.13 (each 1H, s, OH). Found: C, 65.55, H, 5.04%, Calcd for $C_{15}H_{14}O_5$: C, 65.69, H, 5.14%.

Ceratiolin (3). Into a mixture of **2** (3.0 g) and sodium hydride (0.4 g) in dry dimethyl sulfoxide (60 ml) was added methyl iodide (4.6 g) under cooling with ice-water; the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was worked up in the usual manner and the resulting crude product was chromatographed on a column of silica gel (Wakogel C-200) with carbon tetrachloride-ethyl acetate-acetic acid (6 : 1 : 1) to give **3** (1.57 g, 48%) as light yellow crystals. Mp 148—149 °C (from benzene) (lit,1) mp 148—149 °C). MS *m/z* 302 (M^+). ES λ_{max} (MeOH) 227, 326, and 354 nm (log ε=4.46, 4.48, and 4.52). IR (KBr) ν 3450, 1668, 1639, 1578, 1520, 1468, 1285, 1240, 1072, 1056, 1020, and 700 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=1.50 (3H, s, Me), 1.85 (3H, s, Me), 2.86—3.31 (4H, m, H_α and H_β), 7.26 (5H, s, Ar-H), 18.86 (1H, s, chelated OH). ^{13}C NMR (CD$_3$OD) δ=7.0 (q), 28.9 (q), 32.4 (t), 41.8 (t), 75.7 (s), 104.0 (s), 105.8 (s), 127.0 (d), 129.2 (d), 142.3 (s), 174.0 (s), 190.6 (s), 197.8 (s), and 201.6 (s).

The synthetic ceratiolin (**3**) was completely identical with a natural specimen. (Natural ceratiolin, although it has a chiral carbon, is optically inactive1)).

2′,4′,6′-Trihydroxy-3′,5′-dimethyldihydrochalcone (4). A mixed solution of **3** (0.25 g) and activated zinc dust (0.8 g) in acetic acid (10 ml) was refluxed for 10 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo; the residue was recrystallized from benzene to give **4** (0.7 g, 85%) as yellow crystals. Mp 119—120 °C. MS *m/z* 286 (M^+). IR (KBr) ν 3580, 3450, and 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=2.05 (6H, s), 2.97 and 3.42 (each 2H, m), 7.17 (5H, s), and 10.58 (br. s). Found: C, 71.05, H, 6.23%, Calcd for $C_{17}H_{18}O_4$: C, 71.31, H, 6.34%.

Oxidation of 4 with Air. A mixture of **4** (30 mg) and lead (II) acetate (40 mg) in methanol (0.2 ml) was stirred for 4 h with airing at room temperature. The resulting yellow precipitates were treated with 6 M sulfuric acid (1 M=1 mol dm^{-3}) and extracted with ether. The ether layer was washed with water and dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was chromatographed on a column of silica gel with benzene-ethyl formate-formic acid (15 : 5 : 1) as an eluent to afford pale-yellow crystals (mp 148—149 °C, 9.5 mg, 30%). This compound was completely identical with **3**.

The authors are grateful to Professor N. H. Fischer of Louisiana State University for the identification of our synthetic sample with natural ceratiolin. We also wish to express their thanks Dr. Satoru Kumazawa of the Kureha Chemical Industry Co., Ltd., for the measurement of ^{13}C NMR spectra.

References

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