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Synthesis of 2-Alkoxy-3,4,6-trihydroxyacetophenones

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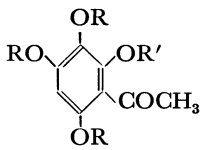
Synopsis. 2-Alkoxy-3,4,6-trihydroxyacetophenones have been prepared from 2,3,4,6-tetrakis(benzyloxy)acetophenone (II) in good yields by the following reactions: hydrolysis of II to 2-hydroxy-3,4,6-tris(benzyloxy)acetophenone (IIIa), alkylation of IIIa to 2-isopropoxy and 2-ethoxy-3,4,6-tris(benzyloxy)acetophenones (IVa and VIb), and hydrogenolysis of IVa and IVb to the corresponding 2-alkoxy-3,4,6-trihydroxyacetophenones (Va and Vb).

Synthsis of two kinds of monomethyl ether of 2,3,4,6-tetrahydroxyacetophenone (I) (3 and 4 position) was reported by Phadke[1] and Krishna.[2] However, 2-alkoxy-3,4,6-trihydroxyacetophenones have not been reported in literature.

In the synthetic course of flavonoid compounds, we found a new synthetic method of 2-alkoxy-3,4,6-trihydroxyacetophenones from 2-hydroxy-3,4,6-tris(benzyloxy)acetophenone (IIIa) which was obtained by the selective hydrolysis of 2,3,4,6-tetrakis(benzyloxy)acetophenone (II). Recently, several polyhydroxy flavonoids (and/or their ether derivatives) have been found in nature.[3,4] Therefore our method offers a good starting material for these flavonoid synthesis.

IIIa was obtained when II was hydrolyzed by 90% acetic acid. The signal of hydrogen bonding OH (13.98 ppm) with ketone in its NMR spectrum and hydrogen bonded ketone (1620 cm^{-1}) in its IR spectrum are observed. IIIa gave isopropoxy-tris(benzyloxy)acetophenone (IVa) by isopropylation. Hydrogenolysis of IVa gave isopropoxy-trihydroxyacetophenone (Va). The compound Va was transformed to the corresponding trimethyl ether (VI) which was also obtained from the known compound, 2-hydroxy-3,4,6-trimethoxyacetophenone (IIIb).[5]

IIIa is an useful compound as a starting material in the synthesis of 2-alkoxy-3,4,6-trihydroxyacetophenones. For example, 2-ethoxy-3,4,6-trihydroxyacetophenone (Vb) was synthesized from IIIa in the same manner as described above.



I, R=R′=H
II, R=R′=CH_2Ph
IIIa, R=CH_2Ph, R′=H
b, R=Me, R′=H
IVa, R=CH_2Ph, R′=Pr(*i*)
b, R=CH_2Ph, R′=Et
Va, R=H, R′=Pr(*i*)
b, R=H, R′=Et
VI, R=Me, R′=Pr(*i*)

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi Model 285 infrared spectrophotometer. The mass spectra were recorded with a JEOL Model JMS-OMS mass spectrometer. The NMR spectra were determined at 100 MHz with a JEOL Model 4H-100 NMR spectrometer, using tetramethylsilane as the internal standard. 2,3,4,6-Tetrahydroxyacetophenone (I)[6] was prepared from 1,2,3,5-benzenetetrol which was obtained by hydrogenolysis of 1,3-bis(benzyloxy)-2,5-benzenediol.[7]

2,3,4,6-Tetrakis(benzyloxy)acetophenone (II). A mixture of 2,3,4,6-tetrahydroxyacetophenone (I)[6] (0.68 g, 3.7 mmol), benzyl chloride (3.14 g, 22 mmol) and potassium carbonate (anhyd 22 g) in *N,N*-dimethylformamide (DMF) (30 ml) was heated for 1 h at 190 °C. The reaction mixture was poured into ice–water, and then extracted with benzene. The benzene layer was chromatographed over silica gel and eluted with benzene to give 0.81 g of crystals of II, mp 81 °C. IR (KBr): 1680 cm^{-1} (C=O); MS *m/e*: 544 (M^+); NMR δ ($CDCl_3$): 2.35 (3H, s, acetyl methyl), 4.98—5.08 (8H, benzyl methylene), 6.36 (1H, s, phenyl) and 7.15—7.45 (20H, phenyl). Found: C, 79.37; H, 5.99%. Calcd for $C_{36}H_{32}O_5$: C, 79.41; H, 5.88%.

2-Hydroxy-3,4,6-tris(benzyloxy)acetophenone (IIIa). A solution of II (1 g, 2 mmol) in 90% acetic acid (65 ml) was refluxed for 17 h. The reaction mixture was poured into ice–water, and then extracted with 300 ml of benzene. The benzene layer was washed with aqueous sodium hydrogencarbonate and water, dried and then evaporated to give IIIa as yellow crystals. Recrystallization from ethanol gave pale yellow needles of IIIa (0.65 g, 78%); mp 141—142 °C. IR (KBr): 1620 cm^{-1} (C=O, hydrogen bonded); NMR δ ($CDCl_3$): 2.50 (3H, s, acetyl methyl), 4.93—5.02 (6H, benzyl methylene), 5.98 (1H, s, phenyl), 7.20—7.50 (15H, phenyl) and 13.98 (1H, s, hydrogen bonding OH). Found: C, 76.41; H, 5.72%. Calcd for $C_{29}H_{26}O_5$: C, 76.65; H, 5.73%.

2-Isopropoxy-3,4,6-tris(benzyloxy)acetophenone (IVa). A mixture of IIIa (0.33 g, 0.7 mmol), isopropyl bromide (0.17 g, 1.4 mmol) and potassium carbonate (anhyd 20 g) in DMF (30 ml) was heated for 1 h at 150 °C. The reaction mixture was poured into ice–water, and then extracted with benzene. The benzene layer was washed with water, dried, and then evaporated. Recrystallization of the residue from hexane gave 0.29 g (80%) of IVa as colorless needles; mp 114 °C. IR (KBr): 1685 cm^{-1}; MS *m/e*: 496 (M^+); NMR δ ($CDCl_3$): 1.16 (6H, d, isopropyl methyl, J=7 Hz), 2.41 (3H, s, acetyl methyl), 4.65 (1H, septet, isopropyl methine, J=7 Hz), 4.93—4.99 (6H, benzyl methylene), 6.32 (1H, s, phenyl) and 7.10—7.45 (15H, phenyl). Found: C, 77.55; H, 6.61%. Calcd for $C_{32}H_{32}O_5$: C, 77.42; H, 6.45%.

2-Ethoxy-3,4,6-tris(benzyloxy)acetophenone (IVb). IVb was prepared according to the procedure described above. In place of isopropyl bromide, ethyl iodide (0.22 g, 1.4 mmol) was used to give 0.3 g (86%) of IVb; mp 87 °C (from hexane). IR (KBr): 1695 cm^{-1}; MS *m/e*: 482 (M^+): NMR δ ($CDCl_3$): 1.28 (3H, t, ethoxyl methyl, J=7.5 Hz), 2.40 (3H, s, acetyl methyl), 4.09 (2H, quartet, ethoxyl methylene, J=7,5 Hz), 4.93—4.99 (6H, benzyl methylene), 6.29 (1H, s, phenyl), 7.20—7.48 (15H, phenyl). Found: C, 77.26; H, 6.26%. Calcd for $C_{31}H_{30}O_5$: C, 77.18; 6.22%.

2-Isopropoxy-3,4,6-trihydroxyacetophenone (Va). A mixture of IVa (0.2 g, 0.4 mmol), 5% palladium–charcoal (3 g), and ethanol (50 ml) was shaken under hydrogen atmosphere for 5 h at room temp. After the removal of the catalyst, ethanol was evaporated to give Va. Recrystallization from

water gave yellow plates of Va (86 mg, 94%); mp 137 °C. IR (KBr): 3450 (OH) and 1630 cm^{-1} (C=O, hydrogen bonded); MS *m/e*: 226 (M^+); NMR δ (CD_3COCD_3): 1.32 (6H, d, isopropyl methyl, J=7 Hz), 2.61 (3H, s, acetyl methine, J=7 Hz), 6.17 (1H, s, phenyl), and 12.87 (1H, s, hydrogen bonding OH). Found: C, 58.69; H, 6.37%. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.19%

2-Ethoxy-3,4,6-trihydroxyacetophenone (Vb). Vb was prepared according to the procedure described above. Recrystallization from 30% ethanol gave yellow plates of Vb (96%); mp 169 °C. IR (KBr): 3350 (OH) and 1610 cm^{-1} (C=O, hydrogen bonded); NMR δ (DMSO-d_6): 1.45 (3H, t, ethoxy methyl, J=7.5 Hz), 4.21 (2H, quartet, ethoxyl methylene, J=7.5 Hz) 6.18 (1H, s, phenyl), 9.80 (2H, broad, s, OH), and 13.42 (1H, s, hydrogen bonding OH). Found: C, 56.76; 5.81%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.66%.

2-Isopropoxy-3,4,6-trimethoxyacetophenone (VI). A solution of 2,4-dihydroxy-3,6-dimethoxyacetophenone[8] (1 g, 4.7 mmol) in ether (10 ml) was treated with excess of etheral diazomethane for 1 h. Evaporation of ether gave a residue which was recrystallized from diisopropyl ether. 2-Hydroxy-3,4,6-trimethoxyacetophenone (IIIb) thereby separated as yellow needles, mp 110—111 °C (lit,[5] mp 112—113 °C). IR (KBr): 1630 cm^{-1} (C=O, hydrogen bonded); NMR δ ($CDCl_3$): 3.64, 3.78 and 3.80 (methoxyl methyl), and 13.60 (1H, s, hydrogen bonding OH). A mixture of IIIb (0.2 g, 0.88 mmol), potassium carbonate (anhyd 5 g) and isopropyl bromide (0.2 g, 1.6 mmol) in DMF (20 ml) was heated for 1 h at 150 °C. The product VI was recrystallized from hexane as colorless needles (0.19 g, 80%); mp 60 °C. IR (KBr): 1710 cm^{-1} (C=O); MS *m/e*: 268 (M^+); NMR δ ($CDCl_3$); 1.26 (6H, d, isopropyl methyl, J=7 Hz), 2.44 (3H, s, acetyl methyl), 3.79—3.88 (9H, methoxyl methyl), 4.56 (1H, septet, isopropyl methine, J=7 Hz), and 6.22 (1H, s, phenyl). Found: C, 62.29; H, 7.78%. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46%.

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