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SYNTHESIS OF 7- (OR 6-)HYDROXY DERIVATIVES OF 3,3-DIMETHYL-3,4-DIHYDROISOQUINOLINE

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When treated with cyanoacetic ester in conc. H_2SO_4 1-(4-hydroxy-3-methoxyphenyl)- and 1-(3-hydroxy-4-methoxyphenyl)-2-methylpropan-1-ol form ethyl 7-hydroxy-6-methoxy-3,3-dimethyl(or 6-hydroxy-7-methoxy- 3,3-dimethyl)-1,2,3,4-tetrahydroisoquinolylidene-1-acetate.

Keywords: vanillin, 3,3-dimethyldehydrosalsoline, 3,3-dimethyldehydroisosalsoline, isovanillin.

6(or 7-)-Hydroxy-7-(or-6-)methoxy derivatives of isoquinolines hydrogenated in the heterocyclic fragment are quite widely distributed in nature. These include e.g. salsoline, isosalsoline, N-methylisosalsoline, lophocerine, corypaline, O-methylanhalonidine, pseudolaudanine, and many others [1-8]. At the same time, 3,3-dimethyl analogs of these compounds have hardly been studied. It can be recalled that 3,3-dimethyl-3,4-dihydroisoquinoline N-oxide [9] is a powerful agent used in septic and traumatic shock and in a recent US patent [10] relating to preparation of 1-substituted 3,3,4,4-tetramethyl-3,4-dihydroisoquinolines. It is clear that reduction of 3,4-dihydroisoquinolines to 1,2,3,4-tetrahydro derivatives is a routine problem.

The simplest method for preparing 3,3-dialkyl-3,4-dihydroisoquinolines is the reaction of dimethylbenzylcarbinol with nitriles [11] or a three-component reaction of an activated arene, isobutyraldehyde, and nitriles in conc. H_2SO_4 [12]. It is known that free phenols are readily sulfonated in conc. H_2SO_4 hence the simplest method for synthesis of 7-hydroxy-6-methoxy-1,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolines is the reaction of carbinol **2** (prepared from the 4-benzyloxy-3-methoxybenzaldehyde (**1**) substituted at the phenol oxygen atom using isopropyl magnesium bromide) and cyanoacetic ester with subsequent hydrolysis of the ethyl 7-benzyloxy-6-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (**3**) to 7-benzyloxy-6-methoxy-1,3,3-trimethyl-3,4-dihydroisoquinoline (**4**) and removal of the benzyl protection by hydrogenation with simultaneous reduction to the tetrahydro derivative.

It was found that, the cyclization reaction conditions to compound **3** were accompanied by removal of the benzyl group and immediate formation of the 7-hydroxy derivative **5** which was readily transformed to the 3,3-dimethyldehydroisosalsoline **6**. A small amount of compound **3** was also separated in which the benzyl group was retained.

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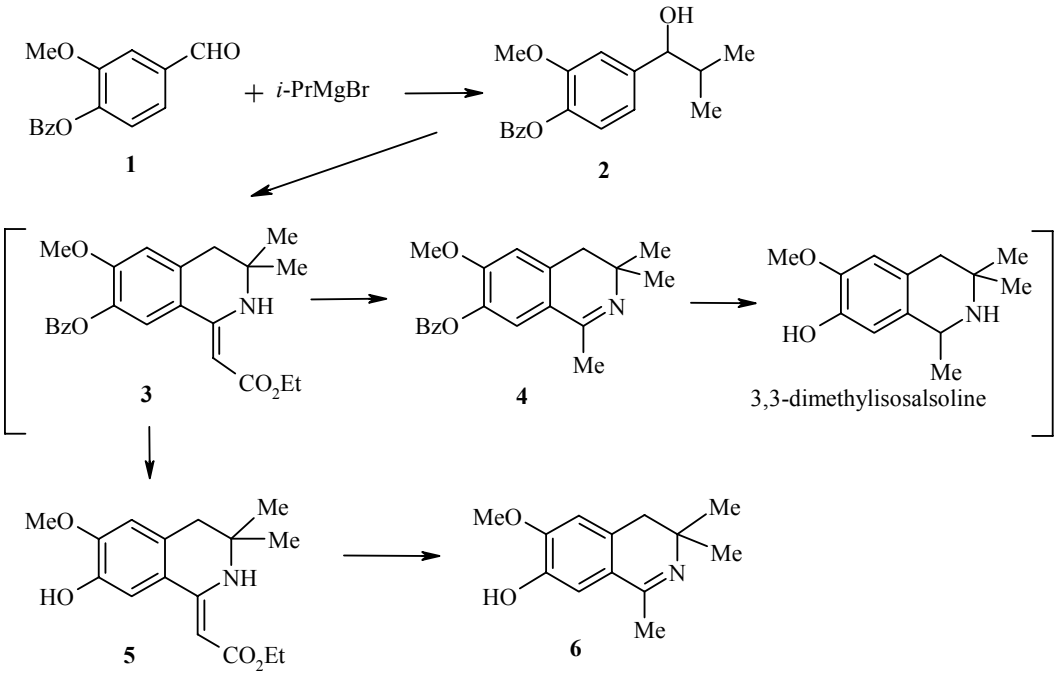
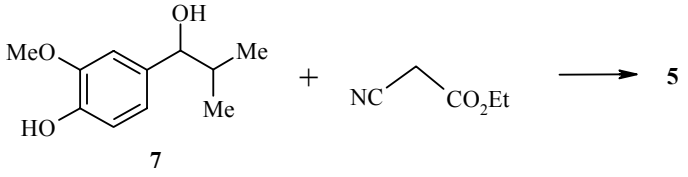
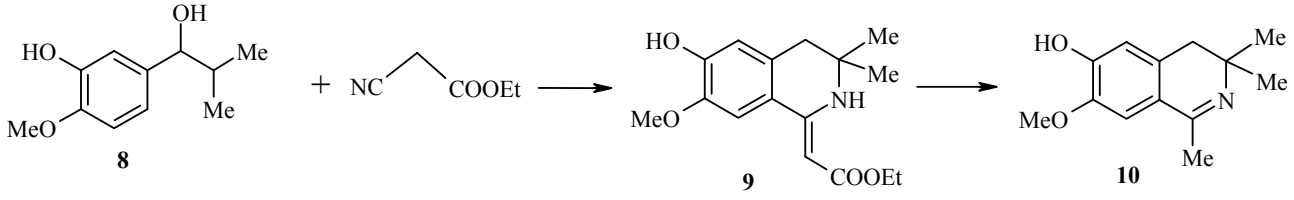


Separation of compound **5** from the reaction product led us to study the possibility of its synthesis from carbinol **7** prepared directly from vanillin and this gave an almost 2.5 times increase in the yield of the target compound **5**.



A similar reaction with carbinol **8** prepared from isovanillin gave compound **9** in 24% yield. This is due to the difficulty of crystallizing ester **9** since chromato gas chromatographic data on the neutralized reaction product shows the yields of compounds **5** and **9** from the corresponding carbinols to be around 70%. Ester **9** is readily converted to 3,3-dimethyldehydrosalsoline **10** *via* hydrolysis with 10% sulfuric acid.



Hence we have discovered routes to preparation of 7(or 6)-hydroxy-3,4-dihydroisoquinolines which open up broad possibilities for synthesizing analogs of known alkaloids modified at the ring 3 position.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument using vaseline oil. ^{1}H NMR spectra were registered on a MercuryPlus-300 spectrometer (300 MHz) using DMSO-d_6 and HMDS internal standard. Mass spectra were

obtained on an Agilent GC 6890N MSD 5975B spectrometer (EI, 70 eV). Elemental analysis was performed on a CHNS-932 LECO Corporation analyzer. Monitoring of the reaction course and purity of the compounds obtained was carried out by TLC on Silufol plates in the system chloroform–acetone (9:1) and revealed using a 5% solution of chloranil in toluene.

Carbinols **2, 7** and **8** were prepared *via* organomagnesium synthesis from isopropylmagnesium bromide and benzylvanillin, vanillin, and isovanillin respectively as a mixture with the corresponding styrene (~ 3:2 by LC) and were used without additional purification [13].

Synthesis of Compounds 3, 5, 6, 9, **and 10 (General Method)**. A mixture of 1-(4-hydroxy-3-methoxyphenyl)-2-methylpropanol (**7**) (for preparing compounds **5** and **6**) or 1-(3-hydroxy-4-methoxyphenyl)-2-methylpropanol (**8**) (for compounds **9** and **10**) (1.95 g, 0.01 mol) and cyanoacetic ester (1.13 g, 0.01 mol) was added dropwise with vigorous stirring to 98% H_2SO_4 (8 ml) cooled to 5-10ºC. The product was stirred for 30 min at room temperature. The reaction mixture was poured into water and neutralized using sodium carbonate to pH 7-8, extracted with chloroform (3×50 ml), and the combined organic layer was washed with water and dried over magnesium sulphate. Chloroform was distilled off and the residue was crystallized from the appropriate solvent. Compound **3** was separated by fractional crystallization of the mixture of esters **3** and **5** from methanol. The yield of compound **5** by this method was 22%.

Compounds **6** and **10** were prepared by refluxing compounds **5** and **9** in 10% H_2SO_4 for 3 h, cooling to room temperature, and subsequent separation as reported above.

Ethyl 7-benzyloxy-6-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (3). Mp 207-209ºC (methanol); yield 8%. IR spectrum, ν, cm^{-1}: 3360 (NH), 1630 (sh, C=O); 1620 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.09 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 1.17 (6H, s, 3,3-$(CH_3)_2$); 2.70 (2H, s, H-4); 3.87 (3H, s, 6-OCH_3); 3.92 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 4.24 (2H, s, $OCH_2C_6H_5$); 4.54 (1H, s, CH=CH–); 6.80 (1H, s, H-5); 8.40 (1H, s, H-8). Mass spectrum, *m/z* (I_{rel}, %): 381 $[M]^+$ (60), 352 (10), 336 (13), 290 (35), 262 (20), 230 (14), 178 (19), 165 (20).

Ethyl 7-Hydroxy-6-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (5). Mp 148-151ºC (ethanol); yield 56% (carbinol **7**). IR spectrum, ν, cm^{-1}: 3460, 3270, 1640, 1602, 1574, 1512. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (6H, s, 3,3-$(CH_3)_2$); 1.30 (3H, m, $OCH_2C\underline{H}_3$); 2.72 (2H, s, H-4); 3.91 (3H, s, 6-OCH_3); 4.12 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 5.00 (1H, s, –CH=C–); 5.50 (1H, br. s, 7-OH); 6.58 (1H, s, H-5); 7.21 (1H, s, H-8); 8.90 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 291 $[M]^+$ (52), 276 $[M\text{-}CH_3]^+$ (20), 246 $[M\text{-}OC_2H_5]^+$ (20), 230 $[M\text{-}OOC_2H_5]^+$ (100), 219 (23), 204 (27). Found, %: C 66.18; H 7.21; N 4.85. $C_{16}H_{21}NO_4$. Calculated, %: C 65.96; H 7.27; N 4.81.

7-Hydroxy-6-methoxy-1,3,3-trimethyl-3,4-dihydroisoquinoline (6). Mp 194-204ºC (a mixture of ethyl acetate and hexane); yield 53% (29% based on the starting carbinol **7**). IR spectrum, ν, cm^{-1}: 1632, 1612, 1560, 1512. ^1H NMR spectrum, δ, ppm: 1.19 (6H, s, 3,3-$(CH_3)_2$); 2.29 (3H, s, 1-CH_3); 2.60 (2H, s, H-4); 3.91 (3H, s, 6-OCH_3); 6.61 (1H, s, H-5); 7.07 (1H, s, H-8). Mass spectrum, *m/z* (I_{rel}, %): 219 $[M]^+$ (91), 204 $[M\text{-}CH_3]^+$ (100), 189 (20), 177 (41), 162 (14). Found, %: C 71.29; H 7.76; N 6.44. $C_{13}H_{17}NO_2$. Calculated, %: C 71.21; H 7.81; N 6.39.

Ethyl 6-Hydroxy-7-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (9). Mp 135-137ºC (ethanol); yield 24%. IR spectrum, ν, cm^{-1}: 3280, 3000, 1636, 1592, 1516. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (6H, s, 3,3-$(CH_3)_2$); 1.28 (3H, m, $OCH_2C\underline{H}_3$); 2.71 (2H, s, H-4); 3.90 (3H, s, 7-OCH_3); 4.15 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 4.99 (1H, s, –CH=C–); 5.86 (1H, s, 6-OH); 6.68 (1H, s, H-5); 7.11 (1H, s, H-8); 8.93 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 291 $[M]^+$ (31), 276 $[M\text{-}CH_3]^+$ (20), 246 $[M\text{-}OC_2H_5]^+$ (17), 230 $[M\text{-}OOC_2H_5]^+$ (100), 219 (15), 204 (40). Found, %: C 65.83; H 7.33; N 4.86. $C_{16}H_{21}NO_4$. Calculated, %: C 65.96; H 7.27; N 4.81.

6-Hydroxy-7-methoxy-1,3,3-trimethyl-3,4-dihydroisoquinoline (10). Mp 195-196ºC (mixture of ethyl acetate and hexane); yield 20% (based on starting carbinol **8**). IR spectrum, ν, cm^{-1}: 3200, 1615, 1585, 1512. ^1H NMR spectrum, δ, ppm: 1.30 (6H, s, 3,3-$(CH_3)_2$); 2.45 (3H, s, 1-CH_3); 2.67 (2H, s, H-4); 3.79 (3H, s,

7-OCH_3); 5.50 (1H, br. s, 6-OH); 6.44 (1H, s, H-5); 6.85 (1H, s, H-8). Mass spectrum, *m/z* (I_{rel}, %): 219 $[M]^+$ (100), 204 $[M\text{-}CH_3]^+$ (85), 189 (34), 177 (53), 162 (15). Found, %: C 71.34; H 7.75; N 6.43. $C_{13}H_{17}NO_2$. Calculated, %: C 71.21; H 7.81; N 6.39.

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