Sodium–Ammonia Reduction of Flavonols[1]

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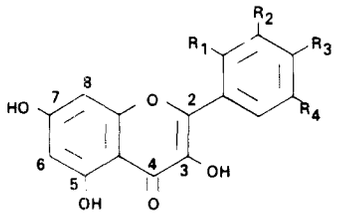
The sodium–ammonia reduction of flavonol 3-*O*-methyl ethers proceeds with regiospecific reduction of the carbonyl-conjugated olefin to yield α-methoxydihydrochalcones, which are further reduced to dihydrochalcones. Under similar conditions, flavonols themselves (free 3-OH) are converted mainly to α-hydroxydihydrochalcones via the selective reduction of an acyclic 1,2-diketo intermediate. Scheme I rationalizes the formation of all the products characterized in this study.

The reduction of flavonols, both at the carbonyl and the $\Delta^{2,3}$ double bond sites, is known to proceed with difficulty in comparison with typical α,β-unsaturated ketones. The reduction of the carbonyl has been observed with dissolving metals [Na(amalgam)/EtOH, Zn/AcOH],[2] with $LiAlH_4$,[3] and under electrolytic conditions.[4] The double bond, which is unusually refractory to catalytic hydrogenation, was found to reduce with sodium dithionite in the case of quercetin (**1**),[5]



1: $R_2 = R_3 = OH$; $R_1 = R_4 = H$

2: $R_3 = OH$; $R_1 = R_2 = R_4 = H$

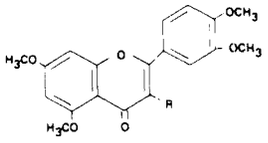
3: $R_2 = R_3 = R_4 = OH$; $R_1 = H$

4: $R_1 = R_3 = OH$; $R_2 = R_4 = H$

kaempferol (**2**), and myricetin (**3**)[6] to yield the corresponding 2,3-*trans*-dihydro derivatives. The reduction failed, however, on morin (**4**), perhaps due to steric factors.[7]

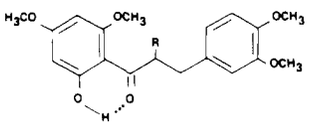
As part of a search for alternative two-electron reduction of the carbonyl in this series of compounds, we have investigated the reduction of several flavonols with sodium in liquid ammonia (Birch reduction).

Reduction of 3,3′,4′5,7-pentamethylquercetin (**5**) with an eightfold excess of Na in liquid NH_3 for 1 h gave 2′-hydroxy-3,4,4′6′-tetramethoxydihydrochalcone (**6**) as the major



5 R = OCH_3

10 R = OH



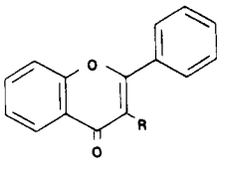
6 R = H

11 R = OH

17 R = OCH_3

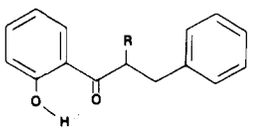
product in 54% yield. The NMR, IR, and MS data were in complete accord with the assigned structure (mp 124–125.5 °C; lit.[8] 125–126 °C).

As a second example, 3-methoxyflavone (**7**) was reduced under similar conditions, using a mixture of THF and NH_3 to ensure complete solubility. The major product (32% yield) was again the dihydrochalcone (**8**). In addition 27% of a highly insoluble product, mp 255–256 °C, was also formed. This compound was found to be the dimeric dihydrochalcone (**9**), a structure supported by its spectral data and elemental composition. Particularly informative was the mass spectrum, which showed a molecular ion peak at *m/e* 450 and fragments



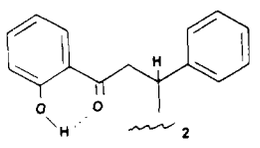
7 R = OCH_3

12 R = OH



8 R = H

13 R = OH



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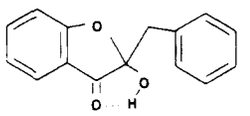

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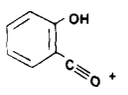
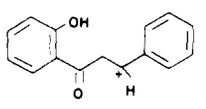
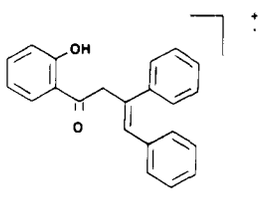
at *m/e* 121, 225, and 314, which were readily assigned as follows:



m/e 121

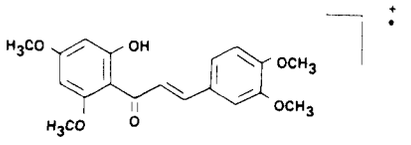


m/e 225

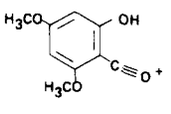


m/e 314

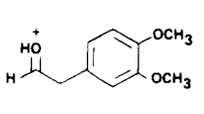
When 3′,4′5,7-tetramethylquercetin (**10**) was reduced with excess Na as previously, however, the corresponding α-hydroxydihydrochalcone (**11**), mp 118–120 °C, was formed instead of dihydrochalcone **6**. The NMR spectrum of **11** showed a 2 H multiplet at δ 2.75–3.05 for the benzyl CH_2, and a broad 1 H quartet at δ 5.3–5.5 for the proton α to the keto group. The mass spectrum included fragments at *m/e* 151, 181, 211, and 344, which were assigned as follows:



m/e 344

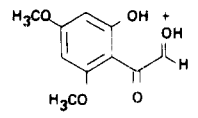


m/e 181

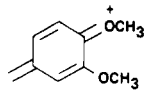


m/e 181

0022-3263/79/1944-1494$01.00/0



m/e 211

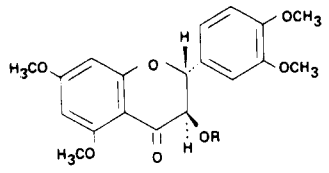


m/e 151

Reduction of flavonol (**12**) in THF–NH_3 gave two major products, the α-hydroxydihydrochalcone (**13**) (oil, oxime mp 136–137 °C) and the 2-hydroxy-2-benzylcoumaranone (**14**), mp 102.5–103.5 °C (lit.[9] 104 °C). In both cases, the spectral data were in complete accord with the assigned structures.

Based on all the results discussed above, the mechanism pictured in Scheme I is proposed for the Birch reduction of flavonols.

Further support for this scheme was obtained from the reduction of 3,3′,4′,5,7-pentamethyl-2,3-*trans*-dihydroquercetin (**15**) and 3′,4′,5,7-tetrametyl-2,3-*trans*-dihydroquercetin (**16**). From **15**, two products were obtained: the dihydrochalcone



15 R = CH_3

16 R = H

6 (31% yield) and the corresponding α-methoxydihydrochalcone (**17**), mp 143.5–145 °C (12% yield). The structure of the latter compound followed from its NMR spectrum (five OCH_3 groups, $ArCH_2$ at δ 2.8–3.1, 1 H as quartet at δ 5.08 for the proton α to the carbonyl) and from the MS data (*m/e* 376, 344, 181, and 151). The reduction of **16** gave a mixture of **6** (16%) and **11** (23%).

The formation of β–β' dimers on the reduction of α,β-unsaturated ketones finds extensive precedence in both the metal–ammonia[10] and electrochemical[11] literature, while the cleavage of hydroxy and methoxy groups α to a carbonyl has been noted in electrolytic[4,12] and metal/acid reductions.[13]

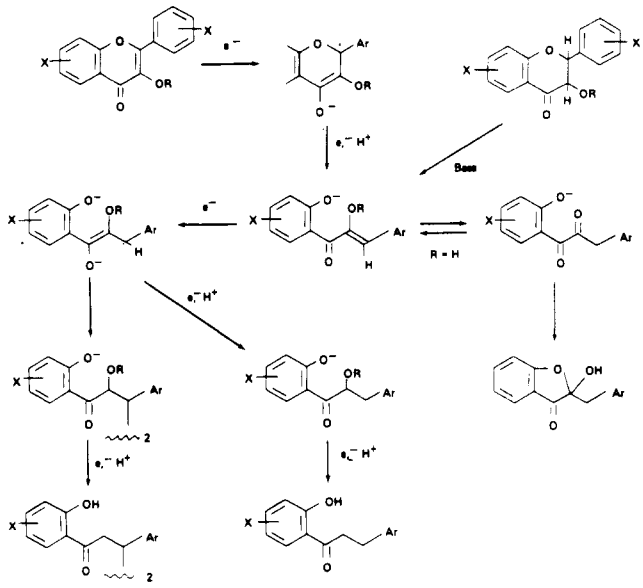
The formation of 2-hydroxy-2-benzyl-2(3*H*)-benzofuranones is known to occur to a variable extent upon the reduction of flavonols in base, as a result of a base-catalyzed rearrangement of the intermediary 2,3-dihydroflavonol via the acyclic 1,2-diketone. In the case of polyhydroxylated flavonols, further deoxygenation to the 2-benzyl-2(3*H*)-benzofuranone was observed on dithionite[14] and sodium–ammonia reductions.[15]

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts are given in parts per million downfield from Me_4Si. Coupling constants (J) are in hertz. Abbreviations: s = singlet; br s = broad singlet; d = doublet; t = triplet; m = multiplet. Ammonia was supplied by Matheson and was used without further purification. Tetrahydrofuran was distilled from $LiAlH_4$ before use. All other reagents were used as received from the supplier and were reagent grade. Microanalyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn.

Na–NH_3 Reduction of Pentamethylquercetin (5). To a stirred suspension of 1.0 g (2.7 mmol) of pentamethylquercetin in 40 mL of liquid ammonia was added 400 mg (17.4 mmol) of Na in three portions over 10 min. Stirring was continued for 1 h, then 1.0 g of NH_4Cl was added and the ammonia was allowed to evaporate. To the solid residue was added 100 mL of 1% HOAc and the mixture was extracted with 3 × 25 mL of $CHCl_3$. Drying (Na_2SO_4) and evaporating the $CHCl_3$ gave a light brown oil which was crystallized from MeOH to afford 518 mg (54%, 2 crops) of **2′,3,4,4′-tetramethoxy-6′-hydroxydihydrochalcone (6):** mp 124–125.5 °C (lit.[7] 125–126 °C); NMR δ 2.8–3.4 (4 H, m, CH_2), 3.8 (12 H, s, OCH_3), 6.0 (2 H, q, C_3 and C_5-H), and 6.8 (3 H, s, C_2, C_5, and C_6H); MS *m/e* (rel intensity) 346 (57), 181 (100), 164 (85), and 151 (42); IR (KBr) 1615, 1585, 1438, 1255, 1220, 1205, 1155, and 1025 cm^{-1}.

Scheme I. Proposed Mechanism for the Na/NH_3 Reduction of Flavonols (R = H, Me)



Reduction of 3-Methoxyflavone (7).[16] To a solution of 450 mg (1.79 mmol) of **3-methoxyflavone** in 10 mL of THF was added 15 mL of NH_3 followed by 200 mg (8.7 mmol) of Na. After stirring for 1 h, the reaction was worked up as above to give a brown oil. Addition of 5 mL of MeOH to the oil produced a white solid, mp 253–255 °C (acetone), 255–260 °C (HOAc). A total of 109 mg (0.242 mmol, 27%) of dimer **9** was obtained having the following spectral characteristics: IR (KBr) 1630, 1605, 1485, 1440, 1295, 1265, 1215, 1150, 745, and 695 cm^{-1}; MS *m/e* (rel intensity) 450 (0.01), 412 (3.5), 314 (29), 225 (19), 122 (20), and 121 (100); UV (dioxane) λ_{max} 252 (log ϵ 4.31) and 325 nm (log ϵ 3.92). Anal. Calcd for $C_{30}H_{26}O_2$: C, 79.98: H, 5.82. Found: C, 79.87; H, 5.88.

The mother liquors from crystallization of **9** were then chromatographed on three 20 × 40 cm preparative TLC silica gel plates using 25% EtOAc–hexane as eluant to give **1-(2-hydroxyphenyl)-3-phenylpropanone (8)** as a thick oil (131 mg, 0.58 mmol, 32%): NMR δ 2.9–3.5 (4 H, m, C_2 and C_3H) and 6.8–7.8 (9 H, m, ArH); MS *m/e* 226, 208, and 121. The spectral data were in complete accord with the assigned structure, although attempts to crystallize the material were unsuccessful. Conversion to the oxime gave a white solid, mp 117–118 °C (lit.[17] mp 117–118 °C).

Reduction of 3′,4′,5,7-Tetramethylquercetin (10).[18] **3′,4′,5,7-Tetramethylquercetin** (200 mg, 0.56 mmol) in 10 mL of NH_3 was reduced with 100 mg (4.35 mmol) of Na to give a light brown oil. Preparative TLC on silica gel using 50% EtOAc–hexane as eluant gave 127 mg (64%) of **2-hydroxy-1-(2,4-dimethoxy-6-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)propanone (11):** mp 118–120 °C (MeOH); NMR δ 2.75–3.05 (2 H, m, C_3H), 3.80–3.85 (12 H, overlapping s, OCH_3), 5.3–5.5 (1 H, m, C_2H), 6.05 (2 H, q, ArH), and 6.75 (3 H, br d, ArH); MS *m/e* (rel intensity) 362 (1), 344 (2.5), 211 (11), 183 (11), 181 (72), and 151 (100); IR (KBr) 3450, 2940, 2900, 1620, 1578, 1510, 1260, 1215, and 1150 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 62.75; H, 6.14.

Reduction of 3-Hydroxyflavone.[16] A solution of 500 mg (2.10 mmol) of 3-hydroxyflavone in a mixture of 10 mL of THF and 15 mL of NH_3 was reduced with 200 mg (8.7 mmol) of Na as above. Preparative TLC of the crude product gave two major bands. The lower one crystallized from EtOAc–hexane to afford 131 mg (0.55 mmol, 26%) of **2-hydroxy-2-benzyl-2(3*H*)-benzofuranone (14),** mp 102.5–103.5 °C (lit.[9] 104 °C).

The upper band was obtained as an oil which could not be induced to crystallize. It was assigned the structure **1-(2-hydroxyphenyl)-2-hydroxy-3-phenylpropanone (13)** based on the spectral data: NMR δ 2.8–3.3 (2, H, m, $ArCH_2$), 3.5 (1 H, br d, OH), 5.3 (1 H, br q, C_2H), and 6.8–7.8 (9 H, m, ArH); IR (neat) 3460, 3050, 1635, 1610, 1485, 1450, 1300, 1250, 1155, 1090, 750, and 695 cm^{-1}; MS *m/e* (rel intensity) 242 (79), 224 (65), 213 (25), 151 (19), 122 (67), 121 (100), and 91 (55).

The oil was converted to its oxime: mp 136–137 °C; MS *m/e* (rel intensity) 257 (46), 209 (22), 166 (36), 148 (28), 120 (60), 103 (19), and

91 (100). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.14; H, 5.91; N, 5.44.

Reduction of 3,3',4',5,7-Pentamethyldihydroquercetin (15). Reduction of 700 mg (1.87 mmol) of pentamethyldihydroquercetin in 30 mL of liquid NH_3 using 200 mg (8.7 mmol) of Na as above gave a light brown oil. Chromatography of the oil on a silica gel column using 25% EtOAc–hexane as eluant afforded two major products. The first to elute, mp 125–126 °C (202 mg, 31%), was identical with the sample of dihydrochalcone **6** prepared previously. The second material was twice recrystallized from MeOH to afford 82 mg (12%) of **2-methoxy-1-(2,4-dimethoxy-6-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)propanone (17)**: mp 143.5–145 °C; NMR δ 2.8–3.1 (2 H, m, C_3H), 3.37 (3 H, s, OCH_3), 3.92 (12 H, s, OCH_3), 5.08 (1 H, q, C_2H), 6.15 (2 H, q, ArH), and 6.86 (3 H, br s, ArH); MS *m/e* (rel intensity) 376 (3), 344 (18), 181 (100), and 151 (39); IR (KBr) 1610, 1580, 1510, 1355, 1315, 1260, and 1210 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.67; H, 6.64.

Reduction of 3',4',5,7-Tetramethyldihydroquercetin (16).[19] Reduction of 3',4',5,7-tetramethyldihydroquercetin (300 mg, 0.83 mmol) in 10 mL of NH_3 with 100 mg (4.35 mmol) of Na gave a complex mixture of products. The two major ones were isolated by preparative TLC on silica gel. Recrystallization from MeOH afforded 48 mg (16%) of dihydrochalcone **6**, mp 125–126.5 °C, and 69 mg (23%) of α-hydroxydihydrochalcone **11**, mp 116–117 °C.

Registry No.—**5**, 1247-97-8; **6**, 65236-01-3; **7**, 7245-02-5; **8**, 3516-95-8; **8** oxime, 69429-57-8; **9**, 69429-58-9; **10**, 1244-78-6; **11**, 65236-02-4; **12**, 577-85-5; **13**, 69429-59-0; **13** oxime, 69429-60-3; **14**, 4940-48-1; **15**, 20754-54-5; **16**, 20754-53-4; **17**, 69429-61-4.

References and Notes

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Metal Catalysis in Organic Reactions. 8. Alkylative Dimerization of 1-Alkynes Induced by Tris(acetylacetonato)manganese/Trialkylalane Systems

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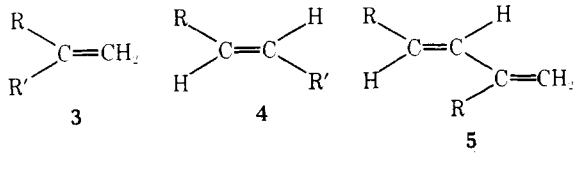
The reaction between trialkylalanes and terminal alkynes in the presence of manganese complexes has been investigated under various conditions. At room temperature, the $Mn(acac)_3$-catalyzed reaction between triisobutylaluminum and 1-alkynes affords (*E,E*)-1-isobutyl-2,4-dialkyl-1,3-butadienes, whose yields depend on the structure of the 1-alkyne used and on the experimental conditions. Using (*S*)-3-methyl-1-pentyne, the reaction was observed to occur without significant racemization. The preparative aspect of this manganese-induced process is discussed together with a mechanistic approach.

Recently we have reported that nickel-promoted dimerization of 1-alkynes provides a useful method for preparing dienes of particular structure.[1,2] In continuing our research, some interesting, although preliminary, results on the formation of (*E,E*)-2-methyl-5-butyl-4,6-undecadiene in a manganese-induced reaction of 1-hexyne with triisobutylaluminum have been described.[3] We have now extended our investigations to elucidate the potential synthetic use of the reaction between aliphatic 1-alkynes and trialkylalanes in the presence of tris(acetylacetonato)manganese(III) [$Mn(acac)_3$].[3] The present paper deals with the dynamics of the reaction along with an investigation on the stereospecificity of the process, carried out with chiral alkynes, and a mechanistic approach on the mode of acting of the catalytic system.

Results and Discussion

The stoichiometric reaction of trialkylalanes with 1-alkynes (**1**) in the presence of nickel complexes leads at room temperature to the formation of little amounts of the corresponding 1-alkenes (**2**), 2-alkyl-1-alkenes (**3**), and (*E*)-1-alkyl-1-alkenes (**4**), together with (*E*)-2,4-dialkyl-1,3-butadienes (**5**) as main product, and 1,3,5-trialkyl- and 1,2,4-trialkylbenzenes (**6** and **7**).[1-4] Using $Mn(acac)_3$ as catalyst under the same conditions, compound **9** is formed principally, along with a series of side products (Scheme I). Most of these products were identified by comparison of their GLC retention times with those of authentic samples,[1,5] while dienes **9** and **10** were isolated from the reaction mixtures and their structures assigned through chemical and spectroscopical techniques.



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For example, the structure of diene **9a** was elucidated by partial ozonation of a sample, followed by treatment of the mixture of the ozonides with $LiAlH_4$ to afford 1-pentanol, 3-methyl-1-butanol, and two α,β-unsaturated carbinols of the

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