CHROMENES AND CHROMANONES. PART I
THE BIRCH REDUCTION OF COUMARINS AND 2H-CHROMENES

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Abstract - The reduction of coumarin, 4-methylcoumarin, 2,2-dimethyl-2H-chromene and 2,2,4-trimethyl-2H-chromene with sodium or lithium in liquid ammonia with the presence or without donor of protons was carried out. The formation of phenolic products was observed when a limited amount of alcohol as a proton donor was present in the reaction medium. In the experiments with excess of alcohol the products with a partially reduced benzene ring were formed.

INTRODUCTION

The alkaline metal-ammonia reduction of aromatic system (the Birch reduction) is a well-known method in synthetic chemistry for the preparation of nonconjugated cyclohexadiene derivatives.\(^{1-5}\) We would like to apply this method for the synthesis of a new class of antijuvenile hormone agents, analogues of precocenes (structures 1, 2 or 3).

![Structures 1, 2, and 3]

It seemed that partial reduction of the benzene ring in the substituted coumarins or 2,2-dimethyl-2H-chromenes could be one of possible ways for the synthesis of these types of compounds. Studying reviews concerning this subject, we could not find any direct information about the Birch reduction of coumarins or chromenes. We have found only one information concerning the
reduction of 2,2-dimethyl-2H-chromene\textsuperscript{6} and a few articles presenting data about the reduction of structurally related compounds like benzofurans,\textsuperscript{7,8} resorcinol ethers,\textsuperscript{10} chromanes,\textsuperscript{11} and ortho esters.\textsuperscript{12} So, it was reasonable for us to try to carry out reduction of coumarin (4a), 4-methylcoumarin (4b), 2.2-dimethyl -and 2,2,4-trimethyl-2H-chromenes (8a and 8b) by this method in our laboratory.

Looking for the most effective conditions of this reduction, lithium or sodium as the most reactive metals in the reduction of benzene\textsuperscript{8,11,13} was used. Reactions were carried out at -33 or -78 °C in the presence of proton donors (EtOH, t-BuOH or MeOH) or without alcohols in ether or tetrahydrofuran as cosolvent. Ammonium chloride in an aqueous saturated solution was used as a quenching agent. The composition of the crude mixture of products was determined by gas chromatography (capillary column HP-5). The pure compounds were isolated from these mixtures by column chromatography.

RESULTS AND DISCUSSION

Reduction of coumarin (4a) and 4-methylcoumarin (4b) with lithium or sodium (5 eq.) at -33 as well as at -78 °C in the presence of ethyl or tert-butyl alcohol as proton donor afforded 2-(3-hydroxypropyl)phenol (5a) and 2-(3-hydroxy-1-methylpropyl)phenol (5b), respectively, as the only products (Scheme 1). Reduction of 4-methylcoumarin (4b) with sodium (5 eq.) in liquid ammonia (-33 °C) carried out without alcohol afforded a complex mixture of products (tlc) from which 3-(2-hydroxyphenyl) butylamide (6b) was isolated as the main component.

The formation of these products with an untouched benzene ring, suggests that the first electron attaches to the styrenoid double bond and the radical anion created is energetically favoured because of stabilization not only by the benzene ring but also by the carbonyl group.

Although we did not isolate 3,4-dihydrocoumarins (7a) or (7b) as a product of experiments carried out, it seems that sequence of addition of proton, electron and proton leads to these compounds Lactones (7a) and (7b) can be then reduced in the presence of alcohol to 5a and 5b, respectively, the same products as obtained from reduction of coumarin with sodium in alcohol. In the absence of alcohol in the reaction medium lactone (7b) reacts with ammonia and amide (6b) is obtained as a product of ammonolysis.
More promising results for our synthetic plans were obtained from reductions of 2,2-dimethyl-2H-chromene (8a) and 2,2,4-trimethyl-2H-chromene (8b). The conditions of the reactions and the compositions of product mixtures obtained are given in the Table.
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a, R=H, b, R=Me
A rough look at contents of this Table indicates that in each experiment carried out a mixture of products (at least two) was obtained. The kind of products formed in the reduction depends basically on the presence or absence of alcohol as a proton donor in the reaction medium.

In the experiments carried out without any alcohol (Entries 4, 8 and 16) compounds with cleaved C-O bond were identified as the only products. The reduction of 2,2-dimethyl-2H-chromene (8a) afforded only two phenolic products (11a and 12a) (Entry 4) whereas the reduction of 2,2,4-trimethyl-2H-chromene (8b) gave also small amounts of 9b and 10b besides 11b and 12b (Entries 8 and 16). Compounds (12a,b) are formed from radical anion (B) whereas 9b, 10b and 11a,b from radical anion (C). These two isomeric radical anions are the result of the rearrangement of the radical anion (A) which is created by the addition of the first electron to the chromene molecule (Scheme 2).

In the experiments with the presence of alcohol in the reaction medium, the bicyclic compounds (13a,b, 14a,b and 15b) besides the phenolic compounds were also identified as products of reduction of chromenes (8a) and (8b). Chromans (13a,b) are formed from the radical anion (D), which is created by the addition of the proton to the radical anion (A) (Scheme 2). The next two
bicyclic compounds, with a partially reduced benzene ring (14a,b and 15a,b) are the products of the further reduction of 13a,b.

Contribution of bicyclic compounds in the product mixture clearly depends on the acidity of alcohol used as well as on its concentration in the reaction medium. The increase of the acidity of alcohol applied caused an increase in the amounts of bicyclic compounds in the product mixture (Entries 6, 11 and 12). When the less acidic t-butyl alcohol was used, only 3% of trimethylchroman (13b) was formed (Entry 11) whereas when the most acidic methyl alcohol was applied the contribution of bicyclic compounds (13b, 14b and 15b) increased to 40% (Entry 12).

The comparison of the compositions of product mixtures obtained from reductions carried out at different concentrations of alcohols in the reaction medium (Entries 1 and 5 or 6 and 9) indicates that the increase of the concentration of alcohol favours the reduction of chromenes to products with the bicyclic system retained and a partially reduced benzene ring. In two experiments (Entries 14 and 15) where 70 equivalents of "acidic" methyl alcohol were used for one equivalent of 2,2,4-trimethyl-2H-chromene (8b), 3,4,5,8-tetrahydro-2H-1-benzopyrane (14b) and 3,4,5,6,7,8-hexahydro-2H-1-benzopyrane (15b) were identified as the major (72% and 24% respectively) products.

Other changeable factors of this reduction like the kind of metal used (Entries 6 and 10 or 7 and 11), its quantity (Entries 14 and 15) and the temperature of the reaction (Entries 2 and 3 or 8 and 16), did not have so much influence on its course and the composition of the product mixture as alcohol did.

CONCLUSIONS

Analysis of composition of product mixtures obtained from experiments presented in the Table indicates that:

1) the best way for synthesis of the β,γ-unsaturated 2-alkenylphenols from 2H-chromenes by the metal-ammonia reduction is to carry out this reaction without additional donor of protons

2) the highest yields of products with a partially reduced benzene ring could be obtained by the application of relatively "acidic" methyl alcohol as a source of protons.
EXPERIMENTAL SECTION

'H Nmr spectra were recorded for solutions (CCI₄ or CCl₄-C₆D₆, 7:1) with TMS as internal standard, on a 80 MHz Tesla BS 587A spectrometer. Infrared spectra were determined with a SPECORD M80 infrared spectrophotometer. Mass spectra were determined on a GC/MS HP 5890/ HP 5971A spectrometer at an ionisation potential of 1800 eV. Gas chromatographic analyses were performed on a Hewlett Packard 5890 instrument using HP-5 (30 m x 0.31 mm) column. The compositions of product mixtures presented in Table were determined by gas chromatographic analyses.

General Procedure for Metal-Ammonia Reduction of Chromenes.

All the reactions were carried out under slight pressure of dry nitrogen.

Method A. The metal was added in pieces for 5 min to a solution of 2,2-dimethyl-2H-chromene (8a) or 2,2,4-trimethyl-2H-chromene (8b) (1.2 mmol) in ammonia (50 ml), containing of THF or Et₂O (10 ml) and waterless proton donor (8.4-84 mmol, see Table). After 1 h or when blue colour disappeared, the reaction was quenched by adding aqueous saturated ammonium chloride solution.

Method B. 2,2-dimethyl-2H-chromene (8a) or 2,2,4-trimethyl-2H-chromene (8b) (1.2 mmol) in THF or Et₂O (10 ml) was added dropwise (5 min) to a solution of the metal (6 mmol) in ammonia (50 ml). Quenching was carried out as in method A. The ammonia was evaporated from the reaction mixture and saturated aqueous sodium chloride (10 ml) was added. Products were extracted by ether (3x10 ml). The combined ethereal solutions were washed with saturated aqueous sodium chloride (3x10 ml), and dried over anhydrous magnesium sulphate. Pure products were separated by column chromatography on 230-400 mesh silica gel 60 (Merck) with hexane-benzene-methanol 100:1:1. Products (14b) and (15b) were isolated from the reaction mixture (Entry 15) by column chromatography with hexane-acetone 600:1. Compounds (9a, 10a and 13a) were synthesised another methods.¹⁴,¹⁵

(E)-2-(1,3-Dimethyl-1-butenyl)phenol (9b): oil; nₒ²⁰=1.5205; 'H nmr (CCI₄) δ: 0.83 (d, J=6.5 Hz, 6H, CH(CH₃)₂), 1.88 (s, 3H, C=C(CH₃)), 2.10 (m, 1H, CH(CH₃)₂), 4.92 (s,1H,OH), 5.43 (d, J=10 Hz, 1H, C=CH), 6.50-7.10 (m, 4H, C₆H₄); ir (cm⁻¹): 3540(s,b), 3028(w), 1624(w), 1584(m).
1388(w), 1384(w), 760(s); mass spectrum m/z 176 (M'). Anal. Calcd for C_{12}H_{16}O: C, 81.77; H, 9.15. Found: C, 81.64; H, 8.95.

(Z)-2-(1,3-Dimethyl-1-butenyl)phenol (10b): oil; n\_D^{20}=1.5205; bp 121 °C (19 mmHg); ^1H nmr (CCl\_4:C\_6D\_6) δ: 1.08 (d, J=6 5 Hz, 6H, CH(CH\_3)\_2), 1.90 (d, J=1.5 Hz, 3H, C=CH\_3), 2.74 (d of sept, J=10 Hz and 6 5 Hz, 1H, CH(CH\_3)\_2), 5.32 (s, 1H, OH), 5.39 (d, J=10 Hz, 1H, C=CH), 6.50-7.10 (m, 4H, C\_6H\_4); ir (cm\(^{-1}\)): 3536(s,b), 3032(w), 1612(w), 1588(m), 1388(w), 1384(w), 760(s); mass spectrum m/z 176(M'). Anal. Calcd for C_{12}H_{16}O: C, 81.77; H, 9.15. Found: C, 81.51; H, 9.03.

2-(1,3-Dimethylbutyl)phenol (11b): oil; n\_D^{20}=1.5080; bp 126 °C (18 mmHg); ^1H nmr (CCl\_4) δ: 0.90 (d, J=6 Hz, 6H, CH(CH\_3)\_2), 1.10 (d, J=7 Hz, 3H, CHCH\_2), 1.20-1.66 (m, 3H, CH, CH(CH\_3)), 3.09 (m, 1H, CHCH\_2), 4.73 (s, 1H, OH), 6.50-7.10 (m, 4H, C\_6H\_4); ir (cm\(^{-1}\)): 3484(s,b), 3060(w), 1600(m), 760(w); mass spectrum m/z 178(M'). Anal. Calcd for C_{12}H_{18}O: C, 80.88. Found: C, 80.87; H, 10.18. Found: C, 80.67; H, 10.15.

2-(1,3-Dimethyl-2-butenyl)phenol (12b): oil; n\_D^{20}=1.5340; bp 136 °C (17 mmHg); ^1H nmr (CCl\_4) δ: 1.21 (d, J=7 Hz, 3H, CHCH\_3), 1.62 (s, 6H, C=C(CH\_3)\_2), 3.74 (m, 1H, CHCH\_2), 5.05 (s, 1H, OH), 5.27 (d, J=10 Hz, 1H, CH=C(CH\_3)\_2), 6.50-7.10 (m, 4H, C\_6H\_4); ir (cm\(^{-1}\)): 3460(s,b), 3032(w), 1600(m), 756(s); mass spectrum m/z 176(M') Anal. Calcd for C_{12}H_{16}O: C, 81.77; H, 9.15. Found: C, 82.01; H, 9.19.

3,4-Dihydro-2,2,4-trimethyl-2H-1-benzopyran (13b): oil; n\_D^{20}=1.5135; bp 114 °C (22 mmHg), ^1H nmr (CCl\_4) δ: 1.27 (d, J=7 Hz, 3H, CHCH\_3), 1.15, 1.30 (2s, 6H, C(CH\_3)\_2), 1.40-1.90 (m, 2H, CHCH\_2), 2.60-3.10 (m, 1H, CHCH\_2), 5.60-6.10 (m, 4H, C\_6H\_4); ir (cm\(^{-1}\)): 3076(w), 3048(w), 1616(m), 1588(m), 1216(s), 756(s); mass spectrum m/z 176(M') Anal. Calcd for C_{12}H_{18}O: C, 80.88. Found: C, 81.77; H, 9.15. Found: C, 82.01; H, 9.19.

3,4,5,6-Tetrahydro-2,2,4-trimethyl-2H-1-benzopyran (14b): oil; n\_D^{20}=1.4915; ^1H nmr (CCl\_4:C\_6D\_6) δ: 1.01 (d, J=7 Hz, 3H, CHCH\_3), 1.18, 1.27 (2s, 6H, C(CH\_3)\_2), 1.40-1.80 (m, 2H, CHCH\_2), 1.80-2.40 (m, 1H, CHCH\_2), 2.64 (m, 4H, CH\_2CH=CHCH\_2), 5.64 (s, 2H, CH=CH); ir (cm\(^{-1}\)): 3045(w), 1708(m), 1668(m), 1228(m), 1160(s); mass spectrum m/z 178(M') Anal. Calcd for C_{12}H_{18}O: C, 80.88; H, 10.18. Found: C, 81.32 H, 10.25.

3,4,5,6,7,8-Hexahydro-2,2,4-trimethyl-2H-1-benzopyran (15b): oil; n\_D^{20}=1.4790 ^1H nmr (CCl\_4:C\_6D\_6) δ: 0.99 (d, J=7 Hz, 3H, CHCH\_3), 1.15, 1.25 (2s, 6H, C(CH\_3)\_2), 1.37-2.50 (m, 11H,
CH₂CH₂CH₂CH₂. CH-CH₃); ir (cm⁻¹): 1688(m), 1224(m), 1160(s); mass spectrum m/z 180(M⁺)

2-(3-Methylbutyl)phenol (11a): oil; nD₂₀=1.5065 (lit., 1.510).

2-(3-Methyl-2-butenyl)phenol (12a): oil, nD₂₀=1.5385 (lit., 1.538).

3.4-Dihydro-2,2-dimethyl-2H-1-benzopyran (13a): oil; nD₂₀=1.5235 (lit., 1.524).

3.4,5,8-Tetrahydro-2,2-dimethyl-2H-1-benzopyran (14a): oil, nD₂₀=1.4950; 'H nmr (CDCl₃) δ:
1.27 (s, 6H, C(CH₃)₃), 1.40-2.00 (m, 4H, CH₂CH₂), 2.67 (s, 4H, CH₂CH=CHCH₂), 5.71 (s, 2H, CH=CH); ir (cm⁻¹): 3048(w), 1716(m), 1668(w), 1228(m), 1164(s); mass spectrum m/z 164(M⁺).

**Procedure for reduction of coumarins**

The sodium (0.144 g, 6.25 mmol) was added at -78 °C to a solution of coumarin or 4-methylcoumarin (0.183 or 0.200 g, 1.25 mmol) in ammonia (50 ml) containing THF (10 ml) and EtOH (0.5 ml). After workup in the same manner as described in procedure for reduction of chromenes, products were separated by column chromatography on 230-400 mesh silica gel 60 (Merck) with hexane-ethyl acetate 2:1. Pure phenols (5a) (0.17 g, 90%) and (5b) (0.17 g, 84%) were obtained.

2-(3-Hydroxypropyl)phenol (5a): oil; nD₂₀=1.5590 (lit., 1.55984).

2-(3-Hydroxy-1-methylethyl)phenol (5b): oil; nD₂₀=1.5395; 'H nmr (CDCl₃) δ: 1.29 (d, J=7 Hz, 3H, CH₃), 1.40-2.20 (m, 2H, CH(CH₃)CH₂), 3.20-3.90 (m, 4H, CH₂OH), 6.80-7.30 (m, 4H, C₆H₄); ir (cm⁻¹): 3324(s,OH), 1608(m), 1594(m), 754(s).

3-(2-Hydroxyphenyl)butylamide (6b). 4-Methylcoumarin (2 g, 12.5 mmol) in THF (30 ml) was added to a solution of the sodium (0.72 g, 31.3 mmol) in 100 ml of ammonia (-33°C). After 1 h the reaction was quenched by adding anhydrous ammonium chloride. The ammonia was evaporated in atmosphere of dry nitrogen, ether (100 ml) was added and the mixture was refluxed for 1 h. The organic layer was filtered. After removal of ethyl ether in vacuum, product (6b) was purified by column chromatography on silica gel with hexane-ethyl acetate-ethyl alcohol 10:6:1. Pure amide (6b) (0.38 g, 17.1%) was isolated as a solid: mp 105-106 °C (C₆H₆); 'H nmr (acetone - d₆) δ: 1.26 (d, J=7 Hz, 3H, CH₃), 2.53 (d, J=8 Hz, 2H, CH₂), 3.39-3.81 (m, 1H, CH), 6.80-7.20 (m, 4H, C₆H₄).
ir (cm⁻¹): (nujol) 3340(m), 3160(w), 1660(s), 1604(s), 768(s).

REFERENCES


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