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STUDIES ON METAL–AMMONIA REDUCTION AND REDUCTIVE METHYLATION OF NAPHTHALENES

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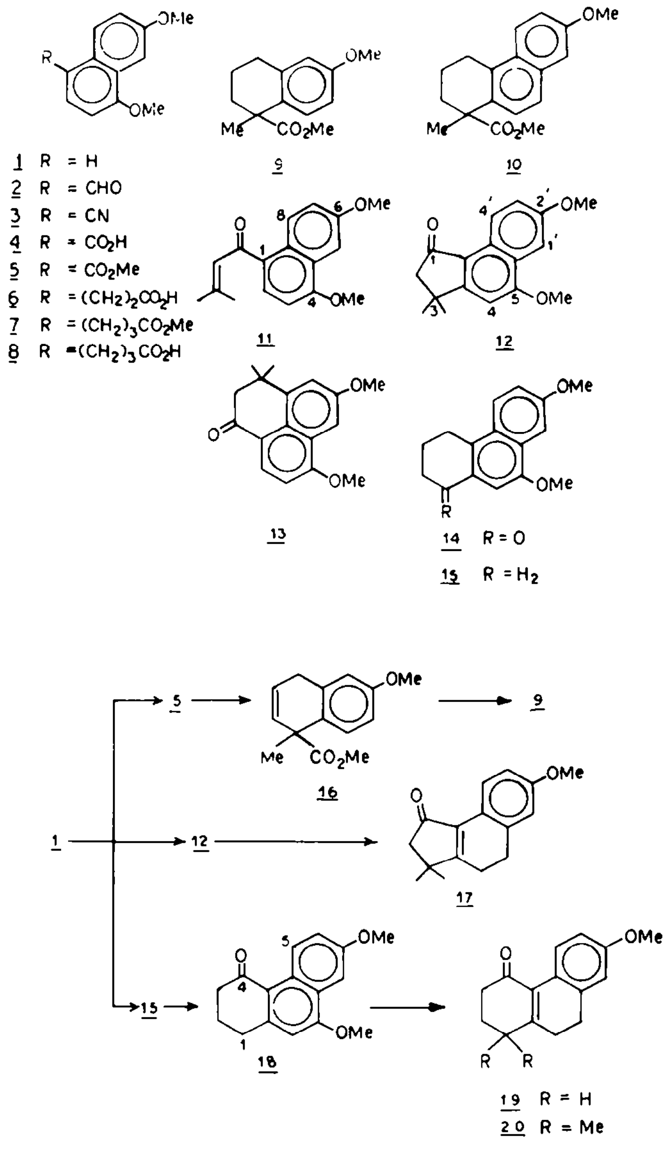
Abstract—Reductive methylation of 1-carbomethoxy-4, 6-dimethoxynaphthalene in anhydrous ammonia gave 1-methyl-1-carbomethoxy-6-methoxy-1, 4-dihydronaphthalene in good yield. Metal ammonia reduction of the ketones **12** and **18** provided an expedient pathway for the synthesis of the α, β-unsaturated ketones **17** and **19** respectively.

In connection with our interest in resin acids and other tricyclic diterpenes, we were seeking (i) a practical method for the incorporation of geminal methyl–methoxycarbonyl substituents at C-1 on a suitable bicyclic (e.g. **9**) or tricyclic (e.g. **10**) skeleton and (ii) convenient methods for the preparation of hydrophenanthrones (e.g. **19** and **20**) and benzhydrindenones (e.g. **17**) as potential intermediates. It appeared to us that metal–ammonia reduction and reductive methylation of appropriate substrates incorporating naphthalene nucleus might lead to the desired compounds, since 11-oxoequilenin derivatives are reduced[1] with Na and EtOH in liquid ammonia to α, β-unsaturated ketones in good yield. We have now realised some of our objectives and we wish to report the results of our studies on the (i) metal–ammonia reduction of two α-naphthyl ketones **12** and **18** and (ii) reductive methylation of the α-naphthoic ester **5**. All three compounds **12**, **18** and **5** containing the naphthalene nucleus were prepared from a common starting material **1** (Scheme 1) and each carries a methoxy group at the para position with respect to the carbonyl or carbomethoxyl group. When the ketones **12** and **18** were subjected to reduction with excess of Na and EtOH in distilled liquid ammonia, the α, β-unsaturated ketones **17** and **19** were obtained in one step in 83.5% and 81% yields respectively. The reduction involved hydrogenolysis of the p-methoxy group and concomitant reduction of the aromatic ring to which the carbonyl group was attached (Scheme 2). Further reduction of the enone system as well as of the other aromatic ring was prevented due to the formation of an anion (e.g. **21**, Scheme 2) in the reaction medium until work-up.[2] Similarly, reductive methylation of the α-naphthoic ester **5** in distilled liquid ammonia proceeded cleanly to give the unsaturated ester **16** in 78% yield with complete loss of the p-methoxy group (a carbonyl group often facilitates such hydrogenolysis[3] during Birch reduction). Catalytic hydrogenation of **16** yielded **9** in almost quantitative yield.

1, 7-Dimethoxynaphthalene **1**, a commercially available compound, was chosen as the starting material for the present studies since it readily undergoes Vilsmeier and Friedel–Crafts reaction mostly at the para-position[4,5] with respect to the 1-methoxy group. Thus the aldehyde **2**,[4] prepared from **1** in 60% yield, was converted into the methyl ester **5** through the nitrile **3** and the acid **4**. Friedel–Crafts reaction of **1** with β, β-dimethylacryloyl chloride in the presence of anhydrous $AlCl_3$ yielded a mixture of products from which three compounds **11**, **12** and **13** could be isolated in 33, 35 and 2.5% yields respectively through crystallisation and column chromatography. The structures of the products were ascertained from their spectral data. All three compounds showed strong carbonyl absorption in the IR characteristic of aromatic ketones. ^1H-NMR of compound **11** showed the presence of an olefinic proton (δ 6.45 ppm) as well as of two vinyl methyl groups (δ 1.93 and 2.15 ppm) supporting the assigned structure. The products **12** and **13** did not show any olefinic proton or vinyl methyl group but could be distinguished clearly from the ^1H-NMR splitting pattern of the aromatic hydrogens. The C-4′ aromatic hydrogen of **12** appeared as a doublet at a very low field (δ 9.01 ppm) which is a characteristic feature for compounds analogous to **12** (C-8 aromatic hydrogen of **11** and C-5 aromatic hydrogen of **18** also appeared as low field doublets in their respective NMR spectra). The C-4 aromatic hydrogen of **12** appeared as a sharp singlet (δ 6.77 ppm) further supporting the structure. ^1H NMR of **13**, on the other hand, indicated the presence of two ortho-coupled and two meta-coupled protons only. The α, β-unsaturated ketone **11** underwent cyclisation on treatment with 89% H_3PO_4 to give the indanone derivative **12** in 58% yield. On treatment with anhydrous $AlCl_3$ in CS_2 **11** furnished a mixture consisting of **11**, **12** and **13** as indicated from VPC and NMR spectrum of the reaction product. The ketone **18** was prepared from a known compound **15** through benzylic oxidation with CrO_3. The reported procedure[5] for the preparation of **15** involves succinoylation of **1** and requires fractional crystallisation at an intermediate stage and two carbonyl removal steps. For the present work, however, **15** was prepared from the easily accessible acid **6**.[6] The acid **6** was converted into the corresponding diazomethyl ketone which underwent rearrangement to the homologous methyl ester **7** in 74% overall yield on treatment with silver benzoate in MeOH in the presence of Et_3N.[7] Hydrolysis of **7** with 10% meth-

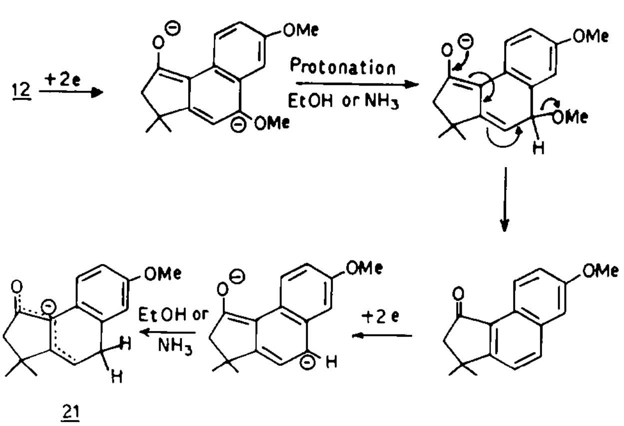


Scheme 1.

anolic KOH followed by intramolecular cyclisation of the resulting acid **8**, with polyphosphoric acid at 80° for 10 min afforded the ketone **14** in 72% yield. Reduction of **14** with $NaBH_4$ followed by catalytic hydrogenation of the crude product in AcOH gave rise to **15**[5] in 75% overall yield. Oxidation of **15** with CrO_3 did not give a satisfactory yield of **18**. However, as the main concern of the present study was the metal-ammonia reduction, no attempt was made to optimise the yield at the oxidation stage.

Since 1-methoxynaphthalene nucleus permits incorporation of carbonyl substituents at the 4-position either through Friedel–Crafts and related reactions or through benzylic oxidation and these α-naphthyl compounds are cleanly and efficiently reduced in one step to the dihydronaphthalene derivatives with the loss of the p-methoxy group with Na and EtOH in distilled liquid ammonia, the present method constitutes a simple synthesis of compounds which would be otherwise difficult to obtain. Application of this useful method for the synthesis of the ring systems of complex organic molecules appears promising. We are currently investigating reductions and alkylations of the α, β-unsaturated ketones **17** and **19** as well as conjugate additions on them under different experimental conditions. We have recently reported[8] very high stereo-selectivity in the reductive methylation of the α, β-unsaturated ketone **20** (prepared from 2-acetyl-6-methoxynaphthalene). Complete stereoselectivity has also been observed by us (unpublished results) during reductive alkylations of the unsaturated ketone **17**. The ketone **17** promises to be a useful intermediate for the synthesis of the colensenone group of diterpenoids[9] as well as for the synthesis of compounds containing propellane ring systems.[10]

As a new approach to hydrophenanthrene nucleus present in natural products, Trost *et al.* recently

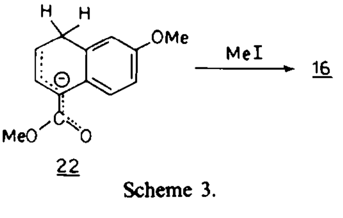


Scheme 2.

performed an alternative synthesis[11] of the α, β-unsaturated ketone **19** following a procedure which involves thionium ion and epoxy ketone cyclisations.

For synthetic entry into the ring systems of diterpenoid resin acids, we are investigating an extension of the method presently used for the preparation of **16**. Although reductive alkylations of aromatic acids have been investigated extensively, we found it more convenient to use the ester **5** than the acid **4** due to greater solubility of the ester. Reductive alkylations of several benzoic esters have recently been reported by Mander *et al.*[12]

Metal-ammonia reduction of α-naphthylalkyl ketones was first observed by Mejer *et al.*[13] and subsequently reported by other workers also. Our results, however, illustrate for the first time that similar reductions to α, β-unsaturated ketones can be accomplished in one step in distilled liquid ammonia even if a p-methoxy group (which might sometimes offer distinct advantage in the preparation of the substrates) is present in the molecule. Mechanism for the reductive removal of the p-methoxy group and simultaneous reduction of the aromatic ring might involve stepwise addition of electrons and protons as outlined in Scheme 2. Similarly, reductive methylation of the ester **5** probably proceeds through the enolate anion **22** to give rise to **16** (Scheme 3).



Scheme 3.

EXPERIMENTAL

Mps were taken for samples in open capillaries. UV spectra were recorded for solutions in 95% EtOH with Beckmann DU spectrophotometer, and IR spectra with a Perkin–Elmer 298 instrument. NMR spectra were determined with a Varian T-60 spectrophotometer (TMS as internal standard). For GLC, a Hewlett-Packard 5730 gas chromatograph with flame ionisation detector was used. Extracts were dried over Na_2SO_4. Light petroleum refers to the fraction of b.p. 60–80°.

1-Cyano-4, 6-dimethoxynaphthalene **3**

A mixture of the aldehyde **2** (2.2 g), $NH_2OH \cdot HCl$ (800 mg), NaOAc (1.7 g) and formic acid (15 ml) was refluxed[14] under N_2 for 1 hr. The mixture was cooled, diluted with water (30 ml) and neutralised with solid Na_2CO_3. Extraction with ether followed by crystallisation from MeOH afforded **3** (1.8 g, 83%), m.p. 133–134° ν_{max} (KBr) 2220, 1625, 1580 cm^{-1}; $\delta(CDCl_3)$ 3.97 (s, 3H), 4.07 (s, 3H), 6.8 (d, 1H, J = 8 Hz), 7.32 (d of d, 1H, J = 9, 3H), 7.58 (d, 1H, J = 3 Hz), 7.7 (d, 1H, J = 8 Hz), 8.08 (d, 1H, J = 9 Hz). (Found: C, 73.12; H, 5.46; N, 6.71. $C_{13}H_{11}NO_2$ requires: C, 73.23; H, 5.20; N, 6.57%).

4, 6-Dimethoxy-1-naphthoic acid **4**

A mixture of **3** (500 mg), KOH (85%, 2 g), water (5 ml) and ethylene glycol (5 ml) was refluxed under N_2 for 10 h. Usual work-up afforded **4** (460 mg, 84.5%), mp 238–239° (MeOH); ν_{max} (KBr) 1680, 1625, 1580 cm^{-1}. (Found: C, 67.19; H, 5.35; $C_{13}H_{12}O_4$ requires: C, 67.23; H, 5.21%).

Methyl 4-6-dimethoxy-1-naphthoate **5**

A mixture of **4** (400 mg), MeOH (10 ml) and conc H_2SO_4 (1 ml) was refluxed for 12 h. Usual work-up afforded **5** (370 mg, 87%), mp 110–111° (light petroleum); ν_{max} ($CHCl_3$) 1715, 1630, 1595 cm^{-1}; $\delta(CDCl_3)$ 3.94 (s, 3H), 3.96 (s, 3H), 4.02 (s, 3H), 6.73 (d, 1H, J = 8 HZ) 7.27 (m, 1H), 7.58 (d, 1H, J = 3 Hz), 8.07 (d, 1H, J = 8 Hz), 8.96 (d, 1H, J = 9 Hz). (Found: C, 68.29; H, 5.95. $C_{14}H_{14}O_4$ requires: C, 68.28; H, 5.73%).

1-Carbomethoxy-1-methyl-6-methoxy-1, 4-dihydronaphthalene **16**

Sodium metal (150 mg) was added in small pieces to distilled liquid ammonia (80 ml) with stirring. A solution of **5** (300 mg) in THF (15 ml) was then added to the resulting deep blue soln during 2 min. The mixture was stirred for another 3 min and then MeI (1 ml) was added. After the disappearance of the blue colour, ammonia was allowed to evaporate. The residue was diluted with water and worked-up with ether. The crude product was filtered through neutral alumina (4 g). Elution with benzene–light petroleum (1:4) followed by evaporative distillation at 130°/0.5 mm furnished **16** (220 mg, 78%), ν_{max} (film) 1730, 1610 cm^{-1}; $\delta(CDCl_3)$ 1.62 (s, 3H), 3.33–3.5 (m, 2H), 3.63 (s, 3H), 3.8 (s, 3H), 5.63–6.17 (m, 2H), 6.67–6.87 (m, 2H), 7.24 (d, 1H, J = 9 Hz). (Found: C, 72.63; H, 7.12. $C_{14}H_{16}O_3$ requires: C, 72.39; H, 6.94%).

1-Carbomethoxy-1-methyl-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene **9**

A soln of **16** (180 mg) in MeOH (10 ml) was hydrogenated over Pd–C (10%, 50 mg) for 1 h. Filtration and removal of the solvent afforded a residue which was evaporatively distilled at 130°/0.5 mm to furnish **9** (170 mg, 94%), ν_{max} (Film) 1730, 1610 cm^{-1}; δ(CDCl$_3$) 1.54 (s, 3H), 1.65–2.88 (m, 6H), 3.66 (s, 3H), 3.78 (s, 3H), 6.62–6.82 (m, 2H), 7.18 (d, 1H, J = 9 Hz). (Found: C, 71.96; H, 7.93. $C_{14}H_{18}O_3$ requires: C, 71.77; H, 7.74%).

Friedel–Crafts reaction of 1, *7-dimethoxynaphthalene* **1** *with* β,β*-dimethyl-acryloyl chloride: formation of the ketones* **11**, **12** *and* **13**

To an ice-cooled and stirred soln of **1** (2 g) and β,β-dimethylacryloyl chloride (1.3 g) in CS_2 (15 ml) was added anhyd $AlCl_3$ (2.8 g) in small portions during 20 min. The mixture was stirred in the cold for 3 h and then left at room temp for another 2 h, poured on ice, and treated with cold dil HCl. The product was extracted with chloroform. The extracts were washed with sat. $NaHCO_3$ aq, water and dried. After the removal of the solvent, the residue was evaporatively distilled at 170°/0.1 mm to afford a semisolid material (2.6 g). Crystallisation of this material from light petroleum afforded **12** (1 g, 35%), mp 165°; λ_{max} 221 (log ϵ 4.58), 250 (log ϵ 4.78), 310 (log ϵ 4.16), 342 (log ϵ 4.02), 355 nm (log ϵ 4.04); ν_{max} (KBr) 1682, 1592, 1580, 1510 cm^{-1}; δ(CDCl$_3$) 1.45 (s, 6H), 2.63 (s, 2H), 3.91 (s, 3H), 4.09 (s, 3H), 6.77 (s, 1H), 7.27 (m, 1H), 7.54 (d, 1H, J = 3 Hz), 9.01 (d, 1H, J = 9 Hz). (Found: C, 75.58; H, 6.81. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%).

The mother liquor from **12** was evaporated and the residue was chromatographed over silica gel (50 g). Elution with ether: light petroleum (4:96) afforded the α,β-unsaturated ketone **11** (900 mg, 33%), b.p. 170° (bath temp)/0.1 mm; λ_{max} 256 (log ϵ 4.48), 318 (log ϵ 4.0), 345 nm (log ϵ 4.01); ν_{max} (Film) 1660, 1620, 1610, 1580, 1512 cm^{-1}; δ(CCl$_4$) 1.93 (d, 3H, J = 1 Hz), 2.15 (d, 3H, J = 1 Hz), 3.87 (s, 3H), 3.92 (s, 3H), 6.45 (m, 1H), 6.54 (d, 1H, J = 9 Hz), 7.11 (d of d, 1H, J = 9, 3 Hz), 7.4 (d, 1H, J = 3 Hz), 7.49 (d, 1H, J = 9 Hz), 8.57 (d, 1H, J = 9 Hz). (Found: C, 75.29; H, 6.60. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%).

Further elution with Et_2O-light petroleum (1:19) afforded mixtures of **12** and **13** in varying proportions (GC retention times for pure **12** and **13** on 10% UCW-982 column at 160° were 25.19 and 27.36 min respectively). Eight such fractions were collected. Repeated crystallisations of the last three fractions from light petroleum afforded the pure ketone **13** (70 mg, 2.5%), m.p. 124°; λ_{max} 224 (log ϵ 4.35), 254 (log ϵ 4.52), 324 (log ϵ 3.96), 346 nm (log ϵ 3.98); ν_{max} (KBr) 1672, 1620, 1585, 1505 cm^{-1}; δ(CDCl$_3$) 1.43 (s, 6H), 2.77 (s, 2H), 3.93 (s, 3H), 4.06 (s, 3H), 6.88 (d, 1H, J = 8 Hz), 7.25 (d, 1H, J = 3 Hz), 7.44 (d, 1H, J = 3 Hz), 8.05 (d, 1H, J = 8 Hz); *m/e* 270 (M$^+$). (Found: C, 75.46; H, 6.99. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%).

Cyclisation of the α,β*-unsaturated ketone* **11** *with* H_3PO_4

A mixture of **11** (100 mg) and H_3PO_4 (89%, 0.7 ml) was stirred at room temp for 1.5 h and then at 85° for 1.5 h. The mixture was cooled, diluted with water and extracted with ether. The extracts were washed with sat $NaHCO_3$, water and dried. After the removal of the solvent, the residue was evaporatively distilled at 170°/0.1 mm to afford a colourless solid product which on crystallisation from light petroleum furnished **12** (58 mg, 58%), mp and mmp 165°.

Sodium–liquid ammonia reduction of 3, 3*-dimethyl-2′, 5-dimethoxy-6:7-benzindan-1-one* **12**; *formation of the benzhydrindenone derivative* **17**

A soln of **12** (200 mg) in dry THF (10 ml) and abs EtOH (1.6 ml) was added with stirring to distilled liquid ammonia (70 ml). Sodium metal (140 mg) was then added in small pieces within 1 min. After the disappearance of the blue colour (3 min), NH_4Cl (1 g) was added and ammonia was allowed to evaporate. The residue was diluted with water and extracted with ether. The extracts were washed with water and dried. Evaporation of the solvent left a solid residue which was crystallised from light petroleum to afford **17** (150 mg, 83.5%), m.p. 87–88°; λ_{max} 246 (log ϵ 4.35), 290 nm (log ϵ 3.93); ν_{max} (KBr) 1690, 1605, 1498 cm^{-1}; δ(CDCl$_3$) 1.27 (s, 6H), 2.42–2.97 (m, 6H), 3.8 (s, 3H), 6.67–6.87 (m, 2H), 8.17 (d, 1H, J = 9 Hz). (Found: C, 79.23; H, 7.67. $C_{16}H_{18}O_2$ requires: C, 79.31; H, 7.49%).

7, 9*-Dimethoxy-4-keto-*1, 2, 3, 4*-tetrahydrophenanthrene* **18**

A soln of CrO_3 (360 mg) in 80% AcOH (1.8 ml) was added dropwise at room temp to a stirred soln of **15**[5] (300 mg) in benzene (0.5 ml) and glacial AcOH (3.5 ml). After the addition the mixture was stirred at room temp for another 20 h, then poured on ice and extracted with ether. The extracts were washed with 5% NaOH aq, water and dried. Evaporation of the solvent left a residue which was chromatographed over silica gel (8 g). Elution with light petroleum–ether (9:1) furnished the desired ketone **18** (70 mg, 22%), m.p. 138–139° (acetone–light petroleum); ν_{max} (KBr) 1660, 1605 cm^{-1}; δ(CDCl$_3$) 1.96–2.32 (m, 2H), 2.56–3.12 (m, 4H), 3.89 (s, 3H), 4.02 (s, 3H), 6.54 (s, 1H), 7.22 (m, 1H), 7.51 (d, 1H, J = 3 Hz), 9.38 (d, 1H, J = 9 Hz). (Found: C, 74.82; H, 6.51. $C_{16}H_{16}O_3$ requires: C, 74.98; H, 6.29%).

7*-Methoxy-4-keto-*1, 2, 3, 4, 9, 10*-hexahydrophenanthrene* **19**

To an efficiently stirred mixture of distilled liquid ammonia (50 ml), and a soln of **18** (50 mg) in THF (5 ml) and abs EtOH (0.5 ml), was added Na metal (40 mg). After the disappearance of the blue colour (3 min), NH_4Cl (1 g) was added and ammonia was evaporated. The residue was diluted with water and worked up with ether to afford the α,β-unsaturated ketone **19** (36 mg, 81%), m.p. 108° (from Et_2O–light petroleum; lit[11] m.p. 108–108.5°); λ_{max} 246 (log ϵ 4.17), 290 (log ϵ 3.69), 310 nm (log ϵ 3.61); ν_{max}(KBr) 1660, 1610, 1598, 1492 cm^{-1}; δ(CDCl$_3$) 1.82–2.85 (m, 10H), 3.8 (s, 3H), 6.67–6.87 (m, 2H), 8.02 (d, 1H, J = 9 Hz). (Found: C, 78.78; H, 7.27. $C_{15}H_{16}O_2$ requires: C, 78.92; H, 7.06%).

Acknowledgements—We are grateful to Prof. B. M. Trost of the University of Wisconsin USA for providing ^{1}H-NMR (270 MHz) comparison of the α,β-unsaturated ketone **19** with that of an authentic sample.

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