SYNTHESIS OF A REDUCED NEOPROAPORPHINE

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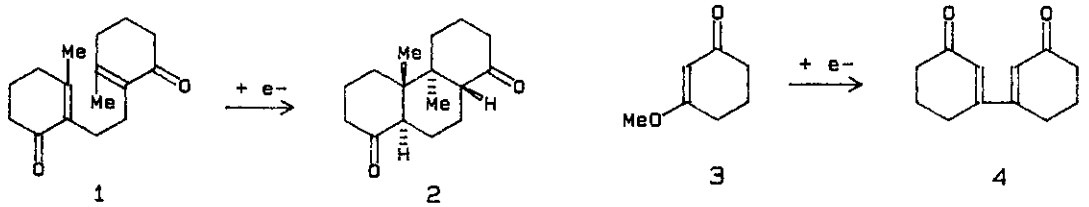
Abstract - Hydrolysis of the Birch reduction product from a 1-benzyltetrahydroisoquinoline, 8, affords a novel reduced neoproaporphine skeleton, 16. The formation of 16 is believed to proceed by initial formation of an intermediate bis-enone, 5, followed by an intramolecular Michael addition.

INTRODUCTION

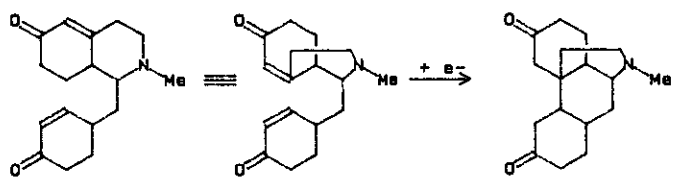
During the course of our investigations in electrosynthesis, we have prepared a reduced neoproaporphine. Our primary focus had been to use electrochemical reduction for establishing carbon-carbon bonds. For example, we have found[4,5] that it is possible to effect the following electrochemical coupling reactions:



1 2 3 4

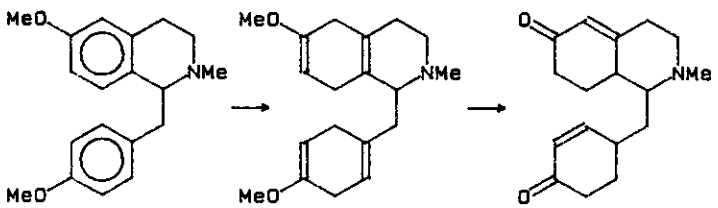
Ref 4 Ref 5

In an effort to extend this reaction for the construction of ring systems related to the morpholine alkaloids, we undertook the synthesis of the diene-dione, 5. Reductive electrochemical coupling on 5 would be expected to produce 6 in a manner analogous to the conversion of 1 to 2.



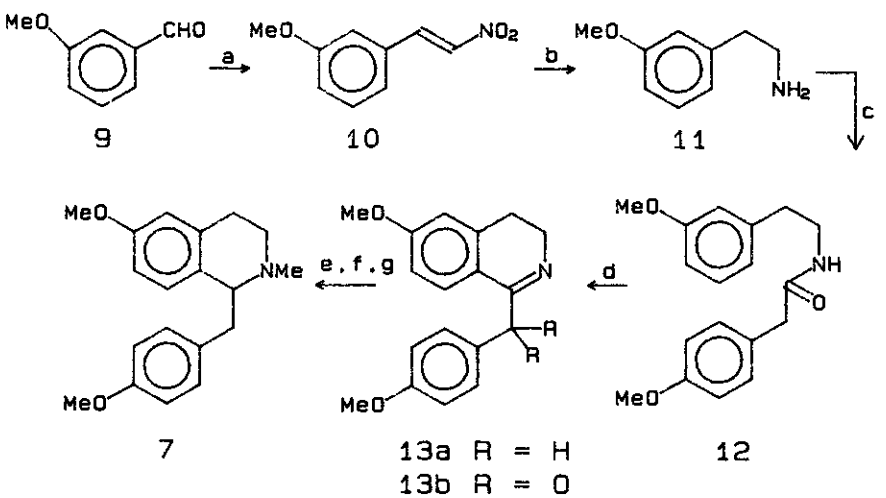
5 5 6

A likely route for the preparation of 5 appeared to entail the Birch reduction of 1-(4-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline, 7. It was anticipated that the resulting reduction product, 8, could be hydrolyzed to the desired conjugated bis-enone, 5.



RESULTS

We prepared 7 following a modification of a procedure reported by Sasaki, Olniski and Satoh[6]. The pathway is shown below. The only ambiguity in this sequence is the Bischler-Napieralski cyclization of 12 to give the dihydroisoquinoline derivative, 13a. The actual regiochemistry was established[6] by oxidative degradation to 4-methoxyphthalic acid, the expected degradation product if the cyclization occurs para to the methoxy groups as shown. Furthermore, the dihydrobenzylisoquinoline, 13a, is air sensitive, especially in the presence of base and must be isolated rapidly or it will undergo benzylic oxidation[7] to give, as the exclusive product, 1-(4-methoxybenzoyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline[6], 13b.

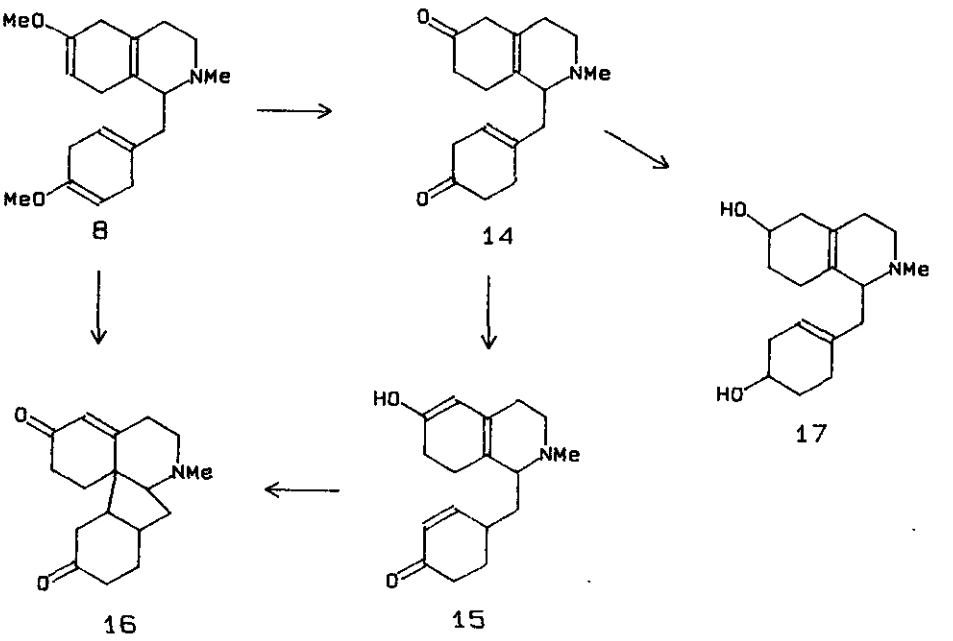


Reagents: a[13], CH_3NO_2/NaOH; b[14], LAH/H_2SO_4; c[15], 4-methoxyphenylacetic acid/xylene; d[16], $POCl_3$; e[17], HCl; f, $NaBH_4$; g, HCO_2H/H_2CO

We were able to attain reduction of both rings[8], 7 to 8, using lithium in liquid ammonia with tert-butyl alcohol as the proton source[9]. The tetraene compound, 8, was isolated, purified, and characterized. The purified or crude material, when subjected to a number of hydrolysis procedures designed to prepare 5, gave, instead, a complex mixture of products. The only product that was isolated and characterized had a structure consistent with the reduced neoproaporphine[10], 16.

DISCUSSION

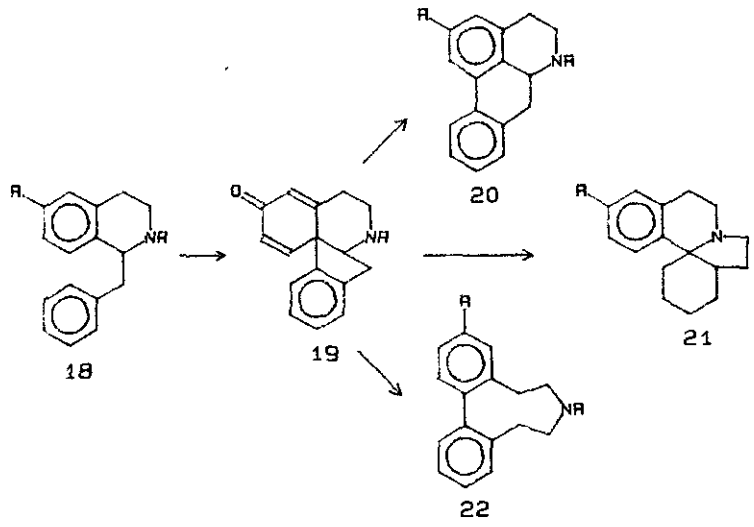
It was possible, with freshly prepared solutions of saturated $KHSO_4$ (room temperature, 35 min), to isolate the bis-β,γ-unsaturated diene-dione, 14. The structure of 14 was assigned on the basis of its spectral properties, (IR, nonconjugated carbonyl, 1709cm^{-1}; H-NMR, olefinic proton multiplet, δ = 5.67 ppm; U.V., no α,β-unsaturated carbonyl absorption). All attempts to convert the labile 14 into diene-dione 5 resulted in formation of the tetracyclic compound 16. We were able to isolate the corresponding diol, 17, by lithium aluminum hydride or sodium borohydride reduction, as shown below.



The structure of 16 was established on the basis of spectral properties [IR, nonconjugated carbonyl, 1701cm^{-1}; α,β-unsaturated carbonyl, 1672cm^{-1}; H-NMR, olefinic proton resonance at δ5.9 ppm; UV, λ max at 240 nm (ε = 14,780) in 95% ethanol; C-NMR α,β-unsaturated carbonyl moiety, 126.23 (d), 163.82 (s), 197.80 (s); and, a nonconjugated carbonyl, 212.57 (s)] and mechanistic rationalization.

Formation of 16 is the product of an intramolecular Michael addition reaction between the two enone functionalities. This reaction is consistent with enolization to form the more substituted enol and subsequent attack of that extended enol on the less substituted enone, 15 to 16, as drawn on the previous page. No conditions were found in which 8 or 14 were stable. In fact, a sample of 8 that was stored in a glass sample vial in a refrigerator for two months underwent partial hydrolysis and cyclization to form 16. Further, 14 was converted into 16 (the only isolated product) upon treatment with dilute acid, dilute base, solution in ethanol, exposure to light as discovered during an attempted photooxygenation, or standing neat at room temperature.

The apparent ease of formation of 16 offers a nice contrast with the synthesis of the related neoproaporphins, 19. Neoproaporphins are biogenetically derived from tetrahydrobenzylisoquinolines, 18, and are biogenetic precursors to aporphine, 20, erythrina, 21, and dibenzazonine, 22, alkaloids.[9] These relationships have been demonstrated synthetically.[11] Analogous chemistry of reduced neoproaporphines has yet to be investigated.[12]



EXPERIMENTAL

Unless stated otherwise, extractions were dried with anhydrous sodium sulfate, evaporations were performed on a Buchi rotary evaporator, and all solvents were reagent grade. H-NMR spectra were obtained on a Varian EM-360L in $CDCl_3$ referenced to tetramethylsilane internal standard. C-NMR spectra were obtained on a Varian CFT-20 in $CDCl_3$ referenced to tetramethylsilane internal standard. IR spectra were obtained on a Perkin Elmer 710B in $CHCl_3$ solutions with .05mm sodium chloride plates and reference cell, calibrated to a polystyrene thin film. UV spectra were obtained on a Cary-14 spectrophotometer. Melting points were recorded on Thomas-Hoover and Mel-Temp capillary apparatus and are uncorrected. CHN analysis were performed by Atlantic Micro Labs, Inc.. Mass spectra were recorded on a Finnegan GC-MS, Model 4000.

Birch Reduction of N-Methyltetrahydroisoquinoline to Prepare 8 - In a 250 ml flame dried, round bottom flask were placed 1.53 g (5.14 mmol) of 7 and 30 ml of THF (fresh histological grade) and 12 ml of tert-butanol (from molecular sieves). Into the round bottom flask, equipped with a cold finger, mechanical stirrer, and addition funnel was distilled 30 ml of ammonia (from Na). Then, 1.38 g (0.20 mole) of lithium rod (cut into small pieces and dipped in hexanes) was added to the reaction with stirring. The solution was approximately 2.8 M in Li and had a top bronze colored layer. The reaction was stirred under reflux for 25 min and then treated with dropwise addition of 1:1 ethanol:tert-butanol solution until the blue color faded (≃ 50 ml of alcohol solution). Stirring was continued for 4 1/2 h while the ammonia evaporated. Then the reaction was diluted with 250 ml of water and extracted with ether (6 x 75 ml). The ether was washed with brine, dried and evaporated. It was placed under vacuum to yield (96%) 1.50 g (4.93 mmol) of yellow powdery solid, 8, mp 80.5-89°C. The product was recrystallized from 1:1 ether:hexane under nitrogen to yield (47% from 7) 0.73 g (2.42 mmol) of 8, mp 92-95°C. After drying in a vacuum dessicator, a sample, mp 93-94.5°C, was used for CHN analysis. CHN analysis for $C_{19}H_{27}NO_2$: C calc. 75.69, found 75.77; H calc. 9.05, found 9.07; N calc. 4.65, found 4.61. H-NMR δ 5.55 (s, 1H), δ 4.70 (s, 2H), δ 3.6 (s, 6H), δ 1.5-3.1 (m, 15H), δ 2.45 (s, 3H); IR, 2976 cm^{-1} (s), 2924 cm^{-1} (s), 2875 cm^{-1} (s), 1587 cm^{-1} (s), 1451 cm^{-1} (m), 1186 cm^{-1} (s). An IR of a sample that had been stored 2 months in a refrigerator showed partial hydrolysis and cyclization to form 16: 2976 cm^{-1} (m), 2924 cm^{-1} (m), 2875 cm^{-1} (m), 1709 cm^{-1} (w), 1681 cm^{-1} (m), 1471 cm^{-1} (m), 1464 cm^{-1} (m), 1399 cm^{-1} (m), 1235 cm^{-1} (broad, m), 1176 cm^{-1} (s).

Hydrolysis and Closure to Form Reduced Neoproaporphine 16 - In a 50 ml round bottom flask under nitrogen with a magnetic stirrer were placed 1.14 g (3.78 mmol) of 8 and 22 ml of 14% methanesulfonic acid. The reaction was stirred under N_2 for 20 h, extracted with benzene (1 x 15 ml) and then basicified with conc NH_4OH. The basic reaction mixture was extracted with benzene (4 x 20 ml) and the benzene extracts washed with a solution containing 50 ml of H_2O, 2.5 g of $NaHCO_3$ and 12 g of NaCl. Then the organic layer was dried, filtered and evaporated. The oil (1.11 g) could not be induced to crystallize and was chromatographed on silica gel[18]. The major fraction (0.45 g) exhibited considerable streaking on T.L.C. silica with 25% ethyl acetate-hexane (1% isopropanol), with major R_f at 0.2. This fraction, when concentrated in the presence of ethyl acetate was induced to crystallize. The crystals were collected by filtration, washed with hexanes and then redissolved in ethyl acetate and methylene chloride. This solution was placed in a closed bell jar with a pool of hexanes and allowed to crystallize. A yield of 0.14 g (5.12 mmol) of analytical sample of 16 was obtained in this manner, mp 157-159°C.

CHN analysis for $C_{17}H_{23}NO_2$: C calc. 74.68, found 74.49; H calc. 8.50, found 8.49; N calc. 5.12, found 5.08; H-NMR, δ 5.9 (s, 1H), δ 1.9-3.0 (m, 22H); IR 3030 cm^{-1} (w), 2985 cm^{-1} (m), 2875 cm^{-1} (w), 1701 cm^{-1} (s), 1672 cm^{-1} (s), 1471 cm^{-1} (w), 1379 cm^{-1} (w), 1282 cm^{-1} (m), 1235 cm^{-1} (broad, m); mass spec m/e 273. (m^+); UV (95% ethanol) λ 240 nm, ε 14,780; C-NMR, δ 27.2 (m), δ 31.23 (m), δ 33.31 (m), δ 34.69 (m), δ 34.84 (m), δ 35.80 (m), δ 35.80 (m), δ 38.13 (m), δ 39.89 (m), δ 42.18 (s), δ 43.11 (m), δ 49.75 (m), δ 56.41 (m), δ 78.92 (m), δ 126.23 (d), δ 163.82 (s), δ 197.80 (s), δ 212.57 (s).

Preparation of Unconjugated Diketone 14 - In a 25 ml round bottom flask, under N_2, was placed 1.85 g (6.14 mmol) of dienol ether 8, and to this was added 30 ml of freshly prepared saturated $KHSO_4$-H_2O solution. Crystals immediately began to separate out and the reaction was stirred at room temperature for 30 min.[19] Then the reaction was basicified with conc NH_4OH and extracted with benzene (4 x 20 ml). The benzene extracts were dried, filtered and then evaporated to yield 1.64 g (6.0 mmol) of crude, unstable[20] product 14 in 98% yield as a yellow oil. H-NMR δ 5.7 (s, 1H), δ 2.0-3.2 (m, 22H); ir 2941 cm^{-1} (m), 1709 cm^{-1} (s), 1672 cm^{-1} (w). The IR indicates a small amount of conjugated carbonyl is present, indicative of partial formation of 16, although that product is not detected by H-NMR.

Reduction of 14 to Diol 17[21] - In a dry 50 ml round bottom flask fit with a condenser, magnetic stirrer and addition funnel were placed, under N_2, 15 ml of histological grade THF and 1.9 g (50 mmol) of LAH. To this was added dropwise a solution of 0.33 g (1.22 mmol) of 14 dissolved in 10 ml of THF. After refluxing for 12 h, the reaction was quenched at room temperature with methanol and diluted with 400 ml of H_2O. This was then extracted with ether (3 x 80 ml) and $CHCl_3$ (2 x 50ml). The combined organic layer was dried, filtered and evaporated to yield 0.17 g (6.12 mmol) of 17 in 50% yield as an oil. H-NMR δ 5.4 (s, 1H), δ 3.9 (s, broad, 2H), δ 1.0-3.5 (m, 21H), δ 2.4 (s, 3H); IR 3571 cm^{-1} (m), 3333 cm^{-1} (m, broad), 2899 cm^{-1} (s), 1429 cm^{-1} (m), 1205 cm^{-1} (m, broad).

Photochemical Formation of 16 - To 0.35 g (1.28 mmol) of 14 was added 30 ml of MeOH with ice cooling and O_2 bubbling. This was irradiated with a W lamp in the prescence of rose bengal for 30 min, treated with 10 ml of saturated Na_2SO_3, and left standing for 5 min. Extraction with CH_2Cl_2 (4 x 30 ml), treatment with activated carbon, filtration through Celite and concentration yielded 0.07 g of an oil identified as 16 by H-NMR and IR.

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18. Flash, gravity and chromatotron chromatography all give similar results. The following solvent systems could be used equally well with any method; CH_2Cl_2, ethyl acetate(25%)/hexane, ether(50%)/hexane.

19. A sample that was treated identically to this reaction except that it was kept in contact with the $KHSO_4$ solution for 24 h showed H-NMR and IR spectral characteristics of 16.

20. Samples of the compound were shown spectrophotometrically to have undergone conversion to 16 upon standing neat at room temperature for 20 h, reaction in a buffered solution of pH 11, or upon solution in ethanol for 30 min.

21. Similar results are obtained with $NaBH_4$ reduction in ethanol at room temperature for 16 h.

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