Preparation of 7,8-Dimethoxy-3,4-dihydroisoquinoline, Facile Route to 7,8-Dioxygenated-3,4-dihydroisoquinolines

A. M. EL-FISHAWY, D. J. SLATKIN, J. E. KNAPP, and P. L. SCHIFF, JR. ˣ

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Abstract □ Oxidation of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline with potassium permanganate in acetone afforded 7,8-dimethoxy-3,4-dihydroisoquinoline as the primary product. Hence, oxidation of the appropriate secondary nonphenolic 7,8-dioxygenated tetrahydroisoquinoline alkaloid is thus a facile method for the generation of the corresponding imine. The imine is not easily prepared *via* the usual synthetic route involving ring closure of β-phenethylamine derivatives.

Keyphrases □ 7,8-Dimethoxy-1,2,3,4-tetrahydroisoquinoline—oxidation with potassium permanganate □ 7,8-Dimethoxy-3,4-dihydroisoquinoline—synthesis, secondary amine, oxidation with potassium permanganate □ 7,8-Dioxygenated-3,4-dihydroisoquinoline—secondary amine, oxidation with potassium permanganate

As a continuation of our studies of the alkaloids of *Tiliacora dinklagei* and of the synthesis of various 7,8-dioxygenated-1,2,3,4-tetrahydroisoquinolines (1), it was considered appropriate to attempt to prepare the isoquinolone analogues of these bases. Thirteen simple isoquinolones have been isolated from higher plants to date with most of these alkaloids possessing 6,7-dioxygenation while a few possess 5,6,7-trioxygenation (2). Although no examples of naturally occurring 7,8-dioxygenated isoquinolone alkaloids could be found in the literature, it was felt that preparation of these bases from their isoquinoline counterparts would provide a ready source of physicochemical and spectral data in anticipation of the possible ultimate isolation of these isoquinolones from natural sources.

Isoquinolones are known to arise in nature *via* the oxidation of benzylisoquinolines or from the *in vivo* oxidation of protoberberines, phthalideisoquinolines, or spirobenzylisoquinolines (2). The use of potassium permanganate as an oxidizing agent in the conversion of isoquinoline-derived alkaloids to isoquinolones is well documented (3–5) and it was thus felt that a facile method for the preparation of 7,8-dimethoxyisoquinolone (1-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline) (I) would be the analogous oxidation of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) with potassium permanganate. In fact, oxidation of isoquinoline II with potassium permanganate in acetone afforded, instead, the imine, 7,8-dimethoxy-3,4-dihydroisoquinoline (III) [as characterized by its physicochemical properties, preparation of the methiodide (IV), and sodium borohydride reduction back to II]. This oxidation was repeated on two additional occasions with the same imine being produced in each case. Although 6,7-dioxygenated imines of this series are easily prepared *via* formylation of the parent β-phenethylamine followed by ring closure (6, 7), this same simple procedure is not possible for the 7,8-dioxygenated series since ring closure always proceeds in a less hindered fashion to afford the 6,7-analogues (6). Hence, oxidation of the appropriate secondary nonphenolic 7,8-dioxygenated alkaloids (7,8-dimethoxy or 7,8-methylenedioxy) with potassium permanganate should be a facile method for generating the corresponding imines. It can be assumed that preparation of phenolic alkaloids of this series would require protection of the phenolic group, *e.g.*, *via* the benzyl ether, to prevent further oxidation during the reaction. Examples of this include the use of sodium hypochlorite in the oxidation of 6,7-dimethoxy-8-benzyloxy-1,2,3,4-tetrahydroisoquinoline to the corresponding imine (8) and mercuric acetate in the oxidation of 2-methyl-7-methoxy-8-benzyloxy-1,2,3,4-tetrahydroisoquinoline to its corresponding quaternary imine (9).

EXPERIMENTAL SECTION[1]

7,8-Dimethoxy-3,4-dihydroisoquinoline (III)—To a stirred solution of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) (145 mg) (1) in acetone (40 mL) was slowly added a solution of potassium permanganate (5%) (10 mL) over a period of 1 h. The reaction was stirred for an additional 48 h after which time TLC [silica gel G; benzene–acetone–methanol–ammonium hydroxide (16:16:4:1)] indicated that all of the starting material II (R_f 0.37) had been oxidized to a second product (R_f 0.63) with no other spots appearing on the chromatogram. Other solvent systems used indicated the same results [chloroform–ethyl acetate–methanol–ammonium hydroxide (20:20:4:0.5)—starting material R_f 0.38 and oxidized product R_f 0.83; chloroform–methanol–ammonium hydroxide (90:10:1)—starting material R_f 0.64 and oxidized product R_f 0.85]. The resulting suspension was filtered and the residue of manganese dioxide washed with hot acetone (20 mL) (4×). The filtrate and washings were combined and evaporated to afford 7,8-dimethoxy-3,4-dihydroisoquinoline (III) as a pale-yellow residue (131 mg; 91% yield). The residue was dissolved in chloroform (2 mL) and passed through a column of silicic acid (10 g). Elution with chloroform (5 mL) followed by chloroform–methanol (95:5) (10 mL) afforded the imine III as the same pale-yellow residue (128 mg) which was crystallized as its methiodide salt. The imine III exhibited the following spectral properties: UV λ_{max} (MeOH) (log ε): 320, (3.34), 262 (3.92), and 227 (4.42) with no bathochromic shift on the addition of 3 drops of 0.1 M methanolic KOH; λ_{max} (MeOH–0.1 M HCl) (log ε): 375 (3.41), 297 (4.04), 237 (sh) (4.10), and 218 (sh) (4.17); IR ν_{max} (KBr): 1625, 1580, 1490, 1455, 1420, 1345, 1295, 1270, 1240, 1085, 1060, 1007, 985, 855, 810, 775, and 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.64 (2 closely overlapping triplets, 4, J = 8 Hz, C-3 and C-4), 3.89 (s, 3, C-7 $ArOCH_3$), 3.93 (s, 3, C-8 $ArOCH_3$), 6.90 (s, 2, C-5 and C-6 ArH), and 8.7

[1] Melting points were determined on a Fisher–Johns hot-stage melting point apparatus and are uncorrected. UV absorption spectra were obtained on a Perkin-Elmer Model 552 UV/VIS spectrophotometer. Infrared absorption spectra were taken on a Perkin-Elmer model 267 Grating Infrared Spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24 High Resolution Spectrometer with deuterochloroform or deuteromethanol as solvent, and with tetramethylsilane as the internal standard; chemical shifts were reported in δ (ppm) units. ^{13}C-NMR spectra were recorded on a JEOL FX-900 high resolution spectrometer with deuterochloroform as solvent. Low resolution mass spectra were taken on a Finnegan EI Mass Spectrometer (Extranuclear Laboratories, Inc., Spectrel). Silica gel G (Camag) was used for TLC and spots were visualized by spraying with $KMnO_4$ (1%) in Na_2CO_3 (1%). Silicic acid (Mallinckrodt) was used for column chromatography.

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ppm (br s, 1, C-1 ArH); ^{13}C-NMR: 24.5 (C-4), 47.4 (C-3), 56.0 (C-7 OCH_3), 61.8 (C-8 OCH_3) 115.0 (C-6), 121.7 (C-8a), 122.4 (C-5), 129.2 (C-4a), 147.2 (C-7), 151.3 (C-8), and 155.8 ppm (C-1) (10-12); MS M^+: *m/z* 191 (83%) (calc. for $C_{11}H_{13}NO_2$, 191.0946; obs., 191.0947), 176 (65), 161 (66), 146 (70), 133 (35), 116 (79), 105 (26), 89 (49), 77 (86), 62 (47) and 51 (100).

7,8-Dimethoxy-3,4-dihydroisoquinoline Methiodide (IV)—To 7,8-dimethoxy-3,4-dihydroisoquinoline (**III**) (100 mg) in acetone (5 mL) was added methyl iodide (0.25 mL), and the resulting solution was allowed to stand overnight. The resulting yellow crystals were removed by filtration, washed with cold acetone, and recrystallized twice from acetone–methanol to afford IV as yellow needles (112 mg), mp 165–166°C; UV λ_{max} (MeOH) (log ϵ): 375 (3.03), 297 (3.77), and 218 (4.06); IR ν_{max} (KBr): 1668, 1582, 1498, 1270, 1254, 1080, 1033, 954, and 820 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 3.39 (2 closely overlapping poorly defined triplets, 4, J = 8 Hz), 3.86 (s, 3, N-2 N^+CH_3), 3.95 (s, 3, C-7 $ArOCH_3$), 4.10 (s, 3, C-8 $ArOCH_3$), 7.15 (d, 1, J = 8 Hz, C-5 ArH), 7.52 (d, J = 8 Hz, C-6 ArH), and 9.27 ppm (br s, 1, C-1 ArH); MS M^+: *m/z* 191 (100%) ($M^+ - CH_3I$), 142 (52), 127 (57), and 77 (23).

7,8-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (**II**)—To 7,8-dimethoxy-3,4-dihydroisoquinoline (III) (60 mg) in methanol (30 mL) was added, with stirring, sodium borohydride (200 mg) over a period of 30 min. The mixture was stirred for an additional 8 h and was then filtered. The filtrate was evaporated to give a residue which was dissolved in HCl (5%) (20 mL), basified with NH_4OH to pH 8–9, and extracted with chloroform (50 mL) (4×). The chloroform extracts were combined, dried (anhydrous sodium sulfate), filtered, and the filtrate was evaporated to afford a residue (50 mg) which was dissolved in methanolic HCl (5%) (4 mL). The solvent was subsequently removed by evaporation and the resulting residue treated with a mixture of acetone–methanol (12:1) (3 mL) to afford yellowish-white crystals of II HCl, mp 189–191°C, identical with authentic 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride by direct comparison [mp, UV, IR (1)].

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Determination of Heparin Activity by a New Laser Nephelometric Method and Comparison to the USP Method

A. ESCOBAR *x, R. T. MAHER, M. L. COURTNEY ‡, and A. J. VALICENTI

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Abstract □ A new method for the determination of heparin activity in solutions has been developed, based on the increase in light scattering observed during the clotting of plasma. The recalcification clotting time (RCT) of sheep plasma is measured in the presence of heparin, using a laser nephelometer. The activity of heparin in the sample is determined from a standard curve of the logarithm of RCT *versus* heparin activity. The results indicate that this method is simpler, faster, and more reproducible than the current USP grading method.

Keyphrases □ Heparin—activity, laser nephelometry method, comparison to USP method, recalcification clotting time □ Laser nephelometry—heparin activity, comparison to USP method, recalcification clotting time □ Recalcification clotting time—heparin activity, laser-nephelometry, comparison to USP method

Heparin is an anticoagulant widely used in the treatment of myocardial infarction and thromboembolic disease (1). The anticoagulant effect of the drug cannot be predicted by chemical analysis because it has not been related to any specific functional group or to molecular weight (2). Therefore, the activity of heparin, rather than its concentration, must be measured.

Evaluation of the anticoagulant activity of heparin is based on the ability of the drug to prolong the clotting of recalcified sheep plasma (*i.e.*, sheep plasma to which calcium ions are added to promote coagulation). This ability can be measured instrumentally and visually. Reed *et al.* (3) developed an instrumental method based on measurement of the time needed for a sample of recalcified sheep plasma to reach a pre-established viscosity, *i.e.*, a predetermined degree of clotting. This time is then related to the times needed for a set of standards to reach the same viscosity. The USP method, which does not use instruments, is based on the visual evaluation of the degree of clotting of samples as compared with that of a set of standards.

This work describes the development of a nephelometric method to determine heparin activity and compares this method with the USP procedure. Woziwodzki (4) used nephelometric techniques to study the clotting of plasma. More recently Tanaka (5) used laser nephelometric techniques to study the structure of polyacrylamide gels. Because a clot is essentially a gel composed of a fibrin polymer (1), it was postulated that a laser nephelometer could be used to measure the clotting time.

EXPERIMENTAL SECTION

Apparatus and Reagents—The cuvette compartment of a laser nephelometer[1] was modified to allow external circulation of water, thus maintaining

[1] Hyland PDQ Laser Nephelometer, Northbrook, Ill.

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