

As required, chemo- and stereoselective reaction at either the C-2 ( $\alpha$ -amino nitrile) or C-6 ( $\alpha$ -amino ether) centers of **3a** and **3b** could be achieved by an appropriate choice of reaction conditions. This is illustrated by the enantiospecific synthesis of both (+) and (-) enantiomers of coniine and dihydropinidine from these new synthons (Scheme II).

Alkylation of the anions of **3a** and **3b** with propyl bromide produced compounds **4a** and **4b** in nearly quantitative yields. Reaction of these products with  $\text{NaBH}_4$  in EtOH (25–80 °C) then gave alcohols **5a** (9:1 mixture 2*S*:2*R* diastereomers, **5a** obtained pure by crystallization from hexane–EtOAc, 80%) and **5b** (98%). Under hydrogenolysis conditions the chiral auxiliary attached to the nitrogen of **5b** was cleaved giving (2*S*)-(+)-coniine (**6**)<sup>10</sup> [**6**·HCl,  $[\alpha]_D^{20} +5.2^\circ$  (EtOH, *c* 1.0)] in 95% yield (ee  $\geq$  98%).<sup>11</sup> More drastic conditions (70%  $\text{H}_2\text{SO}_4$ ,  $\Delta$  15 h) were used to cleave the chiral side chain of **5a**; nevertheless excellent chemical and optical yields (94%, ee  $\geq$  98%) of (+)-coniine (**6**) were obtained.

The high stereoselectivity observed in the reactions of **4a** and **4b** with hydride ion implied a mechanism wherein there is prior formation of an iminium ion by elimination of the cyano group and subsequent approach of  $\text{H}^-$  under complete stereoelectronic control<sup>12</sup> from the axial direction (upper face) to the iminium conformer **17**<sup>13</sup> (generating the 2*S* absolute configuration) (Scheme III).

By the same mechanism a propyl side chain was introduced at C-2 of **3a** in the opposite or *R* configuration on reaction with  $\text{PrMgBr}$ . For this transformation prior complexation of the cyano group with silver ion ( $\text{AgBF}_4$ , THF, 5 min  $\rightarrow$   $\text{PrMgBr}$ , 0 °C, 1 min) was necessary to ensure reaction of the amino nitrile moiety only. Compound **7a**, an 8:2 mixture of C-6 epimeric oxazolidines, was obtained in 25% yield after silica chromatography.<sup>14</sup> Reductive opening of the oxazolidine ring to **8a** ( $\text{NaBH}_4$ , EtOH) and cleavage of the chiral auxiliary by treatment with 70%  $\text{H}_2\text{SO}_4$  then gave (*R*)-(-)-coniine (**9**) [**9**·HCl,  $[\alpha]_D^{20} -5.80^\circ$  (EtOH, *c* 1.0)] in high overall yield.

The key to the synthesis of (+)-dihydropinidine (**12**) from intermediates **4a** and **4b** involved the use of reaction conditions selective for the removal of the cyano group. This was accomplished by complexation of the cyano group with  $\text{AgBF}_4$  followed by reaction with  $\text{Zn}(\text{BH}_4)_2$  at low temperature (THF, -60 °C, 20 min). Compounds **10a** and **10b** (mixtures of oxazolidines with 2*S* configuration, 70–77%) were then reacted with  $\text{CH}_3\text{MgI}$  ( $\text{Et}_2\text{O}$ , -60 °C, 20 h) giving the 2,6-*cis*-dialkylpiperidines **11a** (>95% *cis*, 87%) and **11b** (80:20 *cis*/*trans*, 70% after separation by column chromatography on silica). Hydrogenolysis of **11b** and treatment of **11a** with 70%  $\text{H}_2\text{SO}_4$  led in each case to the formation of optically pure (2*S*,6*R*)-(+)-dihydropinidine (**12**) having the natural configuration [**12**·HCl,  $[\alpha]_D^{20} +12.5^\circ$  (EtOH, *c* 1.0)].<sup>15</sup>

In a similar fashion optically pure (-)-dihydropinidine (**16**) was prepared by selective reduction of **13b**, reaction of product **14b** with  $\text{PrMgBr}$ , and hydrogenolytic cleavage of the chiral auxiliary of **15b**.

In conclusion, reaction conditions were thus established that differentiated the reactivity of the amino nitrile and amino ether moieties of synthons **3a** and **3b** enabling the enantiospecific

synthesis of (+)- and (-)-coniine and -dihydropinidine from a single starting material. Further applications of these versatile synthons to the asymmetric synthesis of more complex alkaloid systems are currently in progress.

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## Oxidation of Organic Compounds by Zinc Permanganate

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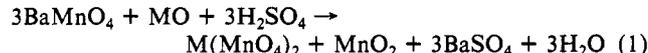
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The reduction of permanganate ion to manganese dioxide in an aqueous medium liberates hydroxyl ions ( $\text{MnO}_4^- + 2\text{H}_2\text{O} + 3e^- \rightarrow \text{MnO}_2 + 4\text{OH}^-$ ). Potassium permanganate reaction mixtures therefore become alkaline as oxidation proceeds. This is not a problem with most substrates but, when the nature of the oxidation is pH dependent,<sup>1</sup> buffering of the medium may be necessary. Reagents employed for this purpose have included magnesium salts,<sup>2</sup> carbon dioxide,<sup>3</sup> and acetic acid.<sup>4</sup>

It was thought that magnesium permanganate and/or zinc permanganate should function as neutral oxidizing agents. Although a search of the literature revealed that this idea was not original,<sup>5</sup> magnesium permanganate and zinc permanganate appear to be virtually unknown as oxidizing agents in organic chemistry.<sup>6</sup>

These salts have now been prepared conveniently, by disproportionation of barium manganate<sup>7</sup> in water according to eq 1,



in the presence of the stoichiometric amounts of sulfuric acid and magnesium oxide or zinc oxide, followed by filtration through Celite, evaporation of the filtrate, and crystallization from water. Both compounds are obtained as hexahydrates.

Astonishingly, both salts reacted instantly, with fires in some cases, when added to common laboratory solvents such as tetrahydrofuran, methanol, ethanol, *tert*-butyl alcohol, acetone, and acetic acid. By comparison, potassium permanganate was innocuous. These unexpected observations indicated that zinc permanganate and magnesium permanganate are powerful general oxidizing agents. Apparently complexation of zinc and magnesium cations to organic substrates greatly enhances their reactivity toward permanganate oxidation.

The oxidations of tetrahydrofuran and anisole were employed to determine whether a safe, general, experimental procedure could be developed. Oxidation in water solvent was inconvenient, because isolation of the product was laborious. A two-phase

(10) Two chiral syntheses of (+)-coniine (**6**) have previously been reported: (a) Aketa, K. I.; Terashima, S.; Yamada, S. I. *Chem. Pharm. Bull.* **1976**, *24*, 621. (b) Archer, J. F.; Boyd, D. R.; Jackson, W. R.; Grundon, M. F.; Khan, W. A. *J. Chem. Soc.* **1971**, 2560 (with an enantiomeric excess of 3–4%).

(11) The enantiomeric excesses were determined from a comparison of the <sup>19</sup>F NMR spectra of the "Mosher's" amide derivatives (Dale, J. A.; Dull, D. L.; Mosher, H. S.; *J. Org. Chem.* **1969**, *34*, 2543) of racemic coniine and the crude reaction products containing **6** and **9**. The signals for the CF<sub>3</sub> fluorines of the two enantiomers were separated by 0.78 ppm.

(12) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833.

(13) Ring inversion of **17** so as to reduce the A<sup>1,2</sup> interactions between the N-1–C-9 and C-6–O-7 bonds is prevented as the resultant conformer is highly strained (as determined from molecular models).

(14) Compound **7a** was present in the crude reaction mixture in approximately equal quantities with the enamine **2a** and the starting material **3a** (probably formed from **2a** by recapture of CN<sup>-</sup>). Formation of **2a** indicates that deprotonation of the intermediate iminium ion by reaction with Grignard reagent competes with transfer of the propyl group.

(15) A chiral synthesis of (-)-dihydropinidine (unnatural enantiomer) has been previously achieved: Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569.

(1) Wolfe, S.; Ingold, C. F.; Lemieux, R. U.; *J. Am. Chem. Soc.* **1981**, *103*, 938–939. Wolfe, S.; Ingold, C. F. *Ibid.* **1981**, *103*, 940–941.

(2) Wiberg, K. B.; Saegbarth, K. A. *J. Am. Chem. Soc.* **1957**, *79*, 2822–2824.

(3) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353–2358.

(4) Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520–521.

(5) Powell, K. A.; Hughes, A. L.; Katchian, H.; Jerauld, J. F.; Sable, H. Z. *Tetrahedron* **1972**, *28*, 2019–2027.

(6) Chambliss, H. Ph.D. Dissertation, Johns Hopkins University, Baltimore, MD, 1900. We thank Professor G. H. Posner for a copy of this Thesis, which reports, *inter alia*, that magnesium permanganate ignites filter paper: Michael, A.; Garner, W. W. *Am. J. Chem.* **1905**, 267–271. Sable, H. Z.; Powell, K. A.; Katchian, H.; Niewoehner, C. B.; Kadlec, S. B. *Tetrahedron* **1970**, *26*, 1509–1524; Cornforth, J. W.; Cornforth, R. H.; Popjak, G.; Yengoyan, L. *J. Biol. Chem.* **1966**, *241*, 3970–3987.

(7) Lux, H. In "Handbook of Preparative Inorganic Chemistry"; Brauer, G., Ed.; Academic Press: New York, 1965; p 1462.

Table I. Oxidation of Organic Compounds by Silica Gel Supported Permanganate Salts<sup>a</sup>

entry	substrate	oxidant	oxidant/ substrate <sup>b</sup>	temp, °C/ solvent	time, h	product	yield, % <sup>c</sup>
1	PhC≡CPh	Zn <sup>d</sup>	1.3	40/CH <sub>2</sub> Cl <sub>2</sub>	0.75	PhCOCOPh	67
2	PhC≡CPh	Mg <sup>e</sup>	1.3	40/CH <sub>2</sub> Cl <sub>2</sub>	24	PhCOCOPh	20
3	PhC≡CPh	K <sup>f</sup>	1.3	40/CH <sub>2</sub> Cl <sub>2</sub>	24	PhCOCOPh	0.5 <sup>g</sup>
4	tetrahydrofuran	Zn	2.0	20/CH <sub>2</sub> Cl <sub>2</sub>	0.25	butyrolactone	51 <sup>h</sup>
5	tetrahydropyran	Zn	2.0	20/CH <sub>2</sub> Cl <sub>2</sub>	0.17	valerolactone	69
6		Zn	2.0	60/CHCl <sub>3</sub>	15	PhCOPh	88 <sup>i</sup>
7		Zn	2.0	60/CHCl <sub>3</sub>	12	PhCOCH <sub>3</sub>	73 <sup>i</sup>
8	cyclohexanone	Zn	2.0	60/CHCl <sub>3</sub>	15	adipic acid	69
9	PhCH <sub>2</sub> NHBoc	Zn	2.0	20/CH <sub>2</sub> Cl <sub>2</sub>	0.17	PhCONHBoc	72
10		Zn	2.0	60/CHCl <sub>3</sub>	13		65
11	PhSCH <sub>3</sub>	Zn	1.2	20/CH <sub>2</sub> Cl <sub>2</sub>	2.5	PhSO <sub>2</sub> CH <sub>3</sub> <sup>j</sup>	92
12		Zn	1.5	20/CH <sub>2</sub> Cl <sub>2</sub>	3.5		36 <sup>i</sup>

<sup>a</sup> Prepared from the permanganate salt as described in ref 9; loadings determined iodometrically. Loadings ranging from 0.2 to 1.0 mM MnO<sub>4</sub><sup>-</sup>/g of reagent give essentially the same conversions. <sup>b</sup> See text. <sup>c</sup> Isolated yield. Reactions have not been optimized. <sup>d</sup> Zn(MnO<sub>4</sub>)<sub>2</sub>/SiO<sub>2</sub>. <sup>e</sup> Mg(MnO<sub>4</sub>)<sub>2</sub>/SiO<sub>2</sub>. <sup>f</sup> KMnO<sub>4</sub>/SiO<sub>2</sub>. <sup>g</sup> 94% of the starting material was recovered. <sup>h</sup> Based on recovered THF, the conversion is 61%. <sup>i</sup> No deprotection was observed with silica gel alone under these conditions. <sup>j</sup> The reaction proceeds via the sulfoxide, which can be detected by TLC after short reaction times. <sup>k</sup> Ft = phthalimido. This new compound has mp 211–214 °C; IR (KBr) 3440, 1765, 1701 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 7.86 (2 H, m), 7.77 (2 H, m), 5.04 (1 H, dd, 4, 11 Hz, CHOH), 4.20 (1 H, ddd, 4, 10, 14 Hz, CHF), 3.65 (1 H, d, 4 Hz, OH), 2.68 (3 H, m), 2.20 (1 H, m), 2.02 (1 H, m), 1.74 (1 H, m); EI-MS 259 (M<sup>+</sup>); CI-MS 260 (M + 1). Anal. CHN. <sup>l</sup> This is the isolated yield; 33% of the starting olefin is recovered, and the products also include phthalimide (12%) and 2-phthalimidoadipic acid (8%).

water–methylene chloride oxidation was also unsuitable, because of the insolubility of the oxidizing agents in the organic phase. Addition of phase-transfer reagents<sup>8</sup> to this solvent system allowed oxidation to proceed, but as expected from the nature of phase transfer catalysis, the potassium, magnesium, and zinc salts gave virtually the same results. Analogous behavior was seen using the inorganic supports Celite, Florisil, and Linde 13X molecular sieves. It was then discovered that support on silica gel<sup>9</sup> preserved the rate enhancements associated with the zinc and magnesium cations, allowed a simple and general oxidation procedure to be developed, and provided oxidizing agents that could be handled safely,<sup>10a</sup> and employed under mild conditions.

Table I summarizes the results obtained from oxidations of a variety of monofunctional systems. Although most substrates were examined using each of the potassium, magnesium, and zinc salts, only one such comparison is given, in entries 1–3. The observations shown here are typical: the zinc salt is the most reactive, and the potassium salt is virtually unreactive under the same conditions.<sup>11</sup> The magnesium salt exhibits intermediate behavior. Addition of zinc sulfate or magnesium sulfate to supported potassium per-

manganate enhanced the reactivity of the latter, but the resulting reagent was not as effective as supported zinc permanganate or magnesium permanganate. Methylene chloride and chloroform were the best solvents for these oxidations, which could be performed either at room temperature or at reflux temperature, as necessary. The supernatant remains clear and colorless, and the workup consists of filtration and removal of the solvent.<sup>12</sup> For most of the examples shown, the resulting material contains only the product shown and unreacted substrate. In some cases, part of the product and/or unreacted starting material remains adsorbed on the support; elution in the normal manner increases the recoveries.

Although no attempt has been made to optimize specific oxidations, some general remarks can be made. The amount of oxidant shown in the oxidant/substrate column of Table I is based on the stoichiometry of the reaction indicated. For ratios between 1.0 and 2.0, the reactions do not proceed to completion because of precipitation of manganese dioxide on the surface of the supported permanganate. Four methods to overcome this problem have been examined: (A) use of excess permanganate; (B) slow addition of the solid oxidant to the substrate; (C) sonication of the reaction mixtures;<sup>13</sup> (D) filtration and addition of fresh oxidant once the initial reaction has ceased. Method D appears to afford the best results.

The following transformations are observed: acetylene → α-diketone (entry 1), cyclic ether → lactone (entries 4,5), cycloethylene ketal → ketone (entries 6,7), cyclic ketone → diacid (entry 8), acylated amine → acylimide (entries 9,10), sulfide →

(8) Foglia, T. A.; Barr, P. A.; Malloy, A. J. *J. Am. Oil Chem. Soc.* **1977**, *54*, 858A–861A. Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1979**, *44*, 2726–2730.

(9) Regen, S. L.; Koteel, C. *J. Am. Chem. Soc.* **1977**, *99*, 3837–3838.

(10) (a) Under conditions of severe confinement and strong initiation, KMnO<sub>4</sub>, Mg(MnO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O, and Zn(MnO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O had energy releases 7%, 11%, and 13% that of trinitrotoluene. All tests of mechanical sensitivity and impact on the pure salts and the silica gel supported salts gave negative results.<sup>10b</sup> DTA and TGA measurements reveal no evidence of thermal instability of zinc and magnesium permanganate relative to potassium permanganate. (b) Personal communication from Dr. R. R. Vandebek, Canadian Explosives Research Laboratory, Canada Centre for Mineral and Energy Technology, Ottawa.

(11) The lithium salt resembles the potassium salt in its oxidation behavior. For recent references to the sodium, silver, barium, and copper salts of permanganate, see: Menger, F. M.; Lee, C. *Tetrahedron Lett.* **1981**, *22*, 1655–1656. Firouzabadi, H.; Vessal, B.; Naderi, M. *Ibid.* **1982**, *23*, 1847–1850. Firouzabadi, H.; Mostafavipour, Z. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 914–917. Lee, D. G.; Nouredin, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 3188–3191.

(12) For example: To a solution of phenyl methyl sulfide (310 mg, 2.5 mmol) in methylene chloride (50 mL) was added 17.4 g (4.00 mmol of permanganate) of zinc permanganate/SiO<sub>2</sub> (loading 0.23 mmol of permanganate/g of reagent). The mixture was stirred at room temperature for 2.5 h and filtered, the solid was washed with methylene chloride, and the combined filtrates were evaporated to give phenyl methyl sulfone, 354 mg (91%), mp 88–89 °C.

(13) We thank Professor D. J. L. Clive for this suggestion. See, e.g.: Han, B.-H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030–5032 and references cited. Yamawaki, W.; Sumi, S.; Ando, T.; Hanafusa, T. *Chem. Lett.* **1983**, 379–380.

