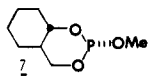
It appears highly significant that population of a twist conformer was not reported for the *trans*-decalin-like system **7**.[9] This may



reflect an important difference between the relatively strain-free system **7**, which Dreiding models indicate potentially can exist in either of two boat forms (or intermediate twist), and our system for which only the one twist form (**6**) is accessible. This restriction arises from the need for C4′–O and C2′–C3 bonds of the sugar ring to approach coplanarity. A closer comparison of these ring systems will be in order so as to establish firmly their conformational properties. These studies are of special importance, even in tervalent phosphorus systems, because of the central role of cyclic nucleotides, e.g., cAMP and cGMP, in biochemical processes and the desire to thoroughly understand the conformational properties of the phosphorus-containing ring. This includes any influence of the strain associated with the trans ring fusion demonstrated for cAMP.[10]

Acknowledgment. This work was supported by a grant from the National Cancer Institute of the Public Health Service (CA 11045).

Registry No. 2, 40652-74-2; **2** carbamate, 87970-11-4; *cis*-**3**, 66386-45-6; *trans*-**3**, 66386-46-7; *cis*-**4**, 87970-09-0; *trans*-**4**, 87970-10-3.

(7) See, e.g.: Reference 3b. (a) Hargis, J. H.; Bentrude, W. G. *Chem. Commun.* **1969**, 1113. (b) Bentrude, W. G.; Tan, H. W. *J. Am. Chem. Soc.* **1973**, *95*, 4666. (c) Mosbo, J. A. *Org. Magn. Reson.* **1978**, *11*, 281. (d) Gerlt, J. A.; Gutterson, N. I.; Drews, R. E.; Sokolow, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 1665. (e) Gorenstein, D. G.; Rowell, R.; Findlay, J. *Ibid.* **1980**, *102*, 5077. Gorenstein, D. G.; Rowell, R. *Ibid.* **1979**, *101*, 4925.

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(9) Haemers, M.; Ottinger, R.; Reisse, J.; Zimmerman, D. *Tetrahedron Lett.* **1971**, 461. Changes of ~2 Hz in the $^3J_{HP}$ values of the CH_2 hydrogens of **7** corresponding to 5′a and 5′b of **3** and **4** were reported without comment. These values could mean that a minor depopulation of the chair occurs.

(10) In the phosphate diesters this amounts to about 5 kcal/mol. (Gerlt, J. A.; Gutterson, N. I.; Datta, P.; Belkeau, B.; Penny, C. L. *J. Am. Chem. Soc.* **1980**, *102*, 1655.)

Chiral 1,4-Dihydropyridine Equivalents: A New Approach to the Asymmetric Synthesis of Alkaloids. The Enantiospecific Synthesis of (+)- and (−)-Coniine and -Dihydropinidine[1]

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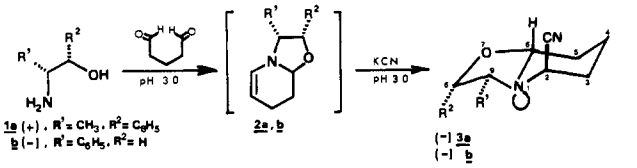
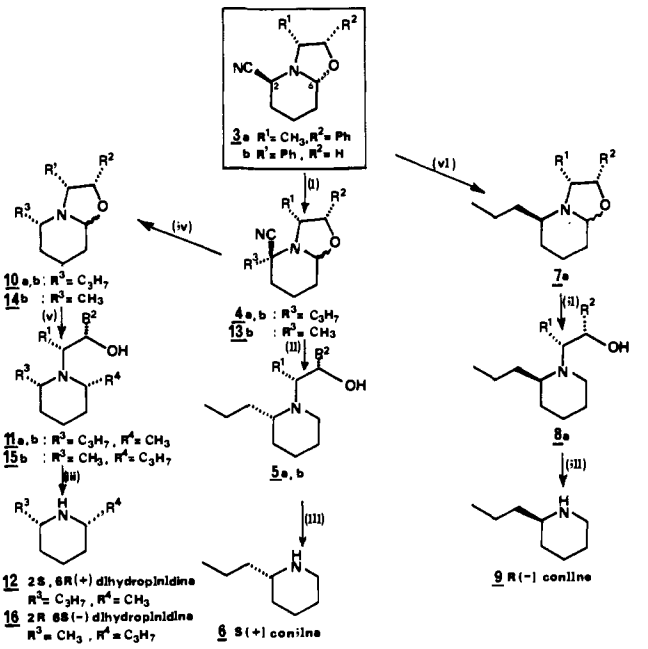
In connection with our work on the synthesis of a number of biologically important 2,6-disubstituted piperidine alkaloids,[2-6] we were prompted to consider the preparation of piperidine synthons based upon the 1,4-dihydropyridine system. It was felt that such synthons should (i) be readily available, (ii) show nonequivalent reactivities at the 2- and 6-positions (providing control over four carbon centers), and (iii) be chiral.

Scheme I

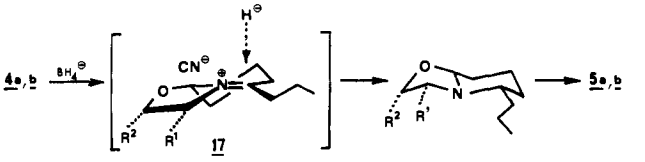


Scheme II[a]



[a] Reagents: (i) LDA, THF, −78 °C; R^3X, 3 h. (ii) $NaBH_4$, EtOH, 25-80 °C, 15 h. (iii) for a, H_2SO_4 70%, 18 h; for b, H_2, Pd/C, MeOH, HCl, 15 h. (iv) $AgBF_4$, THF; $Zn(BH_4)_2$, −60 °C, 30 min. (v) R^4MgX, ether, −60 °C, 20 h. (vi) $AgBF_4$, THF; *n*-PrMgBr, 0 °C, 1 min.

Scheme III



The Robinson–Schopf type condensation of glutaraldehyde with amino alcohols in the presence of KCN appeared as a particularly attractive route to the type of synthon we were seeking.[7] Thus, the condensation of (+)-norephedrine (0.01–0.2 mol) with glutaraldehyde (1.7 equiv) in H_2O at pH 3.0 (1 h) followed by the addition of KCN (1.4 equiv) (room temperature, 72 h) led in a "one-pot reaction" to the formation of a single chiral crystalline 2-cyano-6-oxazolopiperidine **3a** [α^{20}_D −126.5° ($CHCl_3$, *c* 2.3)] in 82% yield[8] (Scheme I). Similarly the reaction with (−)-phenylglycinol as the chiral component gave a single product **3b** [α^{20}_D −278° ($CHCl_3$, *c* 1.0)], in 50% yield.[9]

(1) Dedicated to Professor Sir Derek Barton on the occasion of his 65th birthday. Preliminary communication at the 8th Symposium on Heterocyclic Chemistry, Rennes, France, Sept 1982; see: *Bull. Soc. Chim. Belg.* **1982**, *91*, 985.

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(8) The spectral data for all compounds were in accord with their proposed structures. Satisfactory microanalyses and/or high-resolution mass spectra were obtained for these products.

(9) The trans-H-2_{eq},H-6_{ax} relative configuration was determined for both **3a** and **3b** from an analysis of their 400-MHz ^1H NMR spectra. The absolute configurations 2*S*,6*R* were assigned on the basis of NMR arguments and on the results of theoretical energy calculations (to be reported at a later date).

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As required, chemo- and stereoselective reaction at either the C-2 (α-amino nitrile) or C-6 (α-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 $NaBH_4$ 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**)[10] [**6**·HCl, $[\alpha]^{20}_D$ +5.2° (EtOH, *c* 1.0)] in 95% yield (ee ≥ 98%).[11] More drastic conditions (70% H_2SO_4, Δ 15 h) were used to cleave the chiral side chain of **5a**; nevertheless excellent chemical and optical yields (94%, ee ≥ 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 H^- under complete stereoelectronic control[12] from the axial direction (upper face) to the iminium conformer **17**[13] (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 PrMgBr. For this transformation prior complexation of the cyano group with silver ion ($AgBF_4$, THF, 5 min → 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.[14] Reductive opening of the oxazolidine ring to **8a** ($NaBH_4$, EtOH) and cleavage of the chiral auxiliary by treatment with 70% H_2SO_4 then gave (*R*)-(−)-coniine (**9**) [**9**·HCl, $[\alpha]^{20}_D$ −5.80° (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 $AgBF_4$ followed by reaction with $Zn(BH_4)_2$ at low temperature (THF, −60 °C, 30 min). Compounds **10a** and **10b** (mixtures of oxazolidines with 2*S* configuration, 70–77%) were then reacted with CH_3MgI (Et_2O, −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% H_2SO_4 led in each case to the formation of optically pure (2*S*,6*R*)-(+)-dihydropinidine (**12**) having the natural configuration [**12**·HCl, $[\alpha]^{20}_D$ +12.5° (EtOH, *c* 1.0)].[15]

In a similar fashion optically pure (−)-dihydropinidine (**16**) was prepared by selective reduction of **13b**, reaction of product **14b** with 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.

Acknowledgment. We thank Dr. G. Cahiez for the ^{19}F NMR work and Drs. A. Schoofs and G. Lemoine for valuable discussions.

(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. C* **1971**, 2560 (with an enantiomeric excess of 3–4%).

(11) The enantiomeric excesses were determined from a comparison of the ^{19}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_3 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 $A^{1,2}$ 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^-). 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.

Oxidation of Organic Compounds by Zinc Permanganate

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The reduction of permanganate ion to manganese dioxide in an aqueous medium liberates hydroxyl ions ($MnO_4^- + 2H_2O + 3e^- \rightarrow MnO_2 + 4OH^-$). 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,[1] buffering of the medium may be necessary. Reagents employed for this purpose have included magnesium salts,[2] carbon dioxide,[3] and acetic acid.[4]

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,[5] magnesium permanganate and zinc permanganate appear to be virtually unknown as oxidizing agents in organic chemistry.[6]

These salts have now been prepared conveniently, by disproportionation of barium manganate[7] in water according to eq 1,

$$3BaMnO_4 + MO + 3H_2SO_4 \rightarrow M(MnO_4)_2 + MnO_2 + 3BaSO_4 + 3H_2O \quad (1)$$

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

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(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.

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