Application of Metalated Enamines to Alkaloid Synthesis. An Expedient Approach to the Synthesis of Morphine-Based Analgesics

Sir:

Over the last 50 years, the morphine structure (1) has served as the archetype for the design of nonpeptidic analgesics. It is now well appreciated that morphine-based substructural analogues such as 2-4 still retain significant analgesic properties, and the investigation of new structural variants in this area is still being actively pursued.1

The purpose of this communication is to describe a general approach to the synthesis of morphine-based analogues, which have in common the 4-arylpyridyl synthon, a structural feature common to many active morphine analogues.2,3 We have found that the tetrahydropyridine 5,4 upon metalation with n-C4H9Li now yield.4 This transformation rests on the precedent established by Levine5 on a related acylation reaction and upon the regioselection observed in other metalated enamine alkylations.6

In a representative procedure, 1 equiv of 6 (0.3 M in THF) at -20 °C was added over a 10-min period to 3.3 equiv of 7 (1.0 M in ether) at -50 °C. The reaction was warmed to -20 °C and quenched with saturated salt solution, and the enamine 8b was isolated by successive extraction with cold 1 N aqueous hydrochloric acid and subsequent basification (0 °C) with aqueous sodium hydroxide. Enamine 8a was found to be a versatile precursor to both the phenylpyridines 4 and the phenylmorphin 10. Catalytic hydrogenation of 8a (H2/Pd-C, EtOH, 60 psi) afforded 4 (R1 = CH3, R2 = CH2) in quantitative yield (HCl salt, mp 208-209 °C)5 while treatment of 8a with 1:1 85% H2PO4/HCO2H (25 °C, 66 h) afforded a 91% yield of enamine 9 (HClO4 salt, mp 164-165 °C) which was hydrogenated to the known phenylmorphin 10 (HCl salt, mp 239-240 °C).7 The syntheses of both 4 (R1 = C6H5, R2 = CH3) and 10 via this route constitute a considerable improvement over other published routes to these analogues.5,6

The arydehydrosquiazoline synth 3 of the morphine skeleton has recently been recognized as a potential analgesic, and considerable effort has been expended toward developing efficient routes to this and related structures.8 We have found that the endocyclic enamine 8b is an excellent precursor to both the trans-and cis-fused decahydrosquiazolines 12 and 13. When chloro enamine 8b and sodium iodide (4 equiv) are heated in refluxing acetonitrile (0.06 M, 24 h), the bicyclic enamine 11 (bp 115-120 °C, 0.05 mm Hg) was obtained after solvent evaporation and basification in excellent yield.9 It was found that either the trans- or the cis-perhydrosquiazolines 12 or 13 could be obtained with greater than 95% stereoselection, depending on the conditions chosen for the reduction of 11. Hydrogenation of 11 in the presence of platinum oxide in ethanol (60 psi, 15 h, 60 °C) afforded exclusively 12 (mp 67-69 °C, picrate 220-222 °C),8a,10 Alternatively, if bicyclic enamine 11 was hydrogenated with the same catalyst in acetic acid (60 psi, 15 h, 60 °C), the cis-perhydrosquiazoline 13 (HCl salt, mp 219.5-221.5 °C)11 was obtained in quantitative yield (13:12 ≥ 95:5).4 Information pertinent to developing a rationale for the above stereoselective reductions was obtained in a stereochemical study on the protonation of bicyclic enamine 11. Treatment of an ethereal solution of 11 with ethereal perchloric acid followed by solvent removal afforded the

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trans-fused immonium perchlorate 14 (X = ClO₄) as an oil. The structure of 14 was established by reduction (NaBH₄, MeOH) to 12 (12, 13 ≥ 95:5). Alternatively, if the kinetically generated salt 14 was dissolved in ethanol, after several days the cis-fused perchlorate 15 (X = ClO₄) gradually crystallized from solution (mp 162–163 °C) in 95% yield. As previously described, borohydride reduction of 15 afforded 13 in 95% yield (13:12 ≥ 95:5). We have further shown that the conversion of 14 to 15 as described above is not a consequence of lattice-energy effects and the selective crystallization of a small equilibrium concentration of 15. Methylene chloride solutions of 14 (X = Cl) likewise equilibrate (25 °C, 48 h) to 15 (Keq = 32.3).11 These results correlate well with the dramatic solvent effects noted above in the reduction of the bicyclic enamine 11. It is concluded that 11 is the direct precursor to the trans-fused perhydroisoquinoline 12 in hydrogernations carried out in ethanol while the thermodynamic cis-fused immonium salt 15 (X = OAc) is the species reduced in acetic acid.11 This general approach to 4a-phenyldecahydroisoquinolines 12 and 13 is noteworthy for its brevity in comparison with other published syntheses.8

By inspection, the morphinan and octahydroisoquinoline ring systems differ only by a crucial methylene bridge, and in principle, immonium salts such as 14 or 15 in conjunction with methylene equivalents could lead directly to the morphinan skeleton. In selective crystallization of a small equilibrium concentration of 15. Methylene chloride solutions of 14 (X = Cl) likewise equilibrate (25 °C, 48 h) to 15 (Keq = 32.3).11 These results correlate well with the dramatic solvent effects noted above in the reduction of the bicyclic enamine 11. It is concluded that 11 is the direct precursor to the trans-fused perhydroisoquinoline 12 in hydrogernations carried out in ethanol while the thermodynamic cis-fused immonium salt 15 (X = OAc) is the species reduced in acetic acid.11 This general approach to 4a-phenyldecahydroisoquinolines 12 and 13 is noteworthy for its brevity in comparison with other published syntheses.8

Cation–Medium Control of Hydride Transfer between Carboxyl Groups

Sir:

We report a dramatic demonstration that hydride transfer between two carboxyl groups, as exemplified by the Meerwein–Pondorf–Verley/Oppenauer (MPV/O) reactions, can be affected in diagnostically opposed ways by the cation/base employed, depending on whether or not the transition state allows complexation of both oxygen atoms by a single cation; both trends have been observed simultaneously at the carbonyl group of a single compound.

The experimentally convenient 4-hydroxycyclohexanone 1 undergoes both intra- and intermolecular hydride transfer.1 In a series of comparative experiments with constant t-ProO–/i-ProOH medium, the rate of the intermolecular hydride transfer from t-Pro–M to 1 (ΔΔ only) increases with increasing Lewis acidity of the cation (Al³⁺ > Li⁺ > Ba²⁺ > Na⁺ > K⁺; see Table I), and therefore decreases with increasing effective basicity of the medium, as expected for the accepted cyclic transition state 12 for MPV/O reactions.²,³

However, concurrently in the same medium, the rate of the intramolecular process (→2) increased in the reverse cationic order of increasing metal–oxygen basic character (Ba²⁺ > K⁺ > Na⁺ > Li⁺ > Al³⁺; see Table I), except for Ba²⁺ being out of order. Moreover, for constant K⁺ cation, the rate of the intramolecular hydride shift was found to increase with increasing basicity of the medium (t-AmOK/benzene > t-AmOK/i-AmOH > i-ProOK/i-ProOH > EtOK/EtOH > MeOK/MeOH; see Table II). In agreement, the addition of 18-crown-6 ether or [2.2.2]cryptand to either the t-ProOK/i-ProOH or the t-AmOK/benzene reaction