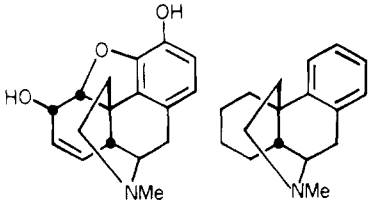
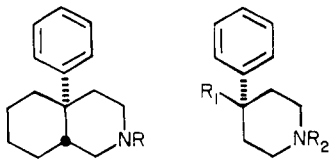
Application of Metalated Enamines to Alkaloid Synthesis. An Expedient Approach to the Synthesis of Morphine-Based Analgesics

Sir:

Over the last 50 years, the morphine structure (**1**) has served as the archetype for the design of nonpeptidic analgesics. It is



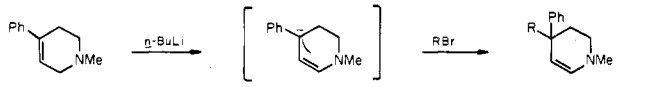
1 **2**



3 **4**

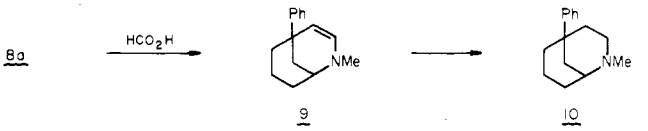
now well appreciated that morphine-based substructural analogues such as **2**–**4** still retain significant analgesic properties, and the investigation of new structural variants in this area is still being actively pursued.[1]

The purpose of this communication is to describe a general approach to the synthesis of morphine-based analgesics, which have in common the 4-arylpiperidyl synthon, a structural feature common to many active morphine analogues.[1d] We have found that the tetrahydropyridine **5**,[2] upon metalation with *n*-C_4H_9Li



5 **6** **8a**, R = $CH_2CH{=}CH_2$; **b**, R = $(CH_2)_4Cl$

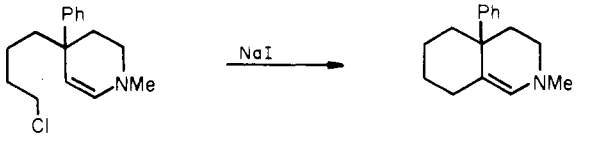
[THF (0.3 M), −10 °C],[3] afforded the metalated enamine **6** as a red solution which was found to react regioselectively with either allyl bromide (1.0 equiv) or 1-bromo-4-chlorobutane (**7**) (3.3 equiv) at −50 °C to give endocyclic enamines **8a** (bp 101–105 °C, 0.1 mmHg, 77%) and **8b** ($HClO_4$ salt, mp 170–172 °C) in 70% yield.[4] This transformation rests on the precedent established by Levine[3a] on a related acylation reaction and upon the regioselection observed in other metalated enamine alkylations.[3b] 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 phenylpiperidines **4** and the phenylmorphan **10**. Catalytic hydrogenation of **8a** (H_2/Pd–C, EtOH, 60 psi) afforded **4** ($R_1 = C_3H_7$, $R_2 = CH_3$) in quantitative yield (HCl salt, mp 208–209 °C)[5] while treatment of **8a** with 1:1 85%



8a **9** **10**

H_3PO_4/HCO_2H (25 °C, 66 h) afforded a 91% yield of enamine **9** ($HClO_4$ salt, mp 164–165 °C) which was hydrogenated to the known phenylmorphan **10**[6] (HCl salt, mp 239–240 °C).[7] The syntheses of both **4** ($R_1 = C_3H_7$, $R_2 = CH_3$) and **10** via this route constitute a considerable improvement over other published routes to these analgesics.[5,6]

The aryldecahydroisquinoline synthon **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-



8b **11**

12 **13**

14 **15**

and cis-fused decahydroisoquinolines **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 mmHg) was obtained after solvent evaporation and basification in excellent yield.[4,9] It was found that either the *trans*- or the *cis*-perhydroisoquinolines **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, 4 h, 25 °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-fused perhydroisoquinoline **13** (HCl salt, mp 219.5–221.5 °C)[8d] 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

(1) (a) Eddy, N. B.; May, E. L. "Synthetic Analgesics", Part IIB; Pergamon Press: London, 1966. (b) *Science (Washington, D. C.)* **1973**, *181*, 407. (c) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. (d) Lednicer, D.; Mitscher, L. A. "The Organic Chemistry of Drug Synthesis"; New York, 1977; Chapter 15.

(2) Schmindle, C. J.; Mansfield, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 425.

(3) (a) Levine, R.; Rell, V. U.S. Patent 3824242, 1974. (b) For a relevant example of enamine metalation–alkylation, see: Martin, S. F.; Dupriest, M. F. *Tetrahedron Lett.* **1977**, 3925.

(4) Satisfactory spectral and elemental analyses were obtained on all compounds reported.

(5) McElvain, S. M.; Clemens, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 3915.

(6) May, E. L.; Murphy, J. G. *J. Org. Chem.* **1954**, *19*, 618.

(7) The transformation of **8a** to **9** is viewed as proceeding via an immonium ion–olefin cyclization followed by transannular hydride transfer.

(8) (a) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650, and references cited therein. (b) Weller, D. D.; Glass, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485. (c) Glass, R. D.; Rapoport, H. *Ibid.* **1979**, *44*, 1324. (d) Finch, N.; Blanchard, L.; Puckett, R. T.; Werner, L. H. *Ibid.* **1974**, *39*, 1118.

(9) The overall yield of **11** from **5** without intermediate purification of **8b** was 61%.

(10) The trans stereochemistry assigned to **12** was confirmed by X-ray analysis.

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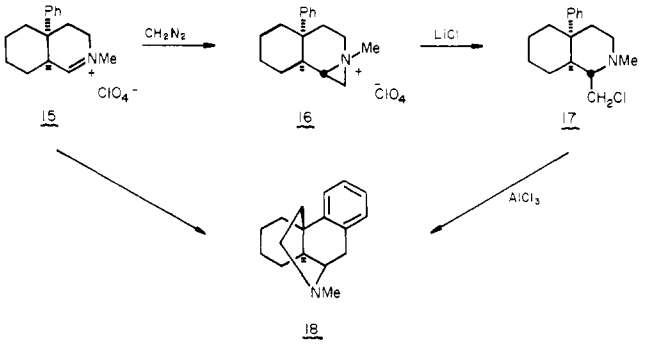
trans-fused immonium perchlorate **14** (X = ClO_4) as an oil. The structure of **14** was established by reduction ($NaBH_4$, MeOH) to **12** (**12**:**13** ≥ 95:5). Alternatively, if the kinetically generated salt **14** was dissolved in ethanol, after several days the cis-fused perchlorate **15** (X = ClO_4) 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** (K_{eq} = 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 hydrogenations 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 conjunction with testing this hypothesis, it was found that upon addition of diazomethane to **15** (X = ClO_4)[12] in methylene chloride



15 16 17 18

at 0 °C followed by solvent removal a crystalline solid was obtained which upon recrystallization (benzene–acetone) was shown to be the aziridinium perchlorate **16** (mp 164–166 °C)[4] whose stereochemistry was established by subsequent transformations (vide infra). The high degree of stereoselection in this addition process was anticipated, based upon ample precedent established in related nucleophilic addition reactions observed in this ring system during the course of this study.[13] Unfortunately, the relevant stereochemical control elements (stereoelectronic[14] vs. steric) in this immonium ion addition reaction are obscured by the two available half-chair conformations accessible to **15**. Regiospecific cleavage of the highly labile aziridinium ring with lithium chloride (3 equiv, 25 °C, MeCN) afforded the crystalline chloro amine **17** (mp 68–70 °C) in 98% yield. Final ring closure of **17** to *N*-methyl-14α-morphinan (**18**) was readily accomplished with $AlCl_3$[15] (6 equiv, C_6H_6, 80 °C, 2 h) in 60% (from **15**) yield.[4,16] It is worth noting that careful scrutiny of the reaction of immonium salt **15** with diazomethane revealed that a 15% yield (30% in acetone) of the morphinan **18** was produced directly in competition with aziridinium ion formation![16]

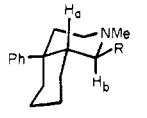
This general approach to the synthesis of morphine-based analgesics embodies the inherent flexibility not only for the efficient construction of analogues but also for the synthesis of the primary morphine alkaloids. Investigations directed toward this latter objective will be reported in due course.

Acknowledgments. Support from the National Institutes of Health (GM-26111) and the Eli Lilly Company is gratefully acknowledged. X-ray analysis of **12** was performed by M. O. Chaney and N. D. Jones.

(11) The solution equilibration of **14** ⇄ **15** was conveniently followed by ^{13}C NMR. The approximate half-lives of 2 M solutions of **14** as a function of counterion X at 25 °C in methanol follow: X = ClO_4, $T_{1/2}$ = 16 h; X = Cl, $T_{1/2}$ = 2 h; X = OAc, $T_{1/2}$ ≤ 5 min.

(12) Leonard, N. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 962.

(13) We have observed that the addition of other nucleophiles such as MeMgI and MeNC to **15** proceeds in a highly stereoselective fashion from the convex face of the bicyclic ring system. The assignment of stereochemistry in these systems was deduced from the vicinal coupling between H_a and H_b; in both cases (*R* = Me, CONHME), J_{ab} = 10–11 Hz, suggesting that conformation **i** is preferred.



i

(14) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(15) For a related cyclization, see: Stella, L.; Raynier, B.; Surzur, J. *Tetrahedron Lett.* **1977**, 2721.

(16) Gates, M.; Woodward, R. B.; Newhall, W. F.; Künzli, M. *J. Am. Chem. Soc.* **1950**, *72*, 1141. These workers have prepared **18** as well as its picrate and methiodide salts. Our melting points were found to be identical with those reported.

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Cation–Medium Control of Hydride Transfer between Carbonyl Groups

Sir:

We report a dramatic demonstration that hydride transfer between two carbonyl groups, as exemplified by the Meerwein–Ponndorf–Verley/Oppenauer (MPV/O) reactions, can be affected in diametrically 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 *i*-PrO^-/*i*-PrOH medium, the rate of the *inter*molecular hydride transfer from *i*-PrO–M to **1** (→**4** only) increases with increasing Lewis acidity of the cation (Al^{3+} > Li^+ > Ba^{2+} > 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.[2-4]

However, concurrently in the same medium, the rate of the *intra*molecular process (→**2**) increased in the reverse cationic order of increasing metal–oxygen basic character (Ba^{2+} > K^+ > Na^+ > Li^+ > Al^{3+}; see Table I), except for Ba^{2+} 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/*t*-AmOH > *i*-PrOK/*i*-PrOH > EtOK/EtOH > MeOK/MeOH; see Table II). In agreement, the addition of 18-crown-6 ether or [2.2.2]cryptand to either the *i*-PrOK/*i*-PrOH or the *t*-AmOK/benzene reaction

(1) Warnhoff, E. W. *Can. J. Chem.* **1977**, *55*, 1635–1643.
(2) Shiner, V. J.; Whittaker, D. *J. Am. Chem. Soc.* **1969**, *91*, 394–398.
(3) Doering, W. E.; Aschner, T. C. *J. Am. Chem. Soc.* **1953**, *75*, 393–397.
(4) Doering, W. E.; Young, R. W. *J. Am. Chem. Soc.* **1950**, *72*, 631–632.

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