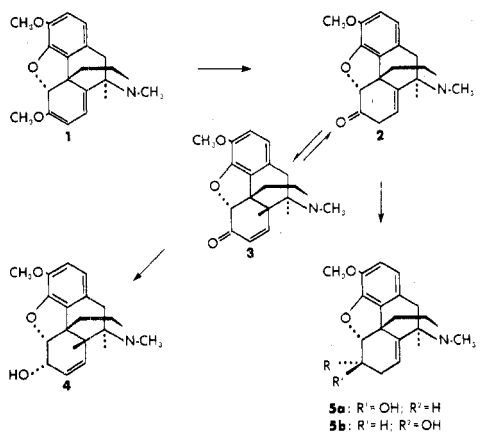
Selective Reductions of Neopinone to Neopine and Isoneopine

Summary: Reduction of neopinone (**2**) with sodium borohydride in alcoholic solvents is not stereoselective because of a balance between steric interference caused by the hydrofuran ring and by the axial hydrogens at C-5 and C-7. When bulky reducing agents are used, the blocking effect of the hydrofuran ring becomes the dominant factor, and stereoselective reduction to neopine (**5a**) is achieved; with a small reducing agent, such as sodium borohydride in an aqueous alkaline medium, the main directing force is represented by the axial hydrogens, leading to a predominance of isoneopine (**5b**).

Sir: Conroy[1] reported that reduction of neopinone (**2**) with sodium borohydride gave neopine (**5a**) as the only product observed and isolated. This was analogous to the report of Gates[2] that codeinone (**3**) is stereospecifically reduced to codeine (**4**). However, more recent studies by Okuda et al.[3,4]



showed that the reduction of neopine is not stereospecific and gives a mixture of neopine (**5a**) and isoneopine (**5b**) in approximately equal amounts. This greatly limits the efficiency of the syntheses of neopine and isoneopine, both of which are of interest, neopine as a natural opium alkaloid[5] and isoneopine as an intermediate in the synthesis of B/C trans-fused morphine analogues.[6]

We would like to report the stereoselective reduction of neopinone to either neopine or isoneopine in nearly quantitative yields under carefully controlled reaction conditions.

The stereochemistry of metal hydride–ketone reductions is determined by a combination of steric interference, torsional strain, and electrostatic effects.[7] Examination of a molecular model of neopinone indicates that the plane of ring A makes an angle of about 110° with the plane of ring C, as illustrated in Figure 1. This implies that the α face of the carbonyl group of neopinone is partially blocked by the hydrofuran ring. Bulky borohydride reducing agents, such as those developed by Brown and Krishnamurthy,[8] are very sensitive to steric influence around the carbonyl group and should, therefore, approach neopinone from the less hindered β face to give the α-alcohol, neopine. This proved to be the case. When neopinone, produced from thebaine (**1**),[9] was treated with either lithium triethylborohydride[10] or lithium tri-*sec*-butylborohydride[11] in tetrahydrofuran, neopine was the sole reduction product detected by TLC and NMR and isolated in 95% yield on a column of neutral alumina (Table I).

Small reducing agents such as the borohydride anion or the aluminum hydride anion appear to have an intrinsic preference for "axial" attack in substituted cyclohexanones.[7] "Product development control"[12] and "torsional strain"[13] are rationalizations that have been offered to explain this preference, although recent work[14,15] seems to indicate that "product development control" is not a viable hypothesis for this reaction. Torsional strain in cyclohexanone systems is the interaction between axial hydrogens α to the carbonyl group and the incoming reducing agent.

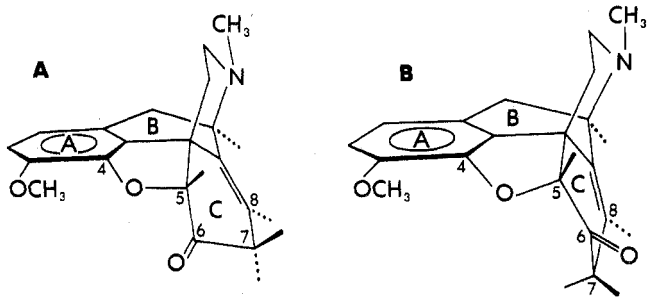


Figure 1. Conformations of neopinone.

Molecular models of neopinone indicate that there are two possible conformations for ring C (Figure 1, A and B). In conformation A the oxygen of the carbonyl group is resting below the plane of the ring, and the C(5) hydrogen and one hydrogen at C(7) are in an axial configuration extending above the plane of the ring. Thus, "axial" attack of a reducing agent would lead to isoneopine. In conformation B the oxygen of the carbonyl group extends above the plane of ring C, and the hydrogen at C(5) assumes a pseudoequatorial orientation. "Axial" attack by borohydride on the carbonyl group in this conformation would give neopine. It is, therefore, necessary to establish the correct conformation of neopinone before considering the effect of torsional strain.

In conformation A (Figure 1) the dihedral angle between the C(7) axial hydrogen and the olefinic hydrogen at C(8) was measured from the molecular model to be about 95°. The dihedral angle between the C(7) equatorial hydrogen and the C(8) hydrogen was found to be about 27°. Calculation of the coupling constants from the Karplus equation, as modified by Conroy,[16] between C(7)–H_{ax} and C(8)–H and between C(7)–H_{eq} and C(8)–H are 0.4 and 6.4 Hz, respectively. In conformation B the dihedral angle was measured from the molecular model to be about 55° between C(7)–H_β and C(8)–H and about 65° between C(7)–H_α and C(8)–H. Calculation of the coupling constants from the modified Karplus

Table I. Effect of Solvent and Bulkiness of Reducing Agent on Reduction of Neopinone

Reducing agent/solvent	Neopinone solvent	Neopine–isoneopine	Total yield **5a** + **5b**, %
$LiEt_3BH$/THF	THF	100:0	95
$Li(s\text{-}Bu)_3BH$/THF	THF	100:0	95
$NaBH_4$/no solvent	CH_3OH	58:42	96
$NaBH_4/C_2H_5OH$	C_2H_5OH	60:40	77
$NaBH_4/i\text{-}PrOH$	*i*-PrOH	63:37	80
$NaBH_4$/diglyme	diglyme + Et_3N	27:73	35
$NaBH_4/H_2O/OH^-$	CH_3OH	42:58	86
$NaBH_4/H_2O/OH^-$	H_2O	11:89	98

equation gave values of 2.4 and 1.2 Hz, respectively. The observed coupling constants were 1.8 and 6.3 Hz. Consequently, the conformation of neopinone corresponds most closely to that illustrated in Figure 1A.

According to the torsional strain concept "axial" attack by sodium borohydride in the reduction of neopinone should lead to a predominance of isoneopine. However, since the reduction of neopinone is very sensitive to the bulkiness of the reducing agent, as shown by the fact that neopine was the only product of reduction with lithium triethylborohydride which is not usually so highly selective, the nature of the solvent must also be considered. In alcoholic solvents the alcohol acts as a catalyst[17] and enters into the transition state, from which a series of alkoxyborohydrides is formed, $R_nBH_{4-n}^-$, where R is the alkoxy group of the solvent.[18] The alkoxyborohydrides reduce the carbonyl group more rapidly than does the borohydride ion.[19] This can result in a change in the ratio of isomers during the course of the reduction,[20-22] presumably because of the added bulkiness of the alkoxyborohydrides formed in the reaction.

When neopinone was reduced with an excess of sodium borohydride in alcoholic solvents, neopine and isoneopine were produced in ratios of approximately 6:4 (Table I). There appeared to be a trend toward a greater proportion of isoneopine with a decrease in the molecular weight of the alcohol, although the difference may be too small to be considered significant. Apparently, the bulkiness of the alkoxyborohydrides formed in any alcoholic solvent is such that steric interference from the hydrofuran ring plays a greater role than torsional strain in directing the borohydride attack.

When sodium borohydride reductions are performed in diglyme in the presence of an excess of triethylamine, the borohydride anion alone is the reducing agent.[22] Subsequent borane is trapped as the aminoborane, which is incapable of further reductions in this system. When neopinone was reduced under these conditions, the ratio of isoneopine to neopine was greatly increased. However, the overall yield of alcohols was poor (35%). Finally, a method was devised for reduction of neopinone in aqueous solution. Neopinone was generated from 400 mg of thebaine in aqueous acetic acid as described by Barber and Rapoport.[9] The neopinone solution was cooled in an ice bath to 0 °C and neutralized slowly with potassium hydroxide to about pH 6.5. A solution of 1 g of sodium borohydride in potassium hydroxide solution (pH ≥13) was added over 5 min and the mixture immediately extracted with chloroform. Evaporation of the solvent left a residue which was chromatographed on neutral alumina, first with 25% chloroform in benzene which eluted neopine (11% yield), then with 60% chloroform in benzene which gave isoneopine (88% yield). The identity of both compounds was confirmed by melting point, TLC, and NMR spectroscopy.[23]

There may be several reasons why this selectivity is achieved when the reduction is carried out in an aqueous alkaline medium. Perhaps the bulkiness of the hydroxyborohydrides formed after the initial step is insufficient to be adversely affected by the steric hindrance posed by the hydrofuran ring. It is also possible that the hydroxyborohydrides are unstable and disproportionate rapidly to boric acid and sodium borohydride. In either case, the major directing influence would be torsional strain resulting in a predominance of the β-alcohol, isoneopine.

Acknowledgment. This work was supported by a grant from the National Institute on Drug Abuse (DA 0014-17) and the NIH Division of Research Resources (RR 00892-1A1).

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(23) Mixture melting point of neopine with an authentic sample[24] showed no depression. The melting point of isoneopine was 158–159 °C (lit.[3] 155–156 °C). The R_f values on alumina with chloroform–methanol (99:1) were 0.54 for neopine and 0.27 for isoneopine, in good agreement with reported values.[4] The most significant difference in the NMR spectra was the chemical shift of C(6)–H observed at 4.23 ppm for neopine (lit.[25] 4.22) and 3.80 ppm for isoneopine (lit.[25] 3.62). The C(5)–H of neopine resonated at 4.63 ppm (d, J = 4.3 Hz) [lit.[25] 4.62 (J = 4.2 Hz)] and of isoneopine at 4.48 ppm (d, J = 8.5 Hz) [lit.[25] 4.54 (J = 8.6 Hz)]. The methoxy protons of neopine showed a chemical shift at 3.86 ppm (lit.[26] 3.86) and of isoneopine at 3.82 ppm (lit.[4] 3.82).
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Received June 7, 1977