Synthesis of Some Epiminocyclohexanes by Hydride Reduction of α,β-Unsaturated Cyclohexanone Oximes and the Pyrolytic *cis*-Elimination of *N*-Acetylepiminocyclohexanes

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Reduction of several 2-benzylidenecyclohexanone oximes with lithium aluminum hydride gave the corresponding 1-benzyl-1,2-epiminocyclohexanes. Reduction of 2-benzylidenecyclohexanone oxime with lithium aluminum deuteride gave an epiminocyclohexane (**8**) which had incorporated two deuterium atoms. A reaction mechanism for the reduction is postulated. The major fragmentation pathways in the mass spectrum of **8** are outlined. Acetylation of 1-benzyl-1,2-epiminocyclohexane with acetic anhydride (15 min reflux) gave 3-acetamido-2-benzyl-1-cyclohexene by a pyrolytic *cis* elimination.

La réduction par $LiAlH_4$ de plusieurs oximes de benzylidène-2 cyclohexanones conduit aux benzyl-1 épimino-1,2 cyclohexanes correspondants. La réduction, par $LiAlD_4$ de l'oxime de la benzylidène-2 cyclohexanone donne l'épiminocyclohexane (**8**) ayant incorporé deux atomes de deutérium. Un mécanisme réactionnel est postulé pour cette réaction. Les modes majeurs de fragmentation de **8** lors de la spectrométrie de masse sont donnés généraux. L'acétylation du benzyl-1 épimino-1,2 cyclohexane avec de l'anhydride acétique (reflux de 15 min) conduit par pyrolyse impliquant une élimination *cis*, à l'acétamido-3 benzyl-2 cyclohexène-1. [Traduit par le journal]

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Introduction

Recently a series of substituted 2-benzylidenecyclohexylamines (**3**) were required as intermediates in the synthesis of some novel anticancer agents. In our earlier work,[3] we described the preparation of the ketones (**1**) shown to have the *E* configuration with relationship of the aromatic ring to the carbonyl function. These ketones were then converted to the corresponding oximes (**2**).[4] It was considered that the ketoximes could be converted to the corresponding amines (**3**) using lithium aluminum hydride (LAH), a reagent known to reduce substituted cyclohexanone oximes to amines (1, 2). The reaction sequence is shown in Scheme 1.

Results and Discussion

Reduction of **2***a* with LAH gave a colorless oil. The n.m.r. spectrum indicated the presence of 17 protons including one proton replaceable with deuterium but the olefinic proton was absent. The u.v. spectrum confirmed the absence of any styrenoid absorption. The mass spectrum indicated a parent peak at 187 with a molecular formula of $C_{13}H_{17}N$. These data show the absence of both **3***a* and the saturated primary amine, 2-benzylcyclohexylamine. The presence of one replaceable proton suggested an imine structure and aziridines have been formed by reduction of saturated cyclic oximes and α,β-unsaturated acyclic ketoximes with LAH (3, 4). The n.m.r., u.v., i.r., and mass spectral data obtained support the structure **4***a* for the compound isolated from the reduction of **2***a* with LAH. We are aware of only one other substituted cyclohexanone oxime which possessed an unsaturated linkage and gave an aziridine on reduction with LAH but in this case the double bond remained intact (5).

Reduction of **2***b* with LAH gave **4***a* which could also be obtained from **2***a* by reduction with lithium borohydride but **2***a* did not react with sodium borohydride, sodium trimethoxyborohydride, or lithium tri-(*t*-butoxy)aluminum hydride. It is interesting to note that reduction of (*Z*)-2-benzylidenecyclohexanone oxime with LAH

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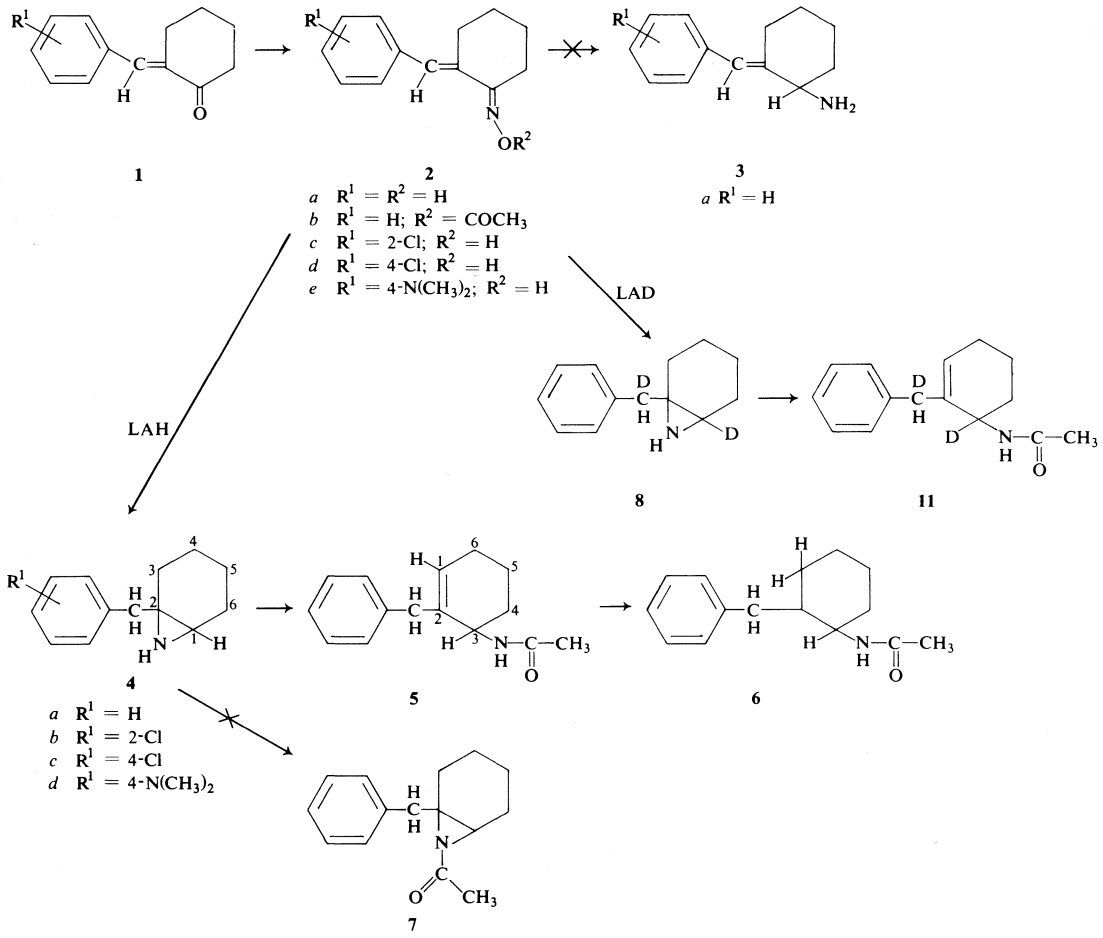

SCHEME 1

afforded **4***a* although in lower yields than reduction of **2***a*. Reduction of **2***a* with lithium aluminum deuteride (LAD) gave a compound with two deuterium atoms (**8**). The n.m.r. spectrum showed no absorption at δ 2.07–1.83 (C(2)H absent) nor the AB quartet with centers of the doublets at δ 2.92 and 2.63 ($C_6H_5CH_2$ absent). However two shaggy multiplets at δ 2.85 and 2.68 integrating for one proton were assigned to the *erythro* and *threo* forms of the product due to the CDH function in the side chain. The postulated reaction mechanism for the synthesis of the deuterated product (**8**) is shown in Scheme 2.

The mass spectrum of **8** had prominent *m/e* peaks at 189 (parent peak) and at 97 and 92 indicating the incorporation of one deuterium atom in the side chain and the other in the epiminocyclohexane portion of the molecule. The principle peaks for **4***a* and **8** are given in Table 1 and the possible fragmentation pattern for **8** is shown in Scheme 3. Work on the mass spectrometry of more complex aziridines has been published recently (6).

Reduction of **2***c* and *d* with LAH gave the corresponding aziridines (**4***b* and *c*) in good yields. In the case of reduction of **2***e*, g.l.c. of the reaction mixture indicated three components to the extent of 59, 24, and 17%. The n.m.r. spectrum of the reduction product from **2***e* was assignable to the aziridine structure **4***d*, indicating **4***d* was the major compound in the mixture. A white solid formed in the reaction mixture over a period of time (3 months) which was identified as 2-(4-dimethylaminobenzyl)cyclohexylamine by n.m.r., i.r., and mass spectral evidence. G.l.c. analysis indicated that this compound represented 24% of the reaction mixture. The third component of the reaction was not identified.

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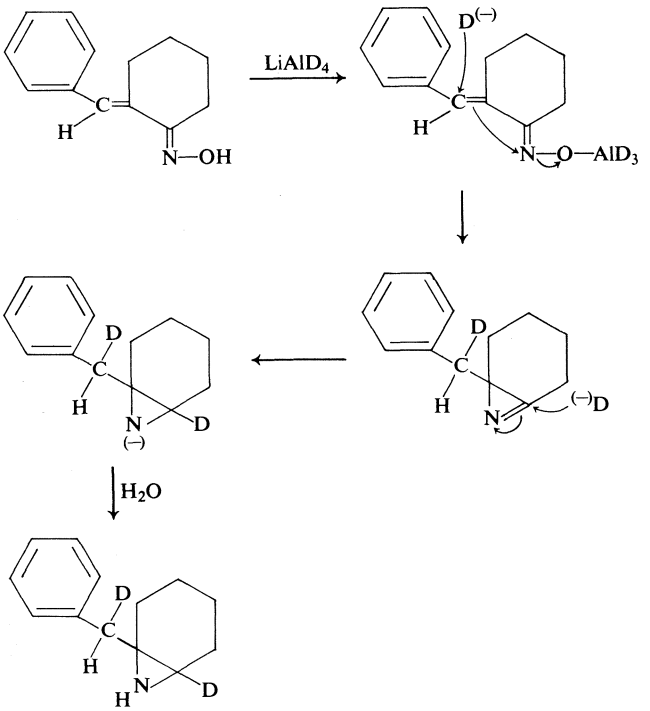
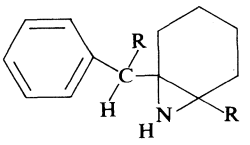


SCHEME 2

TABLE 1. Major peaks in the mass spectra of the aziridines **4*a*** and **8**



4*a* R = H
8 R = D

4*a*		**8**	
m/e	Relative abundance	*m/e*	Relative abundance
187 $[M]^+$	100	189 $[M]^+$	100
186 $[M-1]^+$	56	188 $[M-1]^+$	40
172 $[M-15]^+$	82	174 $[M-15]^+$	36
159 $[M-28]^+$	54	161 $[M-28]^+$	36
158 $[M-29]^+$	74	160 $[M-29]^+$	40
96 $[M-91]^+$	100	97 $[M-92]^+$	60
91 $[M-96]^+$	100	92 $[M-97]^+$	96

An attempt to prepare **7** by acetylation of **4*a*** with acetic anhydride (15 min reflux) gave a compound with a correct molecular weight for **7**. However, spectral evidence did not support this structure. The n.m.r. spectra indicated the presence of an olefinic group and a replaceable proton, while i.r. spectroscopy showed the presence of an NH stretching vibration as well as amide II and I bands at 1535 (NH) and 1640 cm^{-1} (CO). In view of earlier workers report of the preparation of *N*-allylcarboxamides on acylation of aziridines (7) we surmised that one of the structures **5**, **9**, or **10** may have been formed. Compound **10** may be eliminated since the u.v.

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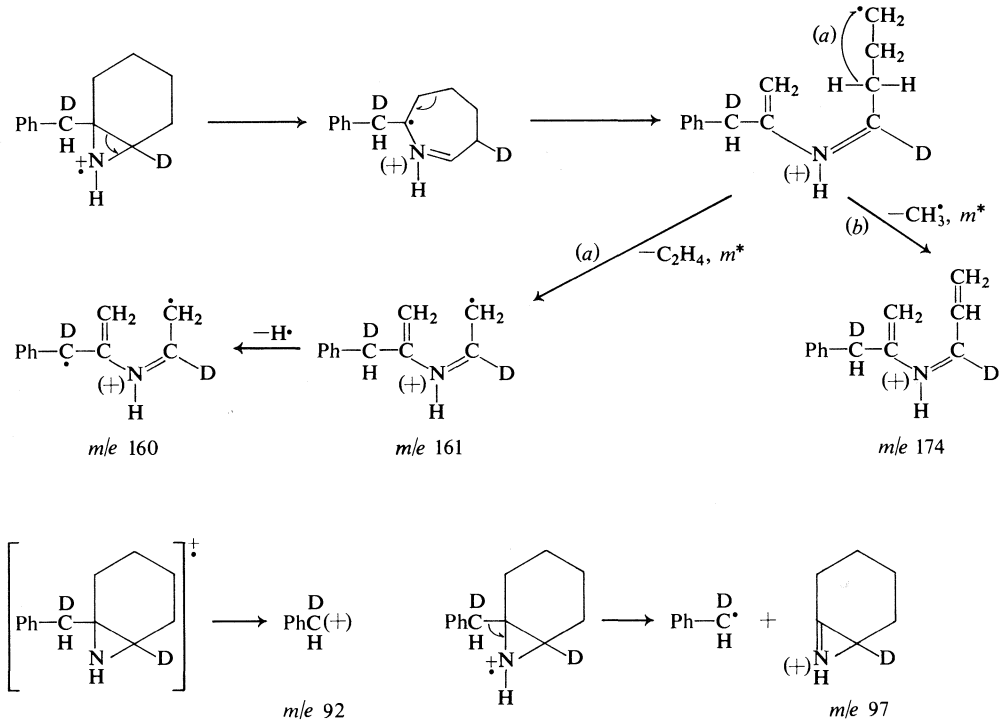
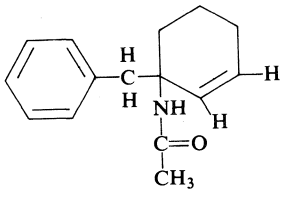


SCHEME 3

spectra indicated the absence of styrenoid absorption and the n.m.r. spectrum indicated the presence of a benzyl side chain.



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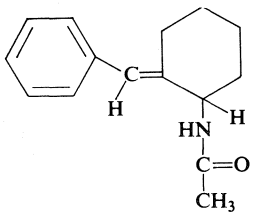

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The n.m.r. spectrum of the amide obtained showed a broad peak at δ 5.77–5.37 integrating for two protons and a peak at δ 4.60–4.20 integrating for one proton. One of the protons at δ 5.77–5.37 could be exchanged with deuterium suggesting that an amide proton was superimposed on an olefinic proton. Catalytic hydrogenation of the amide increased the molecular weight by two mass units indicating the presence of one double bond and the n.m.r. spectra of the reduced product showed no olefinic absorptions at δ 5.77–5.37 while the amide proton was moved upfield to δ 5.71. The presence of only one olefinic proton in the unsaturated amide indicates that the structure is **5** rather than **9**. Acetylation of **8** with acetic anhydride (15 min reflux) gave **11** with no proton at δ 4.60–4.20 indicating that the absorption in **5** at δ 4.60–4.20 was due to the bridgehead proton at C-3 of the cyclohexane ring. The formation of **5** from **4***a* presumably arises by pyrolytic *cis* elimination (8, 9) of the *N*-acetylaziridine via the transition state (**12**).

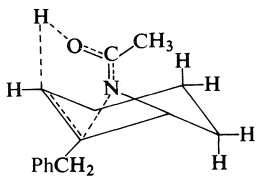

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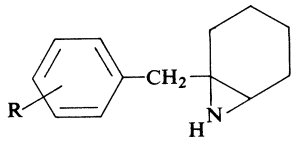
TABLE 2. Substituted 1-benzyl-1,2-epiminocyclohexanes



Compound **4**	R	B.p.(°/mm)	Yield*	Calcd. (%) C	Calcd. (%) H	Found (%) C	Found (%) H
a	H	78/0.2	92†,‡	83.37	9.15	83.20	9.12
b	2-Cl	100–105/0.5	91	70.42	7.27	70.50	7.41
c	4-Cl	126–128/1.3	89	70.42	7.27	70.31	7.26

*Yield is based on the weight of reaction product obtained prior to distillation. G.l.c. analysis of the material showed that one product was present to an extent greater than 99.4%.
†This compound was prepared from **2***b* in 90% yield.
‡Reaction of **2***a* with lithium borohydride using the general reduction procedure gave a product containing **4***a* (65%) and unreacted **2***a* (35%).

The anticancer activity of several of the oximes, aziridines, and related compounds described in this work will be reported elsewhere.

Experimental

General Conditions

The i.r. spectra were recorded on a Unicam SP200G spectrophotometer previously calibrated with polystyrene, using sodium chloride optics or potassium bromide discs. The n.m.r. spectra were obtained in deuterochloroform using a Varian T-60 spectrometer, with tetramethylsilane as the internal standard. Mass spectra were obtained with an AEI MS-12 spectrometer. The u.v. spectra were recorded on a Beckmann DU Spectrophotometer, in 95% ethanol, using quartz cells. All melting points were determined on a Mettler FP-1 melting point apparatus and are uncorrected. Microanalyses were carried out by Mr. O. Douglas, College of Pharmacy, University of Saskatchewan, Saskatoon, on a Coleman Model 33 Carbon–Hydrogen Analyzer. Gas chromatographic analyses were determined on a Pye 104 chromatograph equipped with 5 ft × 0.25 in. o.d. glass columns packed with 4% SE-30 adsorbed onto silanized Chromosorb W (100/120 mesh).

*General Procedure for the Preparation of Substituted 1-Benzyl-1,2-epiminocyclohexanes (**4**)*

A solution of the appropriate ketoxime or ketoxime acetate (**2**) (10) (0.037 mol) in anhydrous ether (180 ml) was added dropwise to LAH (0.057 mol) in anhydrous ether (40 ml) and heated under reflux with stirring for 8 h. The reduction complex was decomposed by the dropwise addition of water and filtered. The filtrate was dried ($MgSO_4$) and evaporation of ether gave the crude reaction product which was purified by distillation (Table 2).

*1-Benzyl-1,2-epiminocyclohexane(**4a**)*

I.r. (smear) 3250s cm^{-1} (NH); n.m.r. δ 7.40–7.00 (5H, m, C_6H_5), 2.92, and 2.63 (2H, centers of two doublets of AB quartet, J = 14 Hz, $C_6H_5CH_2$), 2.07–1.83 (1H, m, C(2)*H*), 1.90–1.50 (4H, m, C(3)H_2, C(6)H_2), 1.50–1.07 (4H, m, C(4)H_2, C(5)H_2), 0.73 (1H, broad s, exchanges with D_2O, N*H*); mass spectrum *m/e* 187 (parent peak).

The deuterium analog (**8**) was prepared in a similar manner (90% yield), using LAD. B.p. 80°/0.5 mm; i.r. (smear) 3256s cm^{-1} (NH); n.m.r. δ 7.47–7.07 (5H, m, C_6H_5), 2.85 and 2.68 (1H, centers of 2m, C_6H_5—C*H*D), 2.00–1.50 (4H, m, C(3)H_2, C(6)H_2), 1.50–1.28 (4H, m, C(4)H_2, C(5)H_2), 0.98 (1H, broad s, replaceable with D_2O, N*H*); mass spectrum *m/e* 189 (parent peak).

*1-(2-Chlorobenzyl)-1,2-epiminocyclohexane (**4b**)*

I.r. (smear) 3258s cm^{-1} (NH); n.m.r. δ 7.47–7.40 (4H, m, C_6H_4Cl), 3.13, and 2.83 (2H, centers of two doublets of AB quartet, J = 14 Hz, C_6H_4Cl—CH_2), 1.97–1.83 (1H, m, C(2)*H*), 1.97–1.60 (4H, m, C(3)H_2, C(6)H_2), 1.60–1.07 (4H, m, C(4)H_2, C(5)H_2), 0.68 (1H, broad s, exchanges with D_2O, N*H*); mass spectrum *m/e* 221 (parent peak).

*1-(4-Chlorobenzyl)-1,2-epiminocyclohexane (**4c**)*

I.r. (smear) 3257s cm^{-1} (NH); n.m.r. δ 7.43–6.97 (4H, m, C_6H_4Cl), 2.85, and 2.58 (2H, centers of two doublets of AB quartet, J = 14 Hz, C_6H_4Cl—CH_2), 2.13–1.83 (1H, m, C(2)*H*), 1.93–1.48 (4H, m, C(3)H_2, C(6)H_2) 1.48–1.07 (4H, m, C(4)H_2, C(5)H_2), 0.44 (1H, broad s, exchanges with D_2O, N*H*); mass spectrum *m/e* 221 (parent peak).

*Reduction of 2-(4-Dimethylaminobenzylidene)cyclohexanone Oxime (**2e**) with LAH*

The general reduction conditions were followed to give an oil (1.43 g), b.p. 138°/0.7 mm. G.l.c. indicated a mixture of components in concentrations of 59, 24, and 17%. The following characteristics could be assigned to 1-(4-dimethylaminobenzyl)-1,2-epiminocyclohexane as the major component of the mixture: i.r. (smear) 3286s cm^{-1} (NH); n.m.r. δ 7.23–6.80 (2H, m, aromatic C(2)*H*, C(6)*H*), 6.80–6.47 (2H, m, aromatic C(3)*H*, C(5)*H*), 2.88 (6H, s, $(CH_3)_2N$), 2.81, and 2.53 (2H, centers of two doublets of AB quartet, J = 14 Hz, $(CH_3)_2N$—C_6H_4—CH_2), 1.97–1.73 (1H, m, C(2)*H*), 2.07–1.53 (4H, m, C(3)H_2, C(6)H_2), 1.53–1.07 (4H, m, C(4)H_2, C(5)H_2), 0.68 (1H, broad s, exchanges with D_2O, N*H*).

A white solid (0.1 g), m.p. 109.5° formed in the distillate over a period of time (3 months), which was identified as 2-(4-dimethylaminobenzyl)cyclohexylamine: i.r. 3376 cm^{-1} (NH_2); n.m.r. δ 7.20–6.87 (2H, m, aromatic C(2)*H*, C(6)*H*), 6.80–6.47 (2H, m, aromatic C(3)*H*, C(5)*H*), 2.70–2.10 (2H, m, $(CH_3)_2N$—$C_6H_4CH_2$), 1.90–1.13 (10H, m, C(1)*H*, C(2)*H*, C(3)H_2, C(4)H_2, C(5)H_2,

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C(6)H_2), 1.63 (2H, s, exchanges with D_2O, NH_2); mass spectrum *m/e* 232 (parent peak).

Reduction of (Z)-2-Benzylidenecyclohexanone Oxime with LAH

Reaction of (*Z*)-2-benzylidenecyclohexanone[3] with hydroxylamine by our general method[4] gave (*Z*)-2-benzylidenecyclohexanone oxime, m.p. 90–92° in a yield of 74%. Mass spectrum *m/e* 201 (parent peak).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.57; H, 7.49.

(*Z*)-2-Benzylidenecyclohexanone oxime (0.00994 mol) was reacted with LAH (0.0198 mol) using the general method, except that the time of heating under reflux was extended to 20 h, to give a pale yellow syrup (1.46 g). G.l.c. analysis indicated **4** (49%), unreacted oxime (33%), and two unidentified compounds (9 and 9%).

Attempted Reduction of 2a with Sodium Borohydride, Sodium Trimethoxyborohydride, and Lithium Tri-(t-butoxy)aluminum Hydride

When a mixture of **2***a* (0.05 mol), sodium borohydride (0.05 mol), ethanol (150 ml), and water (10 ml) was stirred at room temperature for 96 h or alternatively heated under reflux for 12 h, only unreacted **2***a* was isolated from the reaction.

A mixture of **2***a* (0.015 mol) and sodium trimethoxyborohydride (0.072 mol) in anhydrous tetrahydrofuran (50 ml) was heated under reflux for 96 h. The only product isolated was unreacted oxime (**2***a*).

The attempted reduction of **2***a* (0.001 mol) with lithium tri-(*t*-butoxy)aluminum hydride (0.024 mol) in anhydrous tetrahydrofuran (50 ml) heated under reflux for 8 h, gave only the unreacted oxime (**2***a*).

3-Acetamido-2-benzyl-1-cyclohexene (5)

A solution of **4***a* (2.05 g) in freshly distilled acetic anhydride (1.23 g) was heated under reflux for 15 min. The reaction mixture was poured into cold water (10 ml) and excess acetic anhydride was destroyed by the addition of 10% aqueous sodium carbonate solution (20 ml). The aqueous mixture was extracted with ether and the ether extracts were washed with water and dried ($MgSO_4$). Removal of the ether under reduced pressure gave a gummy yellow residue (2.1 g). G.l.c. analysis indicated 55% of **5**. Recrystallization of this residue from ether – Skelly F gave feathery colorless crystals of **5** (0.34 g, 14%): m.p. 103.5°; i.r. (KBr) 1535s (amide II), 1640s (amide I), 3310s cm^{-1} (NH); n.m.r. δ 7.40–7.00 (5H, m, C_6H_5), 5.77–5.37 (2H, m, C(1)H, NH, one proton replaceable by NaOD), 4.60–4.20 (1H, m, C(3)H), 3.27 (2H, s, C_6H_5—CH_2), 2.23–1.77 (2H, m, C(6)H_2), 1.78 (3H, s, CH_3CO), 1.83–1.43 (4H, m, C(4)H_2, C(5)H_2); mass spectrum *m/e* 229 (parent peak).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.40; H, 8.17.

The deuterium analog (**11**) was prepared by a similar acetylation procedure. G.l.c. analysis of the crude product indicated 60% of **11**. Crystallization of the crude product from ether – Skelly F gave pure **11** (3.3%): m.p. 101.5°; i.r. 1532s (amide II), 1637s (amide I), and 3310s cm^{-1} (NH); n.m.r. δ 7.37–6.90 (5H, m, C_6H_5), 5.73–5.47 (1H, m, C(1)H), 5.35 (1H, broad s, exchanges with NaOD, NH), 3.40–3.03 (1H, m, C_6H_5CHD), 2.20–1.80 (2H, m, C(6)H_2), 1.80 (3H, s, CH_3CO), 1.80–1.43 (4H, m, C(4)H_2, C(5)H_2); mass spectrum *m/e* 231 (parent peak).

1-Acetamido-2-benzylcyclohexane (6)

A solution of **5** (0.106 g) in absolute alcohol (200 ml) was hydrogenated over 10% palladium-on-charcoal (0.155 g) at 46 p.s.i. for 23 h. The catalyst was removed by filtration of the mixture through celite in a sintered glass funnel. Removal of the ethanol under reduced pressure gave colorless crystals of **6** (0.105 g, 98%): m.p. 152.5°; n.m.r. δ 7.30–6.87 (5H, m, C_6H_5), 5.71 (1H, broad s, replaceable by NaOD, NH), 4.00–3.20 (1H, m, C(1)H), 3.10–1.97 (2H, m, $C_6H_5CH_2$), 1.90 (3H, s, CH_3CO), 2.00–0.77 (8H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(6)H_2); mass spectrum *m/e* 231 (parent peak).

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