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AZIRIDINE FORMATION BY REDUCTION OF KETOXIMES WITH LITHIUM ALUMINIUM HYDRIDE

ON DIBENZYLKETOXIME AND ITS O-SUBSTITUTED DERIVATIVES*

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Abstract—The reduction of dibenzylketoxime (Ia) with LAH in boiling THF gave *cis*-2-phenyl-3-benzylaziridine (IIa) in excellent yield, together with a small amount of the expected primary amine, 2-amino-1,3-diphenylpropane (III). The LAD reduction of Ia was carried out and the position of deuterium introduced was based on the NMR data. The O-substituted derivatives of Ia, such as O-Me, O-acetyl and O-tosyl derivatives (Ib, Ic and Id), were also reduced with LAH to the aziridine IIa in almost the same yields except for Id

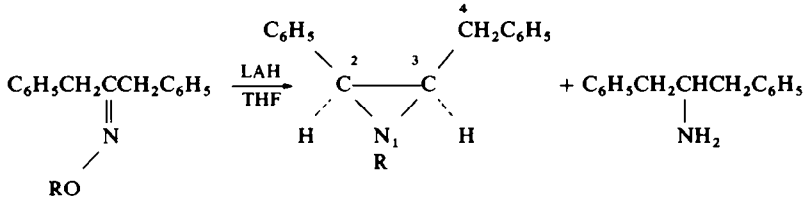
THE LAH reduction of ketoximes usually gives the corresponding primary amines.[3] Actually, Rerick *et al.*[4] reported that the LAH reduction of dibenzylketoxime (Ia) afforded the primary amine III almost quantitatively. In contrast with their result,† it was found that the LAH reduction of the oxime in THF yielded an aziridine, *cis*-2-phenyl-3-benzylaziridine (IIa) as major product, instead of the expected primary amine. In this connection, the O-substituted derivatives of Ia also afforded the aziridine IIa by LAH reduction in THF. These are the subject of this paper.

The LAH reduction of dibenzylketoxime (Ia) was carried out in boiling THF for 3 hr. The reduction products showed two spots (R_f-values, 0·61 and 0·16) on thin-layer plate using SiO_2 and the solvent system of Chf:MeOH (95:5). By elution-chromatography on SiO_2, the products were separated in 77 and 8% yields, respectively. The major product (R_f 0·61) was found to be *cis*-2-phenyl-3-benzylaziridine (IIa) based on the spectral data and chemical evidence. The compound IIa, m.p. 44–45°, corresponded to the molecular formula, $C_{15}H_{15}N$, and showed at 3350 cm^{-1} the absorption band due to a secondary amino group. The NMR spectrum (60 Mc, $CDCl_3$) of IIa showed peaks at about 6·68 τ (C_2—H, poor doublet as the X part of an A_2BX system), about 7·52 τ (C_3—H and two C_4—H, multiplet as the A_2B part of the same A_2BX system) and 8·90 τ (N_1—H, broad singlet) (Fig. 1). Treatment of IIa with phenylisocyanate gave the phenylcarbamoyl derivative IIb, m.p. 123–125°, which showed characteristic absorption bands at 3250 cm^{-1} ($\rangle$NH) and 1661 cm^{-1} (—CONH—). The NMR spectrum of IIb indicated peaks at 6·05 τ (C_2—H, doublet, $J_{2,3}$ = 6·0 c/s), about 7·10 τ (C_3—H, octet (d–q)) and about 7·50 τ

* This paper, of which the outline was presented in our preliminary communication,[1] may be regarded as supplementary part to our previous paper.[2]

† Since the reduction condition used by them was not described in the paper,[4] we cannot discuss here about this contrast. It might be due to the difference of the experimental conditions.

(two C_4—H, octet (d–q)), as shown in Fig. 2. In this case, the proton signal corresponding to C_2—H appears as a sharp doublet and those of two C_4—H appear as AB-type quartet showing the difference from these of IIa. These results may be due to the effect of the phenylcarbamoyl group introduced. These findings suggested the major product to be an aziridine and the coupling constant ($J_{2,3}$ = 6·0 c/s) in the C_2 proton signal of IIb showed the aziridine to have *cis*-configuration.[5] Therefore, the structures of the aziridine and its phenylcarbamoyl derivative were reasonably assigned to IIa and IIb, respectively. This conclusion was also supported by the following chemical evidence. Treatment of IIa with 10% HCl aq gave a chloro-amine IV, characterized as the hydrochloride, $C_{15}H_{16}NCl \cdot HCl$, m.p. 184–185°, which was hydrogenated in the presence of Pd-carbon catalyst in H_2O to a primary amine, resulting from reductive elimination of the chlorine atom at the benzylic position.

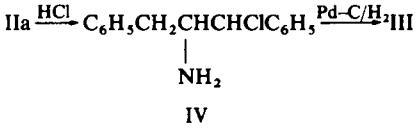


Ia: R = H
b: R = CH_3
c: R = Ac
d: R = Tos

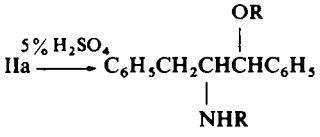
IIa: R = H
b: R = $CONHC_6H_5$

III

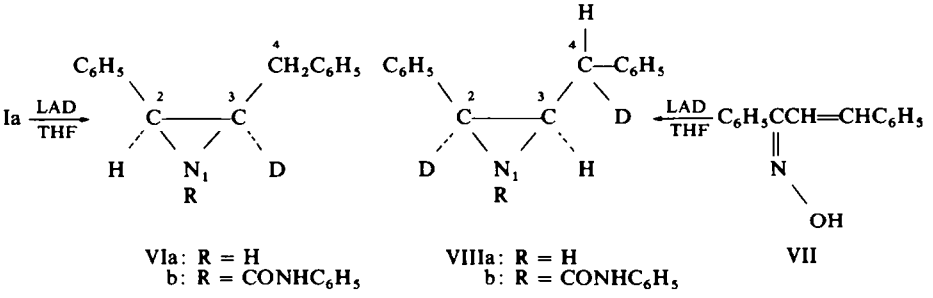
$C_6H_5CH_2NHCH_2CH_2C_6H_5$
IX



IV



Va: R = H
b: R = Ac



VIa: R = H
b: R = $CONHC_6H_5$

VIIIa: R = H
b: R = $CONHC_6H_5$

VII

CHART 1

The amine was characterized as its hydrochloride, m.p. 203–204°, which was identical with the hydrochloride of the authentic 2-amino-1,3-diphenylpropane (III).[6] Furthermore, the product (R_f 0·16), which was isolated by elution with Chf and a mixture of Chf and MeOH from the reduction products of Ia with LAH, was proved to be the same compound as the above III.

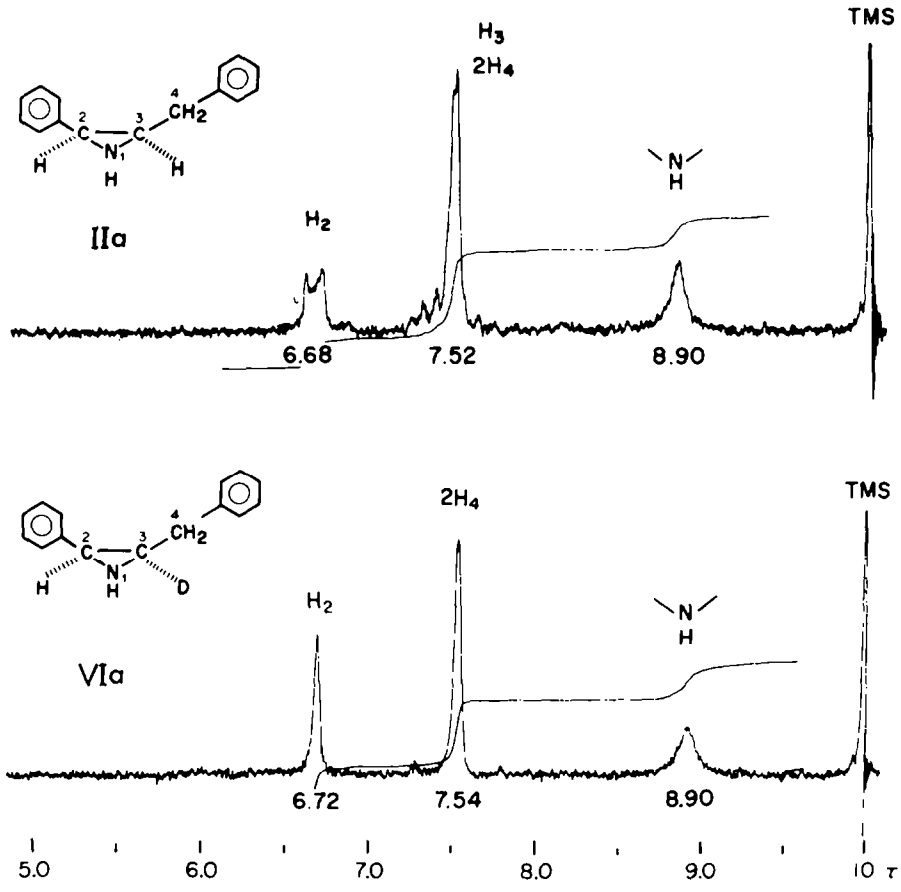


FIG. 1 The NMR spectra of *cis*-2-phenyl-3-benzylaziridine (IIa) and *cis*-2-phenyl-3-deutero-3-benzylaziridine (VIa) (60 Mc, $CDCl_3$).

Refluxing of Ia with 5% H_2SO_4 afforded an amino-alcohol Va which was acetylated with acetic anhydride and pyridine to the O,N-diacetate Vb, m.p. 122–123°. In this case, the cleavage of the aziridine ring with acid occurs probably according to the rule,[7] resulting in the formation of the products belonging to erythro-type, as shown in formulae, Va and Vb. In order to inspect the reaction mechanism, the oxime Ia was reduced with LAD instead of LAH to *cis*-2-phenyl-3-deutero-3-benzylaziridine (VIa), m.p. 43–44° (phenylcarbamoyl derivative VIb, m.p. 128–129°) in 75% yield. The location of deuterium introduced in VIa was determined by the comparison of the NMR spectra of IIa and VIa. As shown in Fig. 1, the NMR spectrum of VIa

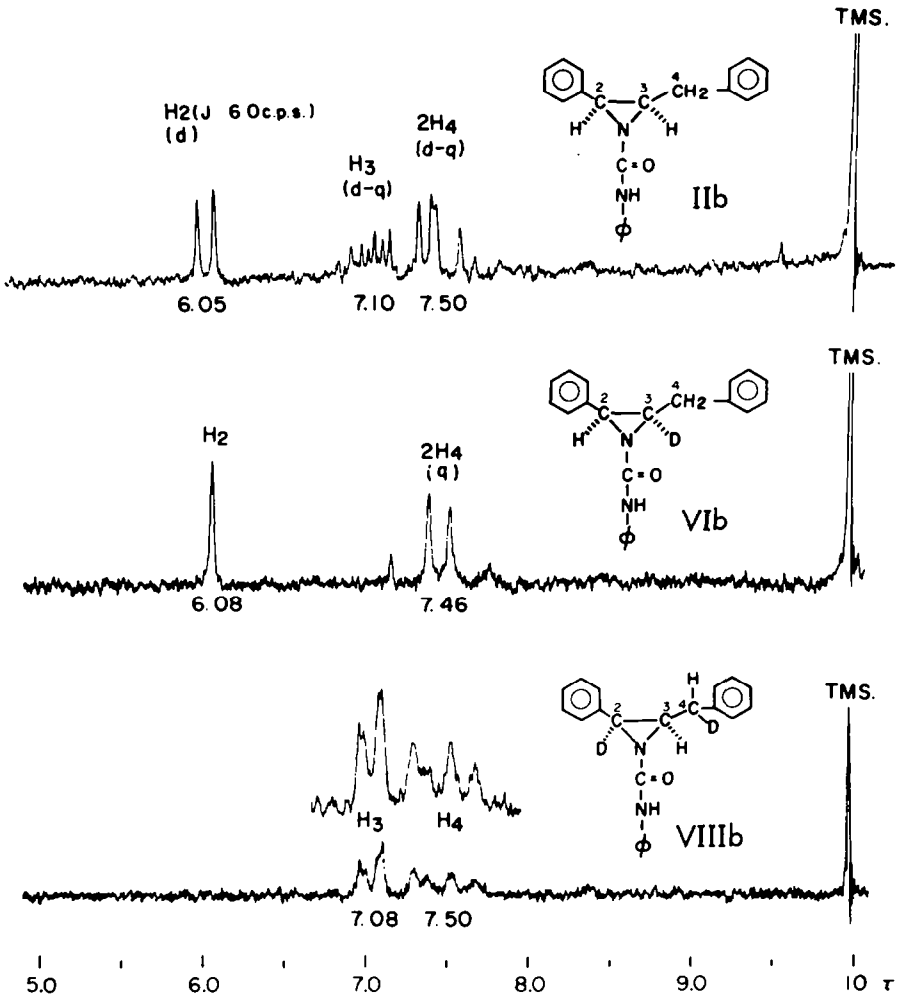


FIG. 2 The NMR spectra of phenylcarbamoyl derivatives (IIb, VIb and VIIIb) of *cis*-2-phenyl-3-benzylaziridine (IIa) (60 Mc, $CDCl_3$).

showed that the proton signals of C_2—H and two C_4—H appear at 6·72 τ and 7·54 τ as singlet, respectively and the signal corresponding to C_3—H disappears. These data clearly indicate the absence of a proton at C_3 in VIa and hence the introduction of deuterium at that position. The existence of a C—D stretching band at 2228 cm^{-1} in the IR spectrum of VIa gave additional evidence for the structure.

Treatment of chalcone oxime (VII) with LAD gave dideuterated *cis*-2-phenyl-3-benzylaziridine (VIIIa), which was transformed to its phenylcarbamoyl derivative VIIIb, m.p. 123–124° in 28% over-all yield from VII. The location of two deuterium introduced in VIIIa and VIIIb was determined by the comparison of the NMR spectra of IIb, VIb and VIIIb. As portrayed in Fig. 2, the NMR spectrum of VIb showed peaks at about 6·08 τ (C_2—H, singlet), about 7·46 τ (two C_4—H, AB type quartet) and the absence of that attributable to C_3—H. On the other hand, the NMR spectrum

of VIIIb showed the absence of the peak near 6·05 τ due to C_2—H, and the presence of peaks at about 7·08 τ (C_3—H, doublet–doublet) and about 7·50 τ (C_4—H, AB-type quartet) in relative peak areas of C_3—H:C_4—H = 1:1. These data clearly indicated the introduction of two deuterium in VIIIb instead of C_2—H and one hydrogen of the methylene group at C_4-position in IIb. Therefore, the above-mentioned data, which were obtained from reduction of Ia and VII with LAD, may provide a clue to inspect the mechanism of this reaction.

In addition, it was found that when the O-substituted derivatives, such as O—Me, O—acetyl and O—tosyl derivatives (Ib, Ic and Id), were used instead of the free oxime Ia for the LAH reduction, the major reduction product was the aziridine IIa, although in smaller yield for Id owing to the formation of the primary amine III and a secondary amine, benzylphenethylamine (IX). In order to confirm these results quantitatively, the LAH reduction of Ia, Ib, Ic or Id was performed under the same condition and the reduction products were analyzed by the technique of GLC.

As shown in Table 1, LAH reduction of Ia, Ib or Ic provided almost the same result, showing predominant formation of the aziridine IIa in ca. 90% yield together with a small amount of the primary amine III in 5–10% yields. On the contrary, LAH reduction of Id showed remarkably reduced formation of IIa accompanied with a considerable amount of III and IX.

TABLE 1. GLC ANALYSES OF REDUCTION PRODUCTS BY LAH OF DIBENZYLKETOXIME (Ia) AND ITS O-SUBSTITUTED DERIVATIVES (Ib, Ic and Id)[a]

Oxime derivative	Product % IIa	III	IX
Ia	92·5	7·2	trace[b]
Ib	90·3	9·3	trace[b]
Ic	87·5	5·6	trace[b]
Id	35·8	27·5[b]	36·3[b]

[a] Reduction procedure: Oxime derivatives, 0·167 mol/l.; LAH, 0·300 mol/l.; refluxed in a sealed tube for 3 hr. GLC analytical procedure: Unless otherwise stated, GLC analyses were carried out by the procedure A* using *p*-Me–benzylbenzyl-ether as internal reference.

[b] Procedure B* was used for the separation of III and IX instead of procedure A.

EXPERIMENTAL

M.ps were taken by capillary tube and uncorrected. The NMR spectra were determined at 60 Mc with a Varian A-60 spectrometer using TMS as internal standard in $CDCl_3$. The IR spectra were measured using a Koken Model D.S. 301 IR double-monochromatic spectrophotometer. The gas chromatography was performed with a Hitachi Model K-53 gas chromatograph using *p*-Me-benzylbenzyleter as internal reference. Unless otherwise stated, solutions were dried over Na_2SO_4.

LAH reduction of dibenzylketoxime (Ia)†. To a slurry of LAH (3·8 g) in THF (350 ml), a soln of Ia (11·27 g),

* Details of the procedures A and B were described in the Experimental section.

† In this connection, the detailed procedure for the synthesis of *cis*-2-phenyl-3-benzylaziridine (IIa) is being in contribution to Organic Syntheses.[8]

m.p. 122–123° in THF (80 ml) was dropwise added with stirring at 20° over a 10 min period. The mixture was refluxed for 3 hr showing colour change for the initial pale green to a permanent, light chocolate colour. The mixture was cooled with ice and decomposed by gradual addition of H_2O (12 ml) at a temp below 20°. The ppt was collected by filtration and washed with ether (400 ml). The ethereal washings were combined with the original filtrate, dried and evaporated to dryness *in vacuo* to give a pale yellow oil (11·0 g), which was dissolved in pet. ether (100 ml) and chromatographed on SiO_2 (75 g, Merck). Fractions eluted with pet. ether : benzene (1 : 1, 1 : 3) and benzene only were combined and evaporated to leave a crystalline residue (9·0 g), which was recrystallized from pet. ether to give IIa (7·8 g), m.p. 44–45° as needles; ν_{max}^{Chf} 3350 cm^{-1} (>NH). NMR: 8·90 τ (N_1—H, broad singlet), ~7·52 τ (C_3—H and two C_4—H, multiplet), ~6·68 τ (C_2—H, poor doublet). (Found: C, 86·25; H, 7·21; N, 6·91. $C_{15}H_{15}N$ requires: C, 86·08; H, 7·22; N, 6·69%). The soln of IIa (100 mg) and phenylisocyanate (62 mg) in ether (3 ml) was stirred at room temp for 3 hr. Evaporation of the solvent left a crystalline residue (160 mg), which was recrystallized from ether to give IIb (110 mg), m.p. 123–125° as needles; ν_{max}^{Nujol} 3250 cm^{-1} (>NH), 1661 cm^{-1} (—CONH—); NMR: 6·05 τ (C_2—H, doublet, $J_{2,3}$ = 6·0 c/s), ~7·10 τ (C_3—H, octet), ~7·00 τ (two C_4—H, octet). (Found: C, 80·71; H, 6·32; N, 8·64. $C_{22}H_{20}ON_2$ requires: C, 80·46; H, 6·14; N, 8·53%).

On the original chromatography over SiO_2, fractions eluted with Chf and a mixture of Chf : MeOH left a yellowish brown oil (1·20 g), which was subjected to vacuum distillation to give an oil (0·81 g), $b.p_{2\,mm}$ 121–126°. Its hydrochloride had a m.p. of 203–205° as needles by recrystallization from EtOH–AcOEt, identical with the hydrochloride of the authentic 2-amino-1,3-diphenylpropane (III).[6] (Ref. 6, m.p. 205–205·5°). (Found: C, 72·76; H, 7·58; N, 5·86; Cl, 14·57. $C_{15}H_{17}N \cdot HCl$ requires: C, 72·71; H, 7·32; N, 5·65; Cl, 14·31%).

Conversion of IIa *via* IV *into* III. After addition of 10% HClaq (5 ml) to the aziridine IIa (100 mg), the mixture was allowed to stand at room temp for ½ hr and evaporated to dryness *in vacuo* to leave a crystalline residue (120 mg), which gave on recrystallization from EtOH–AcOEt the hydrochloride of the chloroamine IV (90 mg), m.p. 184–185° as needles. (Found: C, 63·69; H, 6·33; N, 5·01; Cl, 24·99. $C_{15}H_{16}NCl \cdot HCl$ requires: C, 63·84; H, 6·07; N, 4·96; Cl, 25·13%). A soln of the compound IV–HCl (30 mg) in H_2O (5 ml) was hydrogenated in the presence of 10% Pd-carbon catalyst (35 mg) for 2 hr. After absorption of 1·5 molar equiv of H_2, reduction stopped. Filtration of the catalyst, addition of a small amount of 10% HClaq and evaporation of the filtrate left a crystalline residue (45 mg), which was recrystallized from EtOH to give III–HCl, m.p. 202–203° as needles.

Refluxing of IIa *with* 5% *sulphuric acid* (Va *and* Vb). The aziridine IIa (200 mg) was refluxed with 5% H_2SO_4aq (30 ml) for 1 hr. After cooling, the mixture was made alkaline with Na_2CO_3 and extracted with benzene. The benzene layer was washed with H_2O, dried and evaporated to dryness to leave a crude Va (240 mg), which was acetylated with Ac_2O (5 ml) and pyridine (5 ml). Working up left a crystalline residue (300 mg), which gave, on recrystallization from AcOEt, 2-amino-1,3-diphenyl-1-propanol O,N-diacetate (Vb), m.p. 122–123° as plates; ν_{max}^{Nujol} 3290 (>NH), 1742 (OAc), 1655 cm^{-1} (NHAc). (Found: C, 73·32; H, 6·92; N, 4·77. $C_{19}H_{21}ON_3$ requires: C, 73·29; H, 6·80; N, 4·50%).

LAD *reduction of* IIa (VIa *and* VIb). A soln of IIa (500 mg) in THF (15 ml) was added with stirring to a slurry of LAD (170 mg) in THF (4 ml) at room temp over a 2 min period and the mixture was refluxed for 3 hr. Working up left a crystalline residue (474 mg), which was dissolved in benzene (50 ml) and chromatographed on SiO_2 (10 g, Merck). Elution with benzene and benzene : Chf (2 : 1) left crude crystalline VIa (390 mg), which gave on repeated recrystallization from pet. ether (b.p. ~40°) pure VIa (300 mg), m.p. 43–44° as needles; ν_{max}^{Chf} 3324 (>NH), 2228 cm^{-1} (C—D stretching band); NMR: 8·90 τ (N_1—H, broad singlet), 7·54 τ (two C_4—H, singlet), 6·72 τ (C_2—H, singlet). Treatment of VIa (90 mg) with phenylisocyanate (70 mg) in ether (3 ml) gave crude VIb (130 mg), which was recrystallized from pet. ether to give pure VIb (100 mg), m.p. 128–129° as prisms. From the mother liquor, additional crop (34 mg) of crude VIb, m.p. 124–126° was isolated; ν_{max}^{Nujol} 3245 (>NH), 1660 cm^{-1} (>NCONH—); NMR: 7·46 τ (two C_4—H, AB type quartet), 6·08 τ (C_2—H, singlet).

LAD *reduction of* VII (VIIIa *and* VIIIb). A soln of VII (501 mg), m.p. 107·5–111°, in THF (5 ml) was added with stirring under cooling with ice to a slurry of LAD (171 mg) in THF (20 ml) and the mixture was refluxed for 3 hr. Working up left a light yellow oil (478 mg), which was treated with phenylisocyanate

in ether without the isolation of pure VIIIa. The resulting crude VIIIb (804 mg) was chromatographed over Al_2O_3 (24 g, Woelm, act. II) and fractions eluted with pet. ether and pet. ether:benzene (1:1) were recrystallized from ether–n-hexane to give pure VIIb (210 mg), m.p. 123–124°; ν_{max}^{Nujol} 3236 (>NH), 1658 cm^{-1} (>NCONH—); NMR: 7·08 τ (C_3—H, quartet), 7·50 τ (one C_4—H, AB type quartet).

LAH *reduction of* Ib. A soln of oily Ib (1·07 g), which was synthesized from dibenzylketone and hydroxylamine Me–ether, in THF (50 ml) was added with stirring at 10° to a slurry of LAH (0·75 g) in THF (10 ml) and the mixture was refluxed for 3 hr. Working up left a light yellow oil (1·01 g), which was expected to involve IIa and III etc, by examination using TLC. The reduction products were treated with phenylisocyanate (585 mg) to give a mixture of phenylcarbamoyl derivatives (1·60 g), which was chromatographed on Al_2O_3 (48 g, Woelm, act. II). Elution with pet. ether and pet. ether–benzene (1:1), and recrystallization of the eluate from ether gave pure IIb (930 mg, 63% yield), m.p. 122–123°.

LAH *reduction of* Ic. A soln of oily oxime acetate Ic (1·13 g) in THF (10 ml) was added with stirring at 12° to a slurry of LAH (640 mg) in THF (30 ml) and the mixture was refluxed for 3 hr. Working up left a light yellow oil (932 mg), which was converted with phenylisocyanate (525 mg) to the phenylcarbamoyl derivatives (1·51 g). The derivatives were chromatographed over Al_2O_3 (45 g, Woelm, act. II) to give pure IIb (940 mg, 68% yield), m.p. 122–123° from the fractions eluted with pet. ether and pet. ether–benzene (7:3).

LAH *reduction of* Id. The oxime tosylate Id (1·0 g), m.p. 84–86°, was reduced with LAH (1·02 g) in refluxing THF (110 ml) for 3 hr. Working up left a yellow oil (623 mg), which was treated with phenylisocyanate to give a mixture of phenylcarbamoyl derivatives. Elution-chromatography over Al_2O_3 (20 g, Woelm, act. II) gave besides IIb (234 mg) m.p. 122–123°, the N-phenylcarbamoyl derivative (134 mg), m.p. 113–115° of IX as prisms from ether; ν_{max}^{Nujol} 3301 (>NH), 1637 cm^{-1} (>NCONH—). (Found: C, 79·92; H, 6·80; N, 8·67. $C_{22}H_{22}ON_2$ requires: C, 79·97; H, 6·71; N, 8·48%).

GLC *analyses of the products by* LAH *reduction of* Ia, Ib, Ic *or* Id. LAH used in the experiment was purified according to the method of Davis *et al.*[9] THF was also purified in the way that commercially available THF was refluxed in the atmosphere of Ar over LAH for several days and distilled twice. GLC analyses were carried out using the following procedures, A and B.

Procedure A:		
Apparatus	Hitachi K-53	Support Chromosorb W (80–100 mesh)
Detector	FID	acid washed, DMCS treated
Column	Stainless steel	Coat KF-54 5%
	Diameter 3 mm	Carrier gas N_2, 35 ml/min
	Length 1 m	Column temp 170°
		Inj and FID temp 300°

Retention times of the products obtained by this procedure:
Internal reference (6·3 min), IIa (12 min), III and IX (8·4 min).

Procedure B:		
Apparatus	Hitachi K-53	Coat PEG 20 M 5%
Detector	FID	KOH 5%
Column	Stainless steel	Carrier gas N_2, 20 ml/min
	Diameter 3 mm	Column temp 190°
	Length 2 m	Inj and FID temp 300°
	Support Gas-chrom Q (80–100 mesh)	

Retention times of III and IX: III (8·6 min), IX (7·8 min).

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