Tetrahedron. Vol. 24. pp. 5677 to 5690. Pergamon Press 1968. Printed in Great Britain

STEREOCHEMISTRY OF AZIRIDINE FORMATION BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE ON ARALKYL ALKYL KETOXIMES AND THEIR TOSYLATES*

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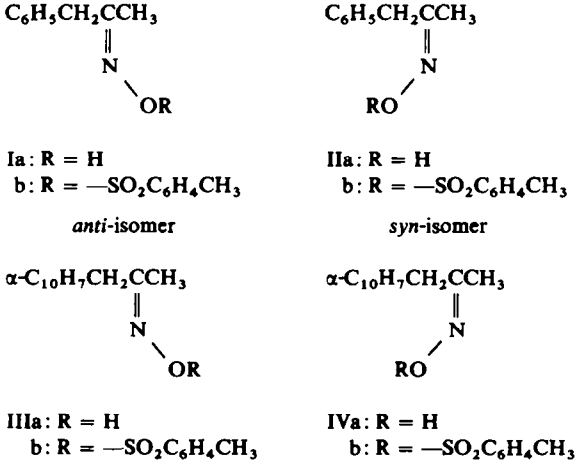
(*Received in Japan* 15 *March* 1968; *Received in the UK for publication* 16 *April* 1968)

Abstract—Separation of *syn*- and *anti*-isomers of aralkyl alkyl ketoximes and their tosylates has been carried out using 1-phenylpropan-2-one and 1-α-naphthylpropan-2-one. With the established configurations, LAH reduction of the oximes and their tosylates has been performed and the products have been analysed by GLC. The results clearly indicate that aziridine formation is strongly influenced by the configurations of the oximes and the oxime tosylates used.

RECENTLY, our group reported a new method for the synthesis of aziridines by LAH reduction of ketoximes.[2] The details and further extention are successively being presented.[3–6] At the earlier stage, it seemed that the general mode of this reaction may be reminiscent of the Neber and the related rearrangements.[7] The investigation of the stereochemistry of aziridine formation, however, indicates clearly that our reaction is of different type from the above reactions.[8] This is the subject of the paper.

(a) *Separation of* syn- *and* anti-*isomers of ketoximes and oxime tosylates*



* The part of this paper was presented in our preliminary communication.[1]

In order to study the stereochemistry of aziridine formation, separation of the isomers of the oximes and the tosylates was first undertaken with some aralkyl alkyl ketones, such as 1-phenylpropan-2-one and 1-α-naphthylpropan-2-one. Reaction of 1-phenylpropan-2-one with hydroxylamine gave a liquid mixture of *anti*- and *syn*-ketoximes in ratio of ca. 3:1, which was analysed by the NMR data. Pure *anti*-oxime Ia, m.p. 62–63°, was separated from a mixture of two isomers, but *syn*-isomer IIa was not obtained pure.* Treatment of Ia with tosyl chloride and pyridine afforded the *anti*-oxime tosylate Ib, m.p. 78–79° (dec), which was rearranged into N-benzyl-acetamide by action of basic alumina for 1 hr. The *syn*-oxime tosylate IIb, m.p. 88–89° (dec) was isolated from a mixture of *anti*- and *syn*-oxime tosylates after the contact with basic alumina for 3 hr, since the *anti*-oxime tosylate Ib was more readily rearranged by action of basic alumina than the *syn*-isomer. The Beckmann rearrangement of IIb with basic alumina for 40 hr gave as sole product, N-methyl-phenyl-acetamide, indicating the *syn*-configuration. Similarly, *anti*-1-α-naphthyl-propan-2-one oxime (IIIa), m.p. 96–97° could be separated from a mixture of two isomers, IIIa and IVa (ca. 1·5:1). The configuration of the oximes was based on the NMR data, which involve low shift owing to deshielding effect by the proximity of the OH group, as shown in Fig. 1. However, the *syn*-oxime IVa was not isolated in a pure state. Treatment of IIIa with tosyl chloride and pyridine afforded the *anti*-oxime tosylate, IIIb, m.p. 90° (dec), which was characterized by the rearrangement to N-α-naphthylmethylacetamide, m.p. 125–126° with basic alumina. Tosylation of a mixture of IIIa and IVa followed by contact with neutral alumina gave the *syn*-oxime tosylate, IVb, m.p. 101° (dec), accompanied with N-α-naphthylmethyl-acetamide (from IIIb) and a small amount of N-methyl-α-naphthylacetamide, m.p. 139–141° (from IVb). In this case, the use of basic alumina was unsuitable, because of concomitant rearrangements of two oxime tosylates. While characterization of the oxime tosylates thus separated was achieved by the Beckmann rearrangement with basic alumina, their NMR data also support the conclusion, indicating a greater deshielding effect by the proximity of the OH function than by the proximity of the unshared pair of electrons on the nitrogen,[9] as summarized in Table 1.

TABLE 1. NMR SPECTRAL DATA ON 1-SUBSTITUTED PROPAN-2-ONE OXIMES (Ia, IIa, IIIa AND IVa) AND THEIR TOSYLATES (Ib, IIb, IIIb AND IVb) (60 Mc, BENZENE)

Compound	$-CH_2-$	Chemical shift (τ) $-CH_3$	$-CH_3$ (tosyl group)
Ia	6·66	8·23	
IIa	6·33	8·39	
IIIa	6·20	8·31	
IVa	5·87	8·50	
Ib	6·97	8·62	8·09
IIb	6·67	8·68	8·13
IIIb	6·55	8·69	8·12
IVb	6·20	8·82	8·15

* Recently, the same finding was independently reported by two groups.[9]

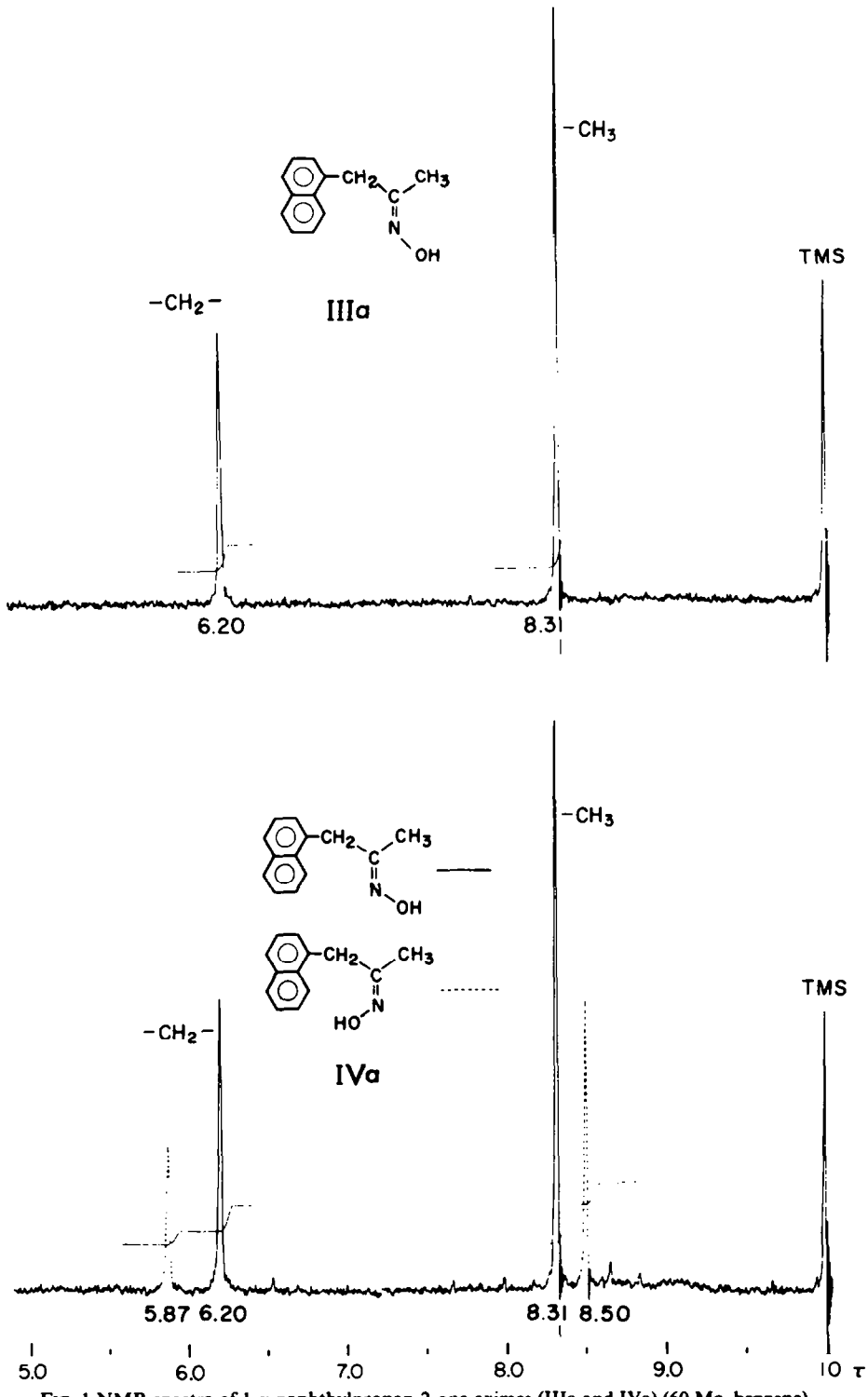
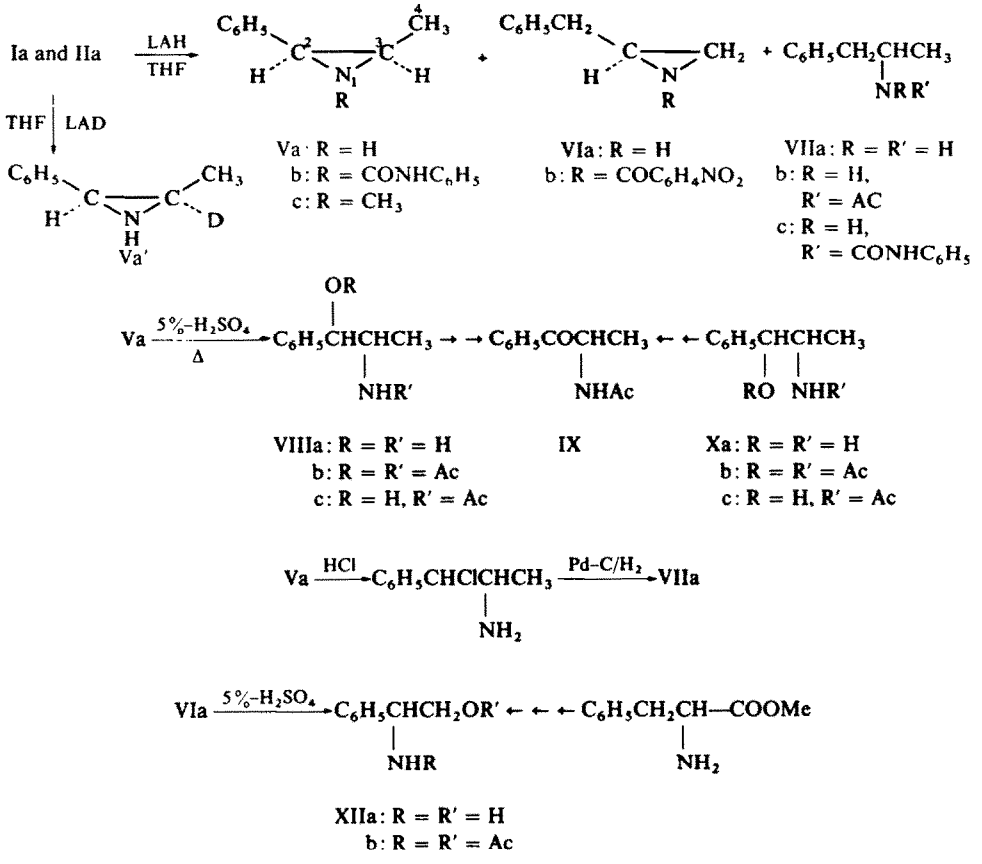


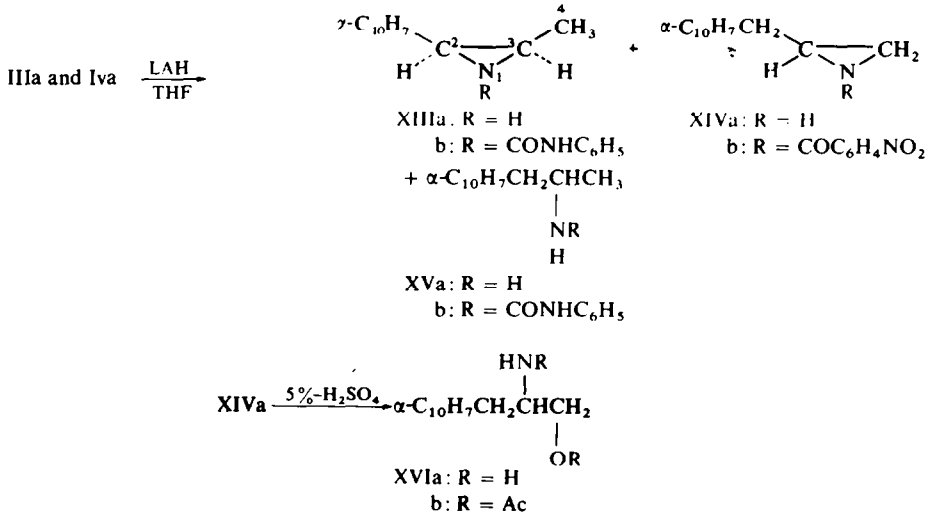
FIG. 1 NMR spectra of 1-α-naphthylpropan-2-one oximes (IIIa and IVa) (60 Mc, benzene).



(b) *Aziridine formation by* LAH *reduction of* 1-*phenylpropan*-2-*one oxime and* 1-α-*naphthylpropan*-2-*one oxime*

LAH reduction of a mixture of two isomers of 1-phenylpropan-2-one oxime (Ia:IIa, ca. 3:1) in boiling tetrahydrofuran (THF) afforded three basic products, which showed three spots (R_f-values, 0·85, 0·65 and 0·23) on TLC using SiO_2 and the solvent system of Chf:MeOH (20:1). Elution-chromatography over SiO_2 separated the products into three components in ratio of ca. 2·3:1:5, of which the product (R_f, 0·85) was proved to be *cis*-2-phenyl-3-methylaziridine (Va), m.p. 41–43°, based on the analytical and spectral data. The product Va corresponded to the molecular formula, $C_9H_{11}N$ with the IR band at 3300 cm^{-1} (>NH). In the NMR spectrum, the proton signals of Va appear at 9·02 τ (s, broad, >N<u>H</u>), 9·12 τ (d, $J_{3,4}$ = 5·5 c/s, —C<u>H</u>$_3$), 7·65 τ (d-q, $J_{3,4}$ = 5·5 c/s, $J_{2,3}$ = 6·5 c/s, C_3—H) and 6·82 τ (d, $J_{2,3}$ = 6·5 c/s, C_2—H), respectively. The NMR spectrum of its phenylcarbamoyl derivative Vb, m.p. 92–94°, shows the proton signal patterns similar to those of Va, such as 8·95 τ (d, $J_{3,4}$ = 5·5 c/s —C<u>H</u>$_3$), 7·06 τ (d-q, $J_{3,4}$ = 5·5 c/s, $J_{2,3}$ = 6·5 c/s, C_3—H) and 6·33 τ (d, $J_{2,3}$ = 6·5 c/s, C_2—H), but the proton signal due to the secondary amino group, which appears at high field in the spectrum of Va, is not recognized at all in Vb. These facts strongly suggest the presence of an aziridine ring in Va and further,

the above coupling constants ($J_{2,3}$ = 6·5 c/s) also permit the assignment of *cis*-configuration of the aziridine.[10] The assigned structure Va is also supported by the following chemical evidence. Refluxing of Va with 5% sulphuric acid gave an amino-alcohol VIIIa, which was converted to IX through the intermediates, VIIIb and VIIIc. In a similar manner, the ketone IX was also derived from the known dl-norephedrine (Xa).[11] This shows that VIIIa must be dl-norpseudoephedrine, resulting from *trans*-cleavage of the aziridine ring with the acid. Furthermore, treatment of Va with hydrochloric acid afforded a chloro-amine XI, which was reduced to the primary amine VIIa with Pd–carbon catalyst. The amine VIIa was identical with the product (R_f, 0·23) from the LAH reduction of 1-phenylpropan-2-one oxime. The amine VIIa was also characterized as its acetate (VIIb) and phenylcarbamoyl derivative (VIIc). Furthermore, the structure and stereochemistry of Va was unequivocally established by the comparison of its N-methyl derivative Vc with an authentic specimen as the picrate.*† The third product (R_f, 0·65), characterized as its *p*-nitrobenzoyl derivative, VIb, m.p. 92·5–94·5°, was found to be another aziridine VIa, reversely cyclized towards the terminal Me group. Refluxing of VIa with 5% sulphuric acid afforded an amino-alcohol XIIa as major product, characterized as its O,N-diacetate Xb, m.p. 114–115°, which was identical with the O,N-diacetate derived from the known dl-phenylalanine methylester. This permits the assignment of the structure VIa. Ultimately, the structure was determined by the synthesis of the aziridine VIa and its phenylcarbamoyl derivative VIb by the known method.[14] In order to inspect the reaction mechanism, LAD reduction of a mixture of the oxime isomers was carried out in boiling THF. Among reduction products, *cis*-2-phenyl-3-methyl-3-deuteroaziridine (Va), m.p. 40–42°, was isolated. The location of deuterium introduced was determined by the comparison of the NMR spectrum of Va with that of Va'. The spectrum of Va' shows the proton signals at 9·08 τ (s, —CH_3), 8·97 τ (s, broad, >N<u>H</u>) and 6·78 τ (s, broad, C_2—H) respectively, and the proton signal near 7·65 τ attributable to the C_3–hydrogen in Va disappears.



* We wish to thank Dr. H. Nishimura for providing valuable sample of Vc–picrate.[12]

† Waight *et al.* reported the synthesis of Va by LAH reduction of phenyl vinyl ketoxime.[13]

In a manner similar to the case of 1-phenylpropan-2-one oxime, LAH reduction of a mixture of 1-α-naphthylpropan-2-one oxime (IIIa: IVa, ca. 1·5:1) was carried out in boiling THF. The products were separated into the following three basic compounds: *cis*-2-α-naphthyl-3-methylaziridine (XIIIa), m.p. 77–79°, characterized as its phenylcarbamoyl derivative, XIIIb, m.p. 139–140° and 2-α-naphthylmethylaziridine (XIVa), characterized as its *p*-nitrobenzoyl derivative, XIVb, m.p. 121·5–122·5° and 1-α-naphthyl-2-aminopropane (XVa), characterized as its hydrochloride, m.p. 214–215° and phenylcarbamoyl derivative, XVa, m.p. 181–182°. The analytical and spectral data support the assignments of the structures, XIIIa, XIVa and XVa.*

(c) *Stereochemistry of aziridine formation by* LAH *reduction*

(i) *With* 1-*phenylpropan-2-one oximes* (Ia *and* IIa) *and their tosylates* (Ib *and* IIb).

$$\text{Ia and/or IIa} \xrightarrow[\text{THF}]{\text{LAH}} \text{Va} + \text{VIa} + \text{VIIa}$$

$$\text{Ib or IIb} \xrightarrow[\text{THF}]{\text{LAH}} \text{Va} + \text{VIa} + \text{VIIa} + \underset{\text{XVII}}{C_6H_5CH_2NHC_2H_5} + \underset{\text{XVIII}}{(C_6H_5CH_2CH_2NHCH_3)}$$

As mentioned above, *anti*-1-phenylpropan-2-one oxime (Ia), and *anti*- and *syn*-oxime tosylates (Ib and IIb) were isolated with the established configurations. In addition, the structures of the reduction products with LAH were also elucidated. In order to investigate the stereochemistry of aziridine formation, LAH reduction in boiling THF was first performed with Ia and a liquid mixture of Ia and IIa with a variety of content ratio under similar conditions and the reduction products were analyzed by GLC. Although the data regarding GLC of aziridine derivatives is insufficient,[15] satisfactory results were obtained from GLC analyses of the reduction products. For example, the gas chromatogram from the *anti*-oxime Ia is shown in Fig. 2.

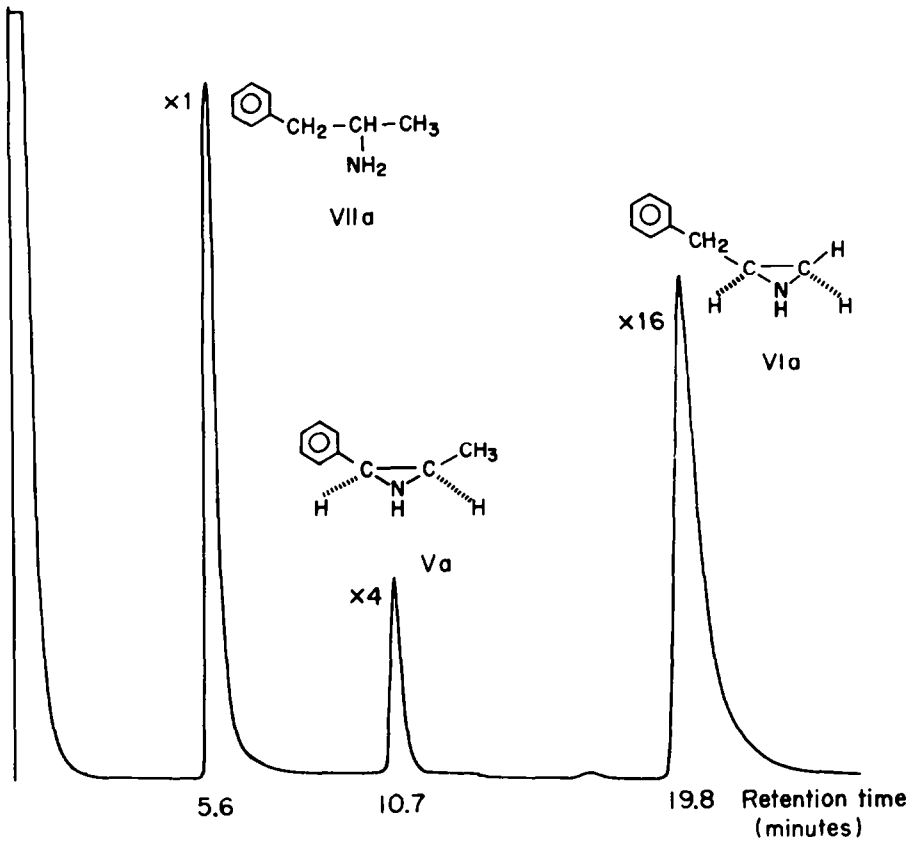
The GLC analytical data obtained from the oximes (Ia and/or IIb) are summarized in Table 2. The results show clearly that the increase of the *syn*-isomer IIa enhances the cyclization to the benzylic position, resulting in the increased formation of the aziridine Va, and when the content of the *anti*-isomer Ia increases, the reverse cyclization towards the terminal Me group occurs predominantly, forming the aziridine VIa.

TABLE 2. GAS CHROMATOGRAPHIC ANALYSES OF LAH REDUCTION PRODUCTS OF 1-PHENYLPROPAN-2-ONE OXIMES (Ia AND IIa)[a]

Isomer ratio of the oxime	Product Va	VIa	VIIa
anti only (Ia)	4·7%	18%	65%
anti:*syn* (Ia:IIa) = 5–7:1	13	13	56
anti:*syn* (Ia:IIa) = 2–3:1	23	8·8	56

[a] In each case, 300 mg of the oxime was reduced by refluxing with 166 mg (2·2 molar equiv.) of LAH in 10 ml of THF for 2 hr.

* Details were described in the experimental section.



Apparatus	Hitachi F6-D	Support	Chromosorb W(80-100 mesh) acid washed, DMCS treated.
Detector	FID	Coat.	Carbo wax 20M, 5%
Column	Stainless steel; Diameter, 3 mm; Length, 2 m	Carrier gas	N_2, 30cc/min.
		Column temp.	130°
		Inj. and FID temp.	160°

FIG. 2 Gas chromatogram of reaction mixture obtained by LAH reduction of *anti*-1-phenylpropan-2-one oxime (Ia).

For further confirmation, LAH reduction was carried out with purely isolated *anti*- and *syn*-oxime tosylates (Ib and IIb) under similar conditions and the products were analyzed by GLC. In these cases, the reduction products were more complicated, because N-ethylbenzylamine (XVII), presumably arising from the *anti*-isomer (Ib), was actually recognized in the reaction mixture. Although the presence of another secondary amine, N-methyl-phenethylamine (XVIII) was expected from the *syn*-isomer (IIb), it could not be confirmed, because of the peak of XVIII overlapping with that of VIIa. The data from Ib and IIb, shown in Table 3, indicates that the aziridine formation depends on the configuration of the oxime tosylate, with the same tendency as the oxime itself.

In both cases, even though pure *anti*-isomer (Ia or Ib) was used, a considerable amount of Va was still formed. This fact may be rationalized by a probable equilibrium between the *anti*- and the *syn*-isomers during the reduction.*

TABLE 3. GLC ANALYSES OF LAH REDUCTION PRODUCTS OF 1-PHENYLPROPAN-2-ONE OXIME TOSYLATES (Ib AND IIb)[a]

Isomer of oxime tosylate	Product Va	VIa	VIIa (XVIII)	XVII
anti (Ib)	6·9%	11·4%	44·7%	8·4%
syn (IIb)	21·0	1·5	55·7	5·4

[a] Reduction procedure: oxime tosylate, 50 mg; LAH, 19 mg (3·0 molar equiv.); THF, 1·5 ml; refluxed for 2 hr.

(ii) *With* 1-α-*naphthylpropan*-2-*one oximes* (IIIa *and* IVa) *and their tosylates* (IIIb *and* IVb). LAH reduction of 1-α-naphthylpropan-2-one oximes (IIIa and/or IVa)

$$\text{IIIa and/or IVa} \xrightarrow[\text{THF}]{\text{LAH}} \text{XIIIa} + \text{XIVa} + \text{XVa}$$

$$\text{IIIb or IVb} \xrightarrow[\text{THF}]{\text{LAH}} \text{XIIIa} + \text{XIVa} + \text{XVa} + \underset{\text{XIX}}{\alpha\text{-}C_{10}H_7CH_2NHC_2H_5} + \underset{\text{XX}}{(\alpha\text{-}C_{10}H_7CH_2CH_2NHCH_3)}$$

was carried out as for the oxime isomers (Ia and IIa) and their tosylates (Ib and IIb) and the products were analyzed by GLC as previously. The results are recorded in Table 4 and the data regarding similar treatment of the oxime tosylates (IIIb or IVb) are given in Table 5.

TABLE 4. GLC ANALYSES OF LAH REDUCTION PRODUCTS OF 1-α-NAPHTHYLPROPAN-2-ONE OXIMES (IIIa AND/OR IVa)[a]

Isomer ratio of the oxime	Product XIIIa	XIVa	XVa
anti only (IIIa)	15·2%	28·9%	53·5%
anti:*syn* (IIIa:IVa) = 3·6–3·8:1	26·1	23·3	41·1
anti:*syn* (IIIa:IVa) = 1·3–1·4:1	39·0	15·0	33·3

[a] Reduction procedure: oxime, 150 mg; LAH, 75 mg (2·66 molar equiv.); THF, 5 ml; refluxed for 3 hr.

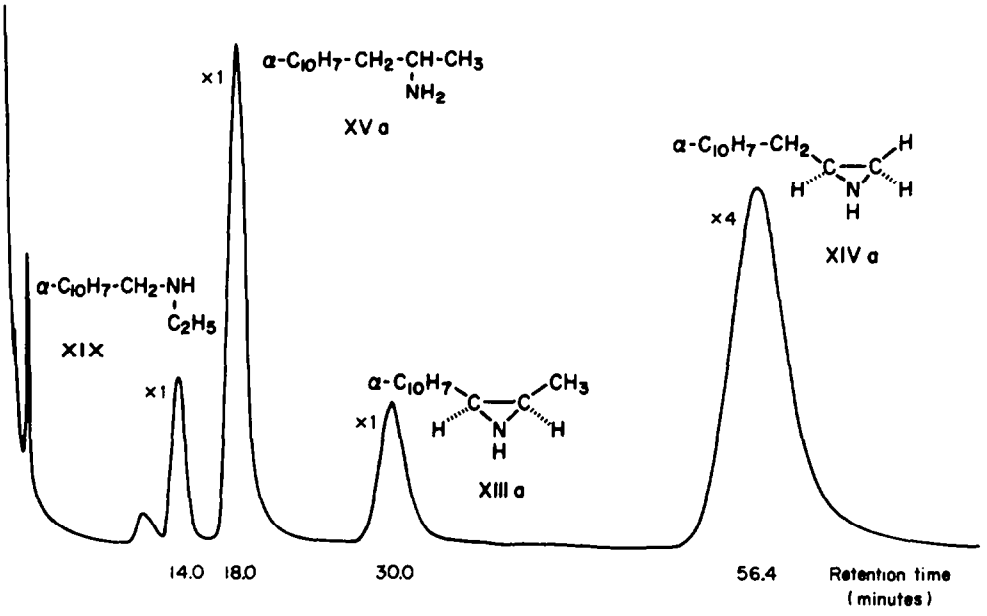
TABLE 5. GLC ANALYSES OF LAH REDUCTION PRODUCTS OF 1-α-NAPHTHYLPROPAN-2-ONE OXIME TOSYLATES (IIIb OR IVb)[a]

Isomer ratio of oxime tosylate	Product XIIIa	XIVa	XVa (XX)	XIX
anti (IIIb)	7·4%	22·1%	36·9%	2·4%
syn (IVb)	20·7	1·5	44·6	1·1

[a] Reduction procedure: oxime tosylate, 70 mg; LAH, 19 mg (2·5 molar equiv.); THF, 2 ml; refluxed for 3 hr.

* It was actually found that when pure *anti*-oxime Ia was refluxed in THF for 2 hr without LAH, about one-tenth of the oxime isomerized to *syn*-isomer IIa.

In both cases, satisfactory results were obtained regarding the GLC analyses of the respective products. For example, the products, XIIIa, XIVa, XVa (XVIII) and XIX show the corresponding peaks having the respective retention times, 30, 56, 18 and 14 min under the conditions used. As an example, the gas chromatogram of the products from the *anti*-oxime tosylate IIIb is shown in Fig. 3.



Apparatus	Hitachi F6-D	Support	Chromosorb W(80-100mesh)
Detector	FID		acid washed, DMCS treated.
Column	Stainless steel;	Coat.	Carbo wax 20M, 5%
	Diameter, 3mm;		KOH, 5%
	Length, 2m	Carrier gas	N_2, 60 cc/min.
		Column temp.	160°
		Inj. and FID temp.	240°

FIG. 3 Gas chromatogram of the reduction products of *anti*-1-α-naphthylpropan-2-one oxime tosylate (IIIb) with LAH.

(d) *Mechanism and conclusion*

As this new method for aziridine formation may be classified as similar to the Grignard reaction of ketoximes (the Hoch–Campbell Syntheses)[16] or the Neber and the related rearrangements,[7] the following two mechanisms,[2] tentatively proposed, are based on the reaction mechanism of the Hoch–Campbell syntheses[16b] or the Neber reaction.[8,17] The first involves the formation of the azirine intermediate through the unsaturated nitrene and the stereoselective reduction of the azirine to the *cis*-aziridine. The second consists of the concerted γ-elimination with the retention of the configuration about the nitrogen, like the Beckmann rearrangement, and the direct formation of the azirine without the nitrene intermediate. However, the results obtained here* can not be reasonably interpreted by either of the two mechanisms.

* In this connection, the same conclusion was obtained regarding the stereochemistry of aziridine formation by LAH reduction of ketoximes of bridged ring systems.[18]

Accordingly, a revised mechanism must be proposed. Although the detailed mechanistical study is being continued* and the aspect of this reaction becomes clear gradually, true features remain uncertain. However, cyclic intermediates such as in cyclopropane formation reactions[19] or the mechanism of concerted γ-elimination leading to the retention of the configuration about the nitrogen atom may be speculated.

EXPERIMENTAL

M.ps were taken by capillary tube and are 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 and the UV spectra were measured using a Hitachi Model E.P.S.-2UV spectrometer. The gas chromatography was performed using a Hitachi Model F-6D gas chromatograph. Unless otherwise stated, solns were dried over anhyd Na_2SO_4.

Isolation of anti-1-*phenylpropan*-2-*one oxime* (Ia). The ketone Ia (27 g), b.p.$_{14\ mm}$ 102·5°, in EtOH (140 ml) was added to an aqueous soln of $NH_2OH \cdot HCl$ (15 g) and AcONa (17 g) in H_2O (50 ml), and the mixture was heated at 80° for ½ hr and allowed to stand overnight at room temp (ca. 25°). The mixture was concentrated to remove EtOH and H_2O was added to the mixture, which was extracted with ether. The ethereal layer was washed with H_2O, dried and evaporated. The residue was distilled under reduced press to give a liquid mixture (20 g), b.p.$_{3\ mm}$ 117°, of *anti*- and *syn*-oximes in the ratio of ca. 3:1, analysed by the NMR spectrum. The mixture of oximes was allowed to stand in a refrigerator and the crystalline Ia gradually separated. The crystals were filtered off and the residue was again allowed to stand in the refrigerator. When this procedure was repeated, crude Ia (ca. 15 g) was obtained. Recrystallization from pet ether gave pure Ia, m.p. 62–63° as prisms; $\nu_{max}^{CCl_4}$ 3603, 3290 cm^{-1} (OH), 1670 cm^{-1} (C=N); NMR (in C_6H_6): 8·30 τ (3H, s, $-CH_3$), 6·68 τ (2H, s, $-CH_2-$). (Found: C, 72·59; H, 7·50; N, 9·41. $C_{10}H_{11}ON$ requires: C, 72·45; H, 7·43; N, 9·39%).

Furthermore, the NMR spectrum of the mixture of oxime isomers showed the proton signals corresponding to the *syn*-isomer IIa at 8·39 τ (3H, s, $-CH_3$) and 6·33 τ (2H, s, $-CH_2$), in addition to the signals for Ia.

anti-1-*Phenylpropan*-2-*one oxime tosylate* (Ib). To a soln of Ia (500 mg) in pyridine (1 ml), a soln of tosyl chloride (800 mg) in pyridine (2 ml) was added with stirring at −10° over a period of 5 min. The mixture was kept at −10° for 20 min and at 0° for 1·5 hr. Benzene (50 ml) was added to the mixture and the benzene soln was passed through the column of neutral Al_2O_3 (15 g, Woelm, Act. II) to remove the by-products. After elution with another 50 ml benzene, combined eluates were evaporated to dryness to give a crystalline residue, which was dissolved in a mixture of ether–n-hexane. Concentration by the stream of N_2 gave crude Ib, which gave, on recrystallization from ether–n-hexane, pure Ib, m.p. 78–79° (dec); NMR (in C_6H_6): 6·97 τ (2H, s, $-\underline{CH_2}-$), 8·62 τ (3H, s, $-\underline{CH_3}$), 8·08 τ (3H, s, $-C_6H_4\underline{CH_3}$). (Found: C, 62·80; H, 5·50; N, 4·84. $C_{16}H_{17}O_3NS$ requires: C, 63·33; H, 5·65; N, 4·62%).

TLC of Ib over SiO_2 readily gave a rearranged amide and recrystallization of Ib with heating gave a yellow-brownish substance which was insoluble in ether.

The Beckmann rearrangement of Ib *with basic* Al_2O_3. The oxime tosylate Ib obtained through the column of neutral Al_2O_3 (Woelm, Act. II) by the same procedure as mentioned above was dissolved in a small amount of benzene and the benzene soln was kept in contact with basic Al_2O_3 (40 g, Woelm, Act. I) for 1 hr. Elution with Chf gave crude N-benzylacetamide which was recrystallized from n-hexane–ether to afford pure amide, m.p. 57–58° (322 mg) as leaflets. (Found: C, 72·45; H, 7·43; N, 9·39. $C_9H_{11}NO$ requires: C, 72·70; H, 7·38; N, 9·58%).

Isolation of syn-*oxime tosylate* IIb. A liquid mixture (2·0 g) of Ia and Ib (ca. 3:1) was tosylated with tosyl chloride (3·2 g) in pyridine (12 ml). The mixture of the tosylates, Ib and IIb, obtained after the treatment of the reaction products with neutral Al_2O_3 (30 g, Woelm, Act. II), was dissolved in a small amount of benzene and the benzene soln was adsorbed with basic Al_2O_3 (100 g, Woelm, Act. I) for 2 hr. Elution with benzene and recrystallization of the eluate from n-hexane–ether at room temp gave pure IIb (355 mg), m.p. 89·5–90° (dec) as prisms; NMR (in C_6H_6): 6·67 τ (2H, s, $-CH_2-$), 8·70 τ (3H, s, $-\underline{CH_3}$), 8·13 τ (3H, s, $-C_6H_4\underline{CH_3}$). (Found: C, 62·96; H, 5·71; N, 4·93. $C_{16}H_{17}O_3NS$ requires: C, 63·33; H, 5·65; N, 4·62%). The *syn*-tosylate IIb was more stable than the *anti*-tosylate Ib.

* Details will be reported in the near future.

The Beckmann rearrangement of the syn-*oxime tosylate* IIb. The tosylate (170 mg) IIb was dissolved in a small amount of benzene and the benzene soln was kept in contact with basic Al_2O_3 (10 g, Woelm, Act. I) for 40 hr. Elution with Chf : MeOH (50:1) and recrystallization of the eluate with n-hexane–ether gave an amide (65 mg), m.p. 54·5–55°, identical with N-methyl-phenylacetamide by comparison with an authentic sample. (Found: C, 72·49; H, 7·23; N, 9·47. $C_9H_{11}ON$ requires: C, 72·45; H, 7·43; N, 9·39%).

Isolation of anti-1-α-*naphthylpropan-2-one oxime* (IIIa). 1-α-Naphthylpropan-2-one (1·85 g),[20] characterized as its semicarbazone, m.p. 193–194° as needles, was dissolved in EtOH (60 ml) and the soln was refluxed with $NH_2OH \cdot HCl$ (1·07 g) and anhyd AcONa (1·43 g) in H_2O (50 ml) for 3 hr. Working up gave a liquid mixture (1·96 g) of the isomers of the oxime, which was chromatographed on SiO_2 (55 g, Merck). Each fraction was eluted with benzene (190 ml). Seven fractions (Nos. 6–12) gave a crystalline residue (1·1 g), which was recrystallized from ether–pet ether to give IIIa (690 mg), m.p. 94–96°, as prisms. The mother liquor (336 mg) and the eluate (190 mg) from the fractions (Nos. 13–14) were combined and crystallized from the same solvent affording crude IIIa (74 mg), m.p. 92–94°. A pure sample for analysis had a m.p. of 96–97° after recrystallization; NMR: 6·23 τ (2H, s, $-CH_2-$), 8·34 τ (3H, s, $-CH_3$). (Found: C, 78·43; H, 6·79; N, 7·16. $C_{13}H_{13}ON$ requires: C, 78·36; H, 6·58; N, 7·03%). The mother liquor (440 mg) from crude IIIa and the oily fractions (Nos. 15–20) (352 mg) were collected and distilled at 155–180° (bath temp) under reduced press (2mm Hg). The distillate (750 mg) was found to be a mixture of IIIa and IVa in ratio of ca. 2:1 by analysis of the NMR spectrum. The proton signals of *syn*-isomer IVa appeared at 5·88 τ (2H, s, $-CH_2-$) and 8·49 τ (3H, s, $-CH_3$).

anti-1-α-*Naphthylpropan-2-one oxime tosylate* (IIIb). To a soln of the *anti*-oxime IIIa (200 mg) in pyridine (0·5 ml), a soln of tosyl chloride (228 mg) in pyridine (1 ml) was added with stirring at −10–−5° over a period of 5 min. The mixture was allowed to stand at the same temp for 15 min and at 0° for 1 hr. Benzene (10 ml) was added to the mixture and the benzene soln was passed through the column of neutral Al_2O_3 (4 g, Woelm, Act. II). The eluate combined with additional benzene eluate was evaporated to give a crystalline residue (350 mg), which was washed with pet ether and recrystallized from ether affording the *anti*-oxime tosylates IIIb (170 mg), m.p. 90° (dec) as prisms; NMR (in C_6H_6): 6·55 τ (2H, s, $-CH_2-$), 8·12 τ (3H, s, $-CH_3$), 8·69 τ (3H, s, $-C_6H_4CH_3$), (Found: C, 67·99; H, 5·49; N, 3·71. $C_{20}H_{19}O_3NS$ requires: C, 67·96; H, 5·42; N, 3·96%).

The Beckmann rearrangement of IIIb *with basic* Al_2O_3. A soln of IIIb (50 mg) in benzene (5 ml) was kept in contact with basic Al_2O_3 (3·5 g, Woelm, Act. I) for 2 hr.

Elution with Chf gave no starting material and afforded crude N-α-naphthylmethyl acetamide (35 mg), which was recrystallized from ether–n-hexane to give the pure amide, m.p. 125–126°[21] as prisms (Ref. 21, m.p. 134–135°); ν_{max}^{Nujol} 3305 (>NH), 1640 cm^{-1} (—C—, ‖ O). (Found: C, 78·45; H, 6·59; N, 6·93. $C_{13}H_{13}ON$ requires: C, 78·36; H, 6·58; N, 7·03%). A soln of the above amide (100 mg) in ether (2 ml) and THF (2 ml) was added to a suspension of LAH (76 mg) in ether (3 ml) and the mixture was refluxed for 5 hr. Working up gave a residue (92 mg), which was once distilled at 110–120° (bath temp) under reduced press (2 mm Hg) to leave an oily distillate (81 mg) of N-ethyl-α-naphthylmethylamine (XIX), characterized as its hydrochloride, m.p. 174–175° (from EtOH and AcOEt). (Found: C, 70·23; H, 7·08; N, 6·72. $C_{13}H_{15}N \cdot HCl$ requires: C, 70·41; H, 7·27; N, 6·32%).

Isolation of the syn-*oxime tosylate* IVb. To a liquid mixture of IIIa and IVa (ca. 1·5:1) in pyridine (3 ml), a soln of tosyl chloride (1·73 g) in pyridine (5 ml) was added with stirring at −10–−5° over a period of 5 min. The mixture was kept at the same temp for 20 min and at 0° for 1 hr. Benzene (70 ml) was added to the mixture and the benzene soln was passed through the column of neutral Al_2O_3 (15 g, Woelm, Act. II). The eluate was combined with a further benzene eluate and evaporated. The residue (3·5 g) in benzene (250 ml) was kept in contact with neutral Al_2O_3 (90 g, Woelm, Act. II) for 25 min. Immediately, the adsorbate was eluted with benzene (250 ml), the eluate washed with pet ether and recrystallized from ether giving IVb (600 mg), m.p. 101° (dec) as plates; NMR (in C_6H_6): 6·20 τ (2H, s, $-CH_2-$), 8·82 τ (3H, s, $-CH_3$), 8·15 τ (3H, s, $-C_6H_4CH_3$). (Found: C, 67·66; H, 5·42; N, 3·94. $C_{20}H_{19}O_3NS$ requires: C, 67·96; H, 5·42; N, 3·96%).

The Beckmann rearrangement of IVb *with basic* Al_2O_3. A soln of IVb (340 mg) in benzene (10 ml) was adsorbed with basic Al_2O_3 (24 g, Woelm, Act. I) for 16 hr.

Elution with Chf:MeOH (20:1) gave crude N-methyl α-naphthylacetamide (190 mg), which was recrystallized from benzene–n-hexane to give the above amide (110 mg), 139–141° as needles; ν_{max}^{Nujol} 3256

(>NH), 1640 cm^{-1} (>C=O). (Found: C, 78·31; H, 6·55; N, 7·27. $C_{13}H_{13}ON$ requires: C, 78·36; H, 6·58; N, 7·03%).

LAH *reduction of a liquid mixture of* 1-*phenylpropan*-2-*one oxime* (Ia *and* IIa). A soln of a liquid mixture (2·6 g) of Ia and IIa (ca. 2·5:1) in THF (70 ml) was added with stirring to a suspension of LAH (1·30 g) in THF (70 ml) at room temp over a period of 10 min and the mixture was refluxed for 2 hr. Working up in the usual manner left an oily residue (2·8 g), which showed three spots (R_f-values, 0·85, 0·65 and 0·23) on TLC using SiO_2 and the solvent system of Chf:MeOH (20:1). The above residue was chromatographed over SiO_2 (60 g, Merck).

Elution with benzene:Chf (2:3, 1:2) gave crude Va (R_f 0·85; 330 mg), which was distilled at 50–60° (bath temp) under reduced press (1 mm Hg). The crystalline distillate was recrystallized from n-hexane to give pure Va (270 mg), m.p. 41–43° as needles; ν_{max}^{Chf} 3300 cm^{-1} (>NH); NMR: 6·82 τ (d, $J_{2,3}$ = 6·5 c/s, C_2—H), 7·65 τ (d–q, $J_{3,4}$ = 5·5 c/s, $J_{2,3}$ = 6·5 c/s, C_3—H), 9·12 τ (d, $J_{3,4}$ = 5·5 c/s, —CH_3), 9·02 τ (s, broad, —NH—); M.W. Found: 140. Calc. for $C_9H_{11}N$: 133. (Found: C, 81·46; H, 8·41; N, 10·57. $C_9H_{11}N$ requires: C, 81·16; H, 8·33; N, 10·52%). A soln of Va (50 mg) in ether (1 ml) was added dropwise to a soln of phenylisocyanate (50 mg) in ether (1 ml) and the mixture was stirred at room temp for 3 hr. Evaporation of the solvent left a crystalline residue (75 mg), which was recrystallized from n-hexane–ether to yield Vb, m.p. 92–94° as needles, ν_{max}^{Nujol} 3230 (>NH), 1668 cm^{-1} (>C=O); NMR: 6·33 τ (d, $J_{2,3}$ = 6·5 c/s, C_2—H), 7·06 τ (d–q, $J_{3,4}$ = 5·5 c/s, $J_{2,3}$ = 6·5 c/s, C_3—H), 8·95 τ (d, $J_{3,4}$ = 5·5 c/s, —CH_3). (Found: C, 75·83; H, 6·52; N, 10·94. $C_{16}H_{16}ON_2$ requires: C, 76·16; H, 6·39; N, 11·10%). A soln of MeI (168 mg) in benzene (4 ml) was added at 0° to a soln of Va (50 mg) and NaH (30 mg) in benzene (5·5 ml). The mixture was allowed to stand at room temp for 13 hr and refluxed for 4 hr. Examination of the reaction mixture on TLC using Al_2O_3 and the solvent system of benzene:Chf (1:1) showed the presence of a considerable amount of the starting Va. Preparative TLC using Al_2O_3 (500 μ) and the same solvent system separated the N–Me derivative Vc as an oil, which was converted to its picrate, m.p. 101–102° as prisms, identical with an authentic sample from the comparison of mixed m.p., TLC and IR spectra (Ref. 12, m.p. 97·5–98·5°).

Elution with benzene:Chf (1:4, 1:10) gave crude VIa (R_f, 0·65; 120 mg) as a light yellow oil, ν_{max}^{Chf} 3325 cm^{-1} (>NH), which, without further purification, was converted to its N-*p*-nitrobenzoyl derivative VIb. That is, a soln of crude VIa (90 mg), $(C_2H_5)_3N$ (86 mg) and *p*-nitrobenzoyl chloride (130 mg) in benzene (1·5 ml) was allowed to stand at room temp for 2 hr. Filtration of the ppt and evaporation of the filtrate left a crystalline residue, which was twice recrystallized from n-hexane–ether to give VIb (53 mg), m.p. 92·5–94·5° as needles; ν_{max}^{Nujol} 1665 cm^{-1} (>NCO—). (Found: C, 68·09; H, 5·02; N, 10·00. $C_{16}H_{14}O_3N_2$ requires: C, 68·07; H, 5·00; N, 9·92%). The product Vb was identical with an authentic sample synthesized by the known method[14] (Ref. 14, m.p. 85·5–86·5°).

The third reduction product, VIIa (R_f 0·23; ca. 900 mg), was eluted with Chf and Chf:MeOH (100:1). The crude product was once distilled at 120–130° (bath temp) under reduced press (20 mm Hg) and converted to the hydrochloride, VIIa–HCl, m.p. 146–148° as scales. (Found: C, 62·81; H, 8·12; N, 7·89; Cl, 21·18. $C_9H_{14}NCl$ requires: C, 62·97; H, 8·22; N, 8·16; Cl, 20·66%). The product VIIa was also characterized as its N–acetate, VIIb, m.p. 69–70° as plates, ν_{max}^{Chf} 3330 (—NH—), 1665 cm^{-1} (>NCOCH$_3$). (Found: C, 74·64; H, 8·51; N, 8·03. $C_{11}H_{15}ON$ requires: C, 74·54; H, 8·53; N, 7·90%) and its N-phenylcarbamoyl derivative, VIIc, m.p. 163–164°, ν_{max}^{Nujol} 3230 (—NH—), 1640 cm^{-1} (>NCONH—). (Found: C, 75·63; H, 7·18; N, 11·12. $C_{16}H_{18}ON_2$ requires: C, 75·56; H, 7·13; N, 11·02%).

Conversion of Va via VIIIa, VIIIb *and* VIIIc *into* IX. The aziridine Va (500 mg) was refluxed with 5% H_2SO_4 (50 ml) for 1 hr. The reaction mixture was basified with Na_2CO_3, saturated with NaCl and extracted with benzene. The benzene layer was washed with the sat NaCl aq, dried and evaporated to dryness leaving a residue (500 mg), which gave, on twice chromatography on Al_2O_3 (Woelm, Act. II), pure VIIIa (150 mg), m.p. 76–77°[22] as plates (from ether). (Found: C, 71·72; H, 8·77; N, 9·48. $C_9H_{13}ON$ requires: C, 71·49; H, 8·67; N, 9·26%). The hydrochloride, VIIIa–HCl, had a m.p. of 168–170°[22] after recrystallization from EtOH–AcOEt. (Found: C, 57·44; H, 7·56; N, 7·51; Cl, 18·99. $C_9H_{13}ON \cdot HCl$ requires: C, 57·60; H, 7·52; N, 7·47; Cl, 18·99%). (Ref. 22, VIIIa, m.p. 71°; VIIIa–HCl, m.p. 169°). From the above

results, the product VIIIa seemed to be dl-norpseudoephedrine. For further confirmation, VIIIa was converted into oily VIIIc through crystalline VIIIb, m.p. 105–109°. The N-monoacetate VIIIc (50 mg) was oxidized at room temp with chromic acid (30 mg) in acetone (8 ml) for 4 hr and overnight in a refrigerator. Evaporation of the solvent, addition of H_2O, saturation with NaCl and extraction of the mixture with ether left a residue (40 mg), which was chromatographed over SiO_2 (1g, Merck). The eluate (30 mg) with Chf showed ν_{max}^{Chf} 3400 (—NH—), 1660 cm^{-1} (>C=O), indicating the presence of the conjugated ketone with the benzene ring. The ketone IX was characterized as its semicarbazone, m.p. 195–197° as plates (from EtOH). (Found: C, 58·05; H, 6·74; N, 22·24. $C_{12}H_{16}O_2N_4$ requires: C, 58·05; H, 6·50; N, 22·57%).

Conversion of Xa via Xb *and* Xc *into* IX. dl-Norephedrine (Xa) synthesized by the known method[11] was converted into the N-monoacetate Xc, m.p. 135–136°, through the O,N-diacetate Xb, ν_{max}^{Chf} 3450 (—NH—), 1745 (OAc), 1675 cm^{-1} (NHAc). The product Xc was oxidized in the same manner into the conjugated ketone IX, which was also converted into its semicarbazone, m.p. 195–197°, identical with that obtained from Va.

Conversion of Va *into* VIIa. Hydrogen chloride was passed through a soln of Va (100 mg) in dry benzene (10 ml) at room temp and the mixture was saturated with HCl. After standing at room temp for 1 hr, the solvent was evaporated to dryness *in vacuo* leaving a crystalline residue (115 mg), which gave, on recrystallization from EtOH–AcOEt, a chloro-amine–HCl, m.p. 199–200° (dec) as needles. (Found: C, 52·35; H, 6·39; N, 6·83; Cl, 34·55. $C_9H_{13}NCl_2$ requires: C, 52·44; H, 6·36; N, 6·80; Cl, 34·40%). A soln of the above chloro-amine–HCl (30 mg) in H_2O (5 ml) was reduced in an atmosphere of H_2 with 10% Pd–carbon catalyst (34 mg). After absorption of 1·4 molar equiv H_2, the reduction stopped. Working up left a crystalline residue (20 mg), which was recrystallized from AcOEt to yield VIIa–HCl, m.p. 147–148°.

Action of sulphuric acid on VIa (XIIa *and* XIIb). The aziridine VIa (83 mg) was refluxed with 5% H_2SO_4 (10 ml) for ½ hr. The mixture was basified with Na_2CO_3, saturated with NaCl and extracted with AcOEt. Working up left an oily residue (64 mg), which was chromatographed on neutral Al_2O_3 (2 g, Woelm, Act. II). Elution with benzene, AcOEt and Chf gave a crude XIIa (33 mg), which, without further purification, was acetylated with Ac_2O and pyridine. The crude O,N-diacetate XIIb (38 mg) was recrystallized from AcOEt–n-hexane to give pure XIIb, m.p. 114–115° as needles, ν_{max}^{Nujol} 3276 (—NH—), 1725 (—OAc), 1640 cm^{-1} (—NHAc). (Found: C, 66·49; H, 7·27; N, 5·82. $C_{13}H_{17}O_3N$ requires: C, 66·38; H, 7·28; N, 5·95%). This diacetate was identical with the O,N-diacetate XIIb, m.p. 113–114·5°, synthesized from dl-phenylalanine Me-ester by the known method.[14,23]

LAD *reduction of a liquid mixture of* Ia *and* IIa. LAD reduction of a liquid mixture of Ia and IIa was carried out in a manner similar to the LAH reduction. Working up left a mixture of deuterated products, which gave, on chromatography over SiO_2 (Merck), 3-deuteroaziridine (Va'), m.p. 40–42°, which indicated a C–D stretching band at 2226 cm^{-1} and the proton signals at 6·78 τ (s, C_2–H), 8·96 τ (s, broad, —NH—) and 9·08 τ (s, —CH_3). These spectral data supported reasonably the assignment of Va'.

LAH *reduction of a liquid mixture of* 1-α-*naphthylpropan-2-one oxime* (IIIa *and* IVa). A suspension of LAH (578 mg) in THF (15 ml) was added to a soln of a liquid mixture (1·51 g) of IIIa and IVa (ca. 1·5:1) over a period of 10 min and the mixture was refluxed for 1·5 hr. Working up left a mixture of reduction products (1·42 g), which showed three spots (R_f-values, 0·56, 0·44 and 0·19) on TLC using SiO_2 and the solvent system of Chf:MeOH (20:1). The mixture of the products was chromatographed on SiO_2 (43 g, Merck). Elution with benzene:Chf (1:1) left a residue (630 mg), which was once distilled at 120–155° (bath temp) under reduced press (2 mm Hg) to yield a crystalline distillate (605 mg). Recrystallization from n-hexane–ether gave pure XIIIa (R_f 0·56, 440 mg), m.p. 77–78°, $\nu_{max}^{CCl_4}$ 3283 cm^{-1} (>NH), NMR: 6·40 τ (d, $J_{2,3}$ = 6·5 c/s, C_2—H), 7·35 τ (d–q, $J_{2,3}$ = 6·5 c/s, $J_{3,4}$ = 5·5 c/s, C_3—H), 9·18 τ (d, $J_{3,4}$ = 5·5 c/s, —CH_3), 8·80 τ (s, broad, —NH—). (Found: C, 85·23; H, 7·35; N, 7·72. $C_{13}H_{13}N$ requires: C, 85·20; H, 7·15; N, 7·64%). Treatment of XIIIa (30 mg) with phenylisocyanate (35·7 mg) in ether (3 ml) gave crude XIIIb (77 mg), which was recrystallized from n-hexane–acetone to afford pure XIIIb, m.p. 139–140° as needles, ν_{max}^{Nujol} 3268 (—NH—), 1660 cm^{-1} (>C=O). (Found: C, 79·47; H, 6·03; N, 9·39; O, 5·54. $C_{20}H_{18}ON_2$ requires: C, 79·44; H, 6·00; N, 9·27; O, 5·29%). Elution with Chf:benzene (1:1) and Chf gave crude XIVa (157 mg) as an oil, which was treated with *p*-nitrobenzoyl chloride and $(C_2H_5)_3N$ to give its *p*-nitrobenzoyl derivative XIVb (130 mg), m.p. 121·5–122·5° as prisms (from ether), ν_{max}^{Nujol} 1666 cm^{-1} (>NCO—). (Found: C, 72·46; H, 4·95; N, 8·40. $C_{20}H_{16}O_3N_2$ requires: C, 72·28; H, 4·85; N, 8·43%). Fractions with Chf:MeOH (10:1) left crude primary amine XVa (480 mg), of which a portion (100 mg) was converted to its hydro-

chloride, m.p. 214–215° as plates. (Found: C, 70·50; H, 7·16; N, 6·63; Cl, 16·14. $C_{13}H_{15}N \cdot HCl$ requires: C, 70·42; H, 7·27; N, 6·32; Cl, 15·99%). Furthermore, crude XVa (50 mg) was treated with phenylisocyanate (36 mg) in ether (3 ml) at room temp for 1·5 hr. The resulting crude XVb was recrystallized from AcOEt to give pure XVb (66 mg), m.p. 181–182° as needles, ν_{max}^{Nujol} 3300 (—NH—), 1629 cm^{-1} ($\rangle C{=}O$). (Found: C, 79·15; H, 6·70; N, 9·36. $C_{20}H_{20}ON_2$ requires: C, 78·92; H, 6·62; N, 9·20%).

Action of XIVa *with sulphuric acid.* The aziridine XIVa (150 mg) was refluxed with 5% H_2SO_4 (16 ml) for 2 hr. Working up in a manner similar to the case of VIa left a crystalline residue (183 mg), which was recrystallized from EtOH to yield an amino-alcohol XVIa (120 mg), m.p. 123–124° as needles. (Found: C, 77·37; H, 7·27; N, 6·94. $C_{13}H_{15}ON$ requires: C, 77·58; H, 7·51; N, 6·96%). The product XVIa (90 mg) was acetylated with Ac_2O (1 ml) and pyridine (3 ml). The resulting crude O,N-diacetate (50 mg) was recrystallized from n-hexane–AcOEt to give pure XVIb (31 mg), m.p. 127–128° as needles, ν_{max}^{Nujol} 3283 (—NH—), 1720 (—OAc), 1645 cm^{-1} ($\rangle NAc$). (Found: C, 71·82; H, 6·71; N, 4·94. $C_{17}H_{19}O_3N$ requires: C, 71·56; H, 6·71; N, 4·91%).

Acknowledgement—We thank Dr. K. Kitahonoki for valuable discussions.

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