Asymmetric Syntheses. Part IX.[1] Reduction of Ketone Oximes and their *O*-Substituted Derivatives with the Lithium Aluminium Hydride–3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose Complex to give Optically Active Amines

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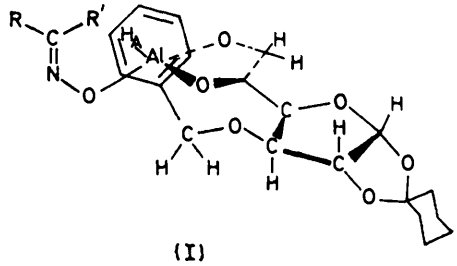
The asymmetric reduction of ketone oximes and their *O*-tetrahydropyranyl and *O*-methyl derivatives with the lithium aluminium hydride–3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex yields optically active amines of up to 56% optical purity. The stereoselectivities obtained from reduction of the *O*-substituted oximes were similar to those from the reduction of the free oximes. All the resulting amines have the *S*-configuration and this method may be used in determining the absolute configurations of amines. Asymmetric reduction with the ethanol-modified glucofuranose complex gives optically active amines of the *R*-configuration.

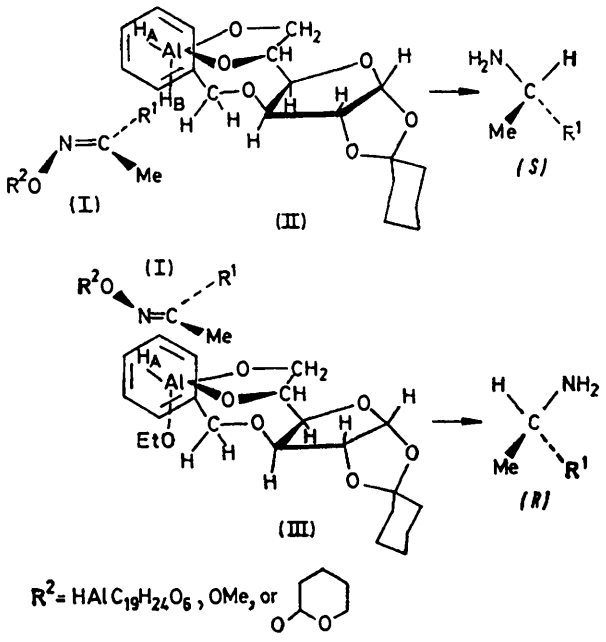
In Parts I—III [2-4] we reported the asymmetric reduction of ketones by lithium aluminium hydride–monosaccharide complexes to give optically active alcohols with up to 70% stereoselectivity. We have now extended these investigations to the reduction of the isoelectronic imino-group and obtained optically active amines. Here the essential mechanistic step is similar to that in the case of the carbonyl group, which must involve a kinetically controlled hydride transfer in which the sterically least hindered transition state predominates. Thus the formation of optically active amines depends on the fact that the free energies of activation corresponding to the approach of the hydride complex to either side of the carbon–nitrogen double bond must be different, leading to the formation of the two enantiomers (*R* and *S*) in unequal amounts; the greater the steric differences and therefore the differences in activation energies, the higher the stereoselectivity obtained.

Although the multiple bonds of the carbonyl and oxime groups are similar, the free oxime possesses an additional hydroxy-group which reacts with the aluminium hydride–monosaccharide reducing complex, hydrogen being evolved. Based on the evidence [3,4]



(I)

reported previously it may be assumed that the hydrogen atom replaced in this reaction is predominantly H_B. However coplanarity of the Al, O, N, and C atoms in the complex (I) thus formed renders intramolecular transfer of H_A to the oxime carbon atom sterically improbable and energetically unfavourable. Hence the asymmetric reduction must proceed by an intermolecular hydride transfer preferentially of H_B from a second molecule of



SCHEME

aluminium hydride–monosaccharide complex (II) to the carbon atom of the oxime group in (I), and this would be predicted to give optically active amines of the *S*-configuration (see Scheme).

This was found to be the case. Ten examples, including both alkyl and aryl ketone oximes (Tables 1 and 2), all gave optically active amines of the *S*-configuration. The three amines for which the configuration had not been previously established have now been assigned the *S*-configuration.

The asymmetric reductions of oximes and their *O*-methyl and *O*-tetrahydropyranyl derivatives all proceeded with similar stereoselectivities (Table 3) as would be expected if a common mechanism involving a second molecule of reducing agent was operative. The *O*-substituent on the oxime is evidently too remote to

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[1] Part VIII, S. R. Landor, B. J. Miller, J. P. Regan, and A. R. Tatchell, *J.C.S. Perkin I*, 1974, 557.

[2] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.* (*C*), (*a*) 1966, 1822; (*b*) 1966, 2280; (*c*) 1967, 197.

[3] S. R. Landor, A. R. Tatchell, and R. H. Williams, unpublished work.

[4] Y. M. Chan, S. R. Landor, and A. R. Tatchell, unpublished work.

have any influence on the stereochemistry of the asymmetric hydride transfer, and only marginal differences in the stereoselectivities are observed (see Scheme).

Reductions of dialkyl ketone oximes showed stereoselectivities which were roughly proportional to the as would be expected from steric considerations only. Apparently π–π interaction between the benzyl residue on the furanose ring and the aromatic substituent on the oxime counteracts the effect of the difference in bulk of the substituents.

TABLE 1

Reduction of aromatic ketone oximes with the glucofuranose complex

Ketone:	Acetophenone		Propiophenone		1-Phenylpropan-2-one		Deoxybenzoin		Methyl 1-naphthyl ketone	
Amine:	1-Phenyl ethylamine *[a]		1-Phenyl-propylamine *[b]		1-Methyl-2-phenylethyl-amine *[c]		1,2-Diphenyl-ethylamine †[d]		1-(α-Naphthyl)-ethylamine †[e]	
$LiAlH_4$ (mol)	$[\alpha]_D^{20}$ [f]	% e.e	$[\alpha]_D^{20}$	% e.e	$[\alpha]_D^{20}$	% e.e	$[\alpha]_D^{20}$	% e.e	$[\alpha]_D^{20}$	% e.e.
0·012	−2·49	6·24	−1·35	6·8	+1·23	3·4	−1·08	8·9	−3·72	4·7
0·018	−2·66	9·18	−1·76	8·9	+3·05	8·56	−2·1	17·2	−4·66	5·8
0·025	−2·75	9·48	−2·6	13·1	+5·70	16·03	−3·05	24·8	−5·82	7·3
0·032	−3·1	10·70	−2·8	14·1	+7·56	21·23	−1·86	15·2	−7·56	9·5
0·039	−2·81	9·70	−1·95	9·8	+4·26	11·98	−2·38	19·5	−6·03	7·5
0·045			−1·62	8·2	+2·11	5·92	−1·52	12·5	−4·32	5·4

% e.e. = excess enantiomer = observed rotation × 100/maximum rotation. * Yields of amine >70%. † Yields of amine *ca.* 60%.

[a] B.p. 64° at 4 mmHg. [b] B.p. 100° at 35 mmHg. [c] B.p. 70° at 5 mmHg. [d] B.p. 138° at 1 mmHg. [e] B.p. 150° at 11 mmHg. [f] Rotations for methanolic solutions (*c* 12·5%).

TABLE 2

Reduction of aliphatic ketone oximes with the glucofuranose complex

Ketone:	Ethyl methyl ketone		Methyl propyl ketone		Isopropyl methyl ketone		Butyl methyl ketone		Isobutyl methyl ketone		Methyl t-butyl ketone		Hexyl methyl ketone		Cyclohexyl methyl ketone	
Amine:	s-Butyl-amine *[a]		1-Methyl-butylamine *[b]		1,2-Dimethyl-propylamine *[c]		1-Methyl-pentylamine *[d]		1,3-Dimethyl-butylamine *[e]		1,2,2-Trimethyl-propylamine *[f]		1-Methyl-heptylamine *[g]		1-Cyclohexyl ethylamine *[h]	
$LiAlH_4$ (mol)	$[\alpha]_D^{20}$	% e.e.	$[\alpha]_D^{20}$	% e.e.†	$[\alpha]_D^{20}$	% e.e.†	$[\alpha]_D^{20}$	% e.e.	$[\alpha[_D^{20}$	% e.e.	$[\alpha]_D^{20}$	% e.e.†	$[\alpha]_D^{20}$	% e.e.	$[\alpha]_D^{20}$	% e.e.
0·012	+0·41	5·6	+0·27		+0·15		+0·18	4·2	+0·19	4·5	+0·18		+0·61	9·2	+0·60	18·8
0·018	+0·50	6·73	+0·61		+0·42		+0·54	12·5	+0·40	9·5	+0·67		+0·93	14·1	+0·90	27·2
0·025	+0·66	8·96	+0·79		+0·65		+0·90	21·00	+0·82	19·5	+0·95		+1·42	21·4	+1·56	48·8
0·032	+1·1	14·60	+0·76		+0·76		+0·95	21·80	+0·74	17·5	+0·91		+1·59	24·00	+1·82	56·2
0·039	+0·58	7·84	+0·56		+0·72		+0·88	20·40	+0·53	12·5	+0·70		+1·43	21·50	+1·59	50·2
0·045	+0·43	5·83	+0·48		+0·48		+0·82	19·00	+0·46	10·90	+0·56		+0·77	11·50	+1·44	45·8

* Yield of amine >70%. † The specific rotation has not been reported previously.

[a] B.p. 63° at 76 cm Hg. [b] B.p. 92—94° at 76 cm Hg. [c] B.p. 85° at 76 cm Hg. [d] B.p. 120° at 76 cm Hg. [e] B.p. 101° at 76 cm Hg. [f] B.p. 102° at 76 cm Hg. [g] B.p. 70° at 25 mmHg. [h] B.p. 58° at 12 mmHg.

TABLE 3

Comparative results from the reduction of ketones, ketone oximes, and *O*-tetrahydropyranyl and *O*-methyl derivatives of the latter

$R^1R^2C=X$		X = O	X = NOH			X = NOThp *		X = NOMe	
R^1	R^2	% e.e.	$[\alpha]_D^{20}$		% e.e.	$[\alpha]_D^{20}$	% e.e.	$[\alpha]_D^{20}$	% e.e.
Me	Ph	33 (−)-(*S*) [2]	−3·1	*S*	10·7	−1·43	3·58	−5·1	12·8
Et	Ph	38 (−)-(*S*) [2]	−2·8	*S*	14·1	−3·27	16·5	−3·61	18·0
Me	$PhCH_2$		+7·56	*S*	21·2	+7·8	22·0	+6·5	18·0
Ph	$PhCH_2$		−3·05	*S*	24·8	−3·12	25·6	−3·32	27·2
Me	1-$C_{10}H_7$	4·8 (−)-(*S*) [4]	−7·56	*S*	9·5	−9·13	11·3	−10·1	13·8
Me	Et	3·0 (+)-(*S*) [3]	+1·1	*S*	14·6	+1·55	20·9	+1·33	18·00
Me	Pr^i	6·1 (+)-(*S*) [3]	+0·79	*S* †		+0·85			
Me	Pr	7·2 (+)-(*S*) [3]	+0·76	*S* †		+0·79			
Me	Bu	8·6; [3] 10·6 [2] (+)-(*S*)	+0·95	*S*	21·8	+1·05	24·3	+0·96	23·0
Me	Bu^i	18·3; [3] 30 [2] (+)-(*S*)	+0·82	*S*	19·5	+0·78	18·5	+0·77	18·4
Me	Bu^t	7·8; [3] 3·0 [2] (+)-(*S*)	+0·95	*S* †		+1·22			
Me	$[CH_2]_5Me$	11·4 (+)-(*S*) [2]	+1·59	*S*	24·00	+1·78	26·8	+1·43	22·6
Me	C_6H_{11}	75 (+)-(*S*) [4] †	+1·82	*S*	56·2	+1·60	49·8	+1·41	44·0

* Thp = tetrahydropyranyl. † Configurational assignment on the basis of the present work.

differences in steric bulk between the alkyl substituents. For alkyl aryl systems, electronic as well as steric factors determine the stereoselectivities, as shown by the fact that maximum stereoselectivity was shown by deoxybenzoin oxime and not by methyl naphthyl ketone oxime,

Maximum stereoselectivities were again obtained (*cf.* refs. 2 and 3) with *ca.* 1 : 1 molar ratios of lithium aluminium hydride to monosaccharide. A comparison of the results from the reduction of oximes with those previously obtained for ketones (Table 3) shows that the

stereoselectivities for alkyl aryl ketone oximes were lower than for the corresponding ketones, but were on average higher for dialkyl ketone oximes than for dialkyl ketones (a notable exception is cyclohexyl methyl ketone).

Asymmetric reductions of ketone oximes and their *O*-substituted derivatives with the ethanol-modified complex (III) gave amines of the *R*-configuration; this observation lends support to the proposed mechanistic scheme. Evidently the ethoxy-group replaces H_B and reduction may only be effected by H_A, leading to the *R*-amine as predicted. Yields of amine in this case are considerably lower (*ca.* 50%) as would be expected, since transfer of the more sterically hindered H_A would have a higher activation energy (Table 4).

TABLE 4

Ethanol-modified reduction of ketone oximes and *O*-substituted derivatives with the glucofuranose complex

	PhMeC=NOH		PhMeC=NOThp		PhMeC=NOMe		$PhCH_2(Me)C$=NOH		EtMeC=NOH	
	Primary amine [b]		Primary amine [b]		Primary amine [b]		Primary amine [b]		Primary amine [b]	
EtOH (mol)	$[\alpha]_D^{20}$	% e.e.[a]	$[\alpha]_D^{20}$	% e.e.[a]	$[\alpha]_D^{20}$	% e.e.[a]	$[\alpha]_D^{20}$	% e.e.[a]	$[\alpha]_D^{20}$	% e.e.[a]
0·012	−3·0	10·3					+1·17	3·3	+0·24	3·2
0·020	+3·0	10·3	+2·41	8·3	+2·67	9·2	+1·92	5·4	−0·36	4·9
0·026	+5·0	17·4	+3·32	11·5	+3·57	12·3	−2·90	8·2	−0·95	13·8
0·032	+5·12	17·8	+3·68	12·7	+5·36	18·5	−4·84	13·6	−0·61	8·3
0·039	+2·5	8·45	+2·09	7·2	+4·29	14·8	−2·60	7·3	−0·38	5·2

[a] All amines have the *R*-configuration. [b] Yields of amine 50—60%.

The detailed mechanism of the reduction of ketone oximes and their *O*-substituted derivatives by alkoxyaluminium hydride complexes has recently been discussed by us.[5]

EXPERIMENTAL

T.l.c. of carbohydrate derivatives was performed on silica gel with benzene–methanol (98 : 2) as solvent system and a naphthoresorcinol–phosphoric acid spray for detection. The ether used in the reductions with lithium aluminium hydride complexes was repeatedly dried over sodium. Solutions in chloroform were dried over calcium chloride and ethereal solutions over magnesium sulphate; solvents were removed under reduced pressure at room temperature. The purity of the amines was established by g.l.c. on a 5 ft glass column of Carbowax 20M on Chromosorb W. Preparative g.l.c. was carried out with a 7 ft preparative column of Carbowax 20M. Rotations (±0·01°) were determined for neat samples unless otherwise stated, with a Stanley photoelectric polarimeter and/or visually.

Maximum specific rotations and absolute configurations of the optically active amines have been reported as follows: (*S*)-1-phenylethylamine, $[\alpha]_D^{20}$ −29° (MeOH); [6,7] (*S*)-1-phenylpropylamine, $[\alpha]_D^{20}$ −19·85°; [8,9] (*S*)-1-methyl-2-phenylethylamine, $[\alpha]_D^{20}$ +35·6°; [10,11] (*S*)-1,2-diphenylethylamine, $[\alpha]_D^{15}$ −12·0°; [12] (*S*)-1-(α-naphthyl)ethylamine, $[\alpha]_D^{20}$ −80·8°; [13] (*S*)-isobutylamine. $[\alpha]_D^{20}$ +7·4° [14] (1-methylbutylamine 1,2-dimethylpropylamine, and 1,2,2-trimethylpropylamine, specific rotations not reported); (*S*)-1-methylpentylamine, $[\alpha]_D^{27}$ +4·3°; [9,15] (*S*)-1,3-dimethylbutylamine, $[\alpha]_D^{19}$ +4·2: (MeOH); [16] (*S*)-1-methylheptylamine, $[\alpha]_D^{20}$ +6·63°; [11] (*S*)-1-cyclohexylethylamine, $[\alpha]_D^{15}$ +3·2°.[11,17]

Reduction of Ketone Oximes [5] *and their* O-*Methyl* [6] *and* O-*Tetrahydropyranyl Derivatives.*[5]—(a) *With the lithium aluminium hydride–*3-O-*benzyl-*1,2-O-*cyclohexylidene-*α-D-*glucofuranose complex.* A solution of the glucofuranose [1] (8·8 g, 0·025 mol) in dry ether (50 ml) was added to a measured volume of a standardised ethereal solution of lithium aluminium hydride (*ca.* 18—20 g l^{-1}). The mixture was heated under reflux for 90 min, then the solution of the oxime or its *O*-substituted derivative (0·0125 mol) in dry ether (20 ml) was added. Heating under reflux was continued for 2·5 h, then the mixture was cooled, the complex was decomposed with water (15 ml), and the precipitated hydroxide was filtered off and washed with ether (2 × 30 ml). The combined filtrate and washings were extracted with dilute hydrochloric acid (3 × 20 ml) to separate all basic components. The aqueous acid layer was strongly basified (6M-NaOH) and extracted with ether (3 × 50 ml), and the extract was washed with water (2 × 30 ml), dried ($MgSO_4$), and evaporated to give an oily product. The optically active primary amine was isolated by fractional distillation under reduced pressure and characterised by i.r. and n.m.r. spectra; its purity was checked by g.l.c.

(b) *With the ethanol-modified complex.* A solution of the glucofuranose [1] (8·8 g, 0·025 mol) in dry ether (50 ml) was added to an ethereal solution of the hydride (1 g, 0·026 mol). The mixture was heated under reflux for 90 min, after which various amounts of ethanol in ether solution were added and heating under reflux was continued for 1 h. A solution of the oxime or derivative (0·0125 mol) in dry ether (20 ml) was added. Heating under reflux was continued for 2·5 h. The mixture was then cooled and the excess of reducing complex was decomposed with water (15 ml). The products were separated as in (a).

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[5] See S. R. Landor, O. O. Sonola, and A. R. Tatchell, *J.C.S. Perkin I*, 1974, 1294, for the preparation of ketone oximes and their *O*-methyl and *O*-tetrahydropyranyl derivatives.

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