Asymmetric Syntheses. Part 10.[1] The Synthesis and Reduction of *N*-Phenylazomethines with a Lithium Aluminium Hydride–3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose Complex to give Optically Active Secondary Amines

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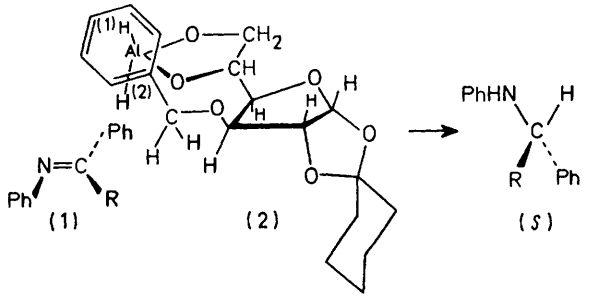
A series of *N*-phenylcyanoamines and *N*-phenylazomethines have been synthesised. The n.m.r. spectra show mesomeric shielding of the Me protons in azomethines by *para*-halogen substituents in the order Br > Cl > F ≫ H, but protonated azomethines show shielding Br > Cl > F = H. The asymmetric reduction of four of these azomethines with a lithium aluminium hydride–3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex gives optically active secondary amines. The absolute configuration of *N*-(α-phenylethyl)aniline was assigned as *S* by *N*-phenylation of *S*-(−)-α-phenylethylamine and hence all these laevorotatory secondary amines obtained by this asymmetric reduction are assigned the *S*-configuration.

In Part 9 [1] of this series, we reported the asymmetric reduction of ketone oximes and their *O*-substituted derivatives by lithium aluminium hydride–monosaccharide complexes to give optically active primary amines. These investigations have now been extended to the reduction of the structurally related *N*-phenyl azomethines which give optically active secondary amines. Prior to this investigation, an asymmetric reduction of azomethines was briefly reported by Cervinka and Suchan [2] who obtained low optical yields of primary amines of known configurations; more recently Solladie and his co-workers [3] described the introduction of a new chiral site on an *N*-chirally substituted imine by stereoselective reduction followed by subsequent hydrogenolysis of the chiral substituent on the nitrogen to give an optically active primary amine. The reduction of azomethines with the lithium aluminium hydride–3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex (2) follows the same pattern as that of the oxime and oxime ethers.[1] We therefore postulate a similar mechanism for the reduction of azomethines and this is shown in the Scheme. Preferential hydride



Scheme

transfer of the less shielded H(2) to the carbon of the imino-group with the phenyl pointing away from the shielding 3-*O*-benzyl group of the monosaccharide derivative is predicted to give optically active secondary amines of the *S*-configuration. The *N*-phenyl group is as remote from the carbohydrate moiety as the tetrahydropyranyloxy-group is in the reduction of ketone *O*-alkyloximes and therefore not likely to play any part in the stereoselective process. The stereoselectivity of the reduction process would thus be determined by the steric and electronic interactions between the *C*-phenyl and alkyl substituents on the azomethines and the 3-*O*-benzyl group of the carbohydrate residue.

Four examples of a homologous series of azomethines were reduced with the aluminium hydride complex (2) (Table 1) and gave optically active secondary amines,

Table 1

Rotations * for the secondary amines obtained in the reaction PhRC=NPh (azomethine) ⟶ PhNH·CH(Ph)R (secondary amine). The products had *S*-configurations, all, except those for R = Me, being assigned on the basis of the present work

$LiAlH_4$ (mol)	R = Me [a]	R = Et [b]	R = Pr [c]	R = Pr^i [d]
0.012	−0.71 (11.5) †	−1.08	−1.40	−1.26
0.018	−0.98 (15.8)	−1.33	−1.54	−1.45
0.025	−1.46 (23.6)	−1.54	−1.65	−1.53
0.032	−0.94 (15.2)	−1.30	−1.66	−1.54
0.039	−0.66 (10.7)	−0.90	−1.30	−1.44
0.045	−0.58 (9.4)	−0.76	−1.08	−1.38

[a] B.p. 142 °C at 1.5 mmHg. [b] B.p. 150 °C at 1.5 mmHg. [c] M.p. 51—52 °C. [d] M.p. 54—55 °C.

* Rotations determined for chloroform solutions (*ca.* 50%). Maximum specific rotation obtained from this work. $[\alpha]_D^{20}$ −6.20°. † Excess of enantiomer percentage.

all laevorotatory, which were characterised by i.r. and n.m.r. spectroscopy and elemental analysis (Table 2).

The absolute configuration of these secondary amines has not previously been reported. It was, therefore, determined for *N*-(α-phenylethyl)aniline by phenylation *via* the benzyne intermediate of (+)- and (−)-α-phenylethylamine and comparison of the products with the

[1] Part 9, S. R. Landor, O. O. Sonola, and A. R. Tatchell, *J.C.S. Perkin I*, 1974, 1902.
[2] O. Cervinka and V. Suchan, *Coll. Czech. Chem. Soc.*, 1965, 30, 2484.
[3] G. Demailly and G. Solladie, *Tetrahedron Letters*, 1975, 2471 and references therein.
[4] I. Tabushi, K. Okazaki, and R. Oda, *Tetrahedron Letters*, 1967, 3827.

product obtained by reduction of the imine. Benzyne, generated by the action of sodamide on bromobenzene in liquid ammonia,[4] reacted with *S*-(−)-α-phenylethylamine [5,6] to give (−)-*N*-(α-phenylethyl)aniline; it has, therefore, the *S*-configuration. This method should give minimum racemisation of the optically active amine and azomethines has, without exception, given products with the *S*-configuration.[1,7]

Several methods for the synthesis of azomethines have been reported in the literature.[8] Recently the condensation of a ketone with a primary aromatic amine in the presence of hydrogen cyanide was briefly reported

TABLE 2

Physical and analytical data for azamethines and *N*-phenylalkylanilines

	PhRC:NPh Chemical shifts in τ		PhNH·CH(Ph)R Chemical shifts in τ				B.p. at 1.5 mmHg or m.p.	Yield	Analyses Found			Required		
R	2 × C_6H_5	R	2 × C_6H_5	H	R	NH	(θc/°C)	%	C	H	N	C	H	N
Me	2.0—3.5 (10H, m)	7.38 (3H, s, CH_3)	2.65—3.70 (10H, m)	5.60 (1H, dd, CH)	8.60 (3H, d, CH_3)	6.20	142	76	85.25	7.45	7.15	85.30	7.60	7.10
Et	2.0—3.4 (10H, m)	9.0 (3H, t, CH_3) 7.45 (2H, dd, CH_2)	2.70—3.70 (10H, m)	5.70 (1H, t, CH)	8.40 (2H, dq-CH_2) 9.20 (3H, t, CH_3)	6.30	150	80	85.2	7.9	6.45	85.31	8.09	6.60
Pr	2.4—3.6 (10H, m)	9.08 (3H, d, CH_3) 8.55 (2H, m, CH_2) 8.00 (2H, t, CH_2)	2.70—3.71 (1H, m)	5.75 (1H, t, CH)	8.60 (2H, m, CH_2) 8.22 (2H, m, CH_2) 9.25 (3H, t, CH_3)	6.35	51—52 (m.p.)	75	85.1	8.7	6.40	85.34	8.44	6.22
Pr^i	2.6—3.6 (10H, m)	8.80 (3H, d, CH_3) 8.60 (3H, d, CH_3) 7.05 (1H, dd, CH)	2.75—3.60 (10H, m)	5.90 (1H, d, CH)	8.65 (1H, m, CH) 9.30 (3H, d, CH_3) 9.35 (3H, d, CH_3)		54—55 (m.p.)	78	85.05	8.75	6.35	85.34	8.44	6.22

TABLE 3

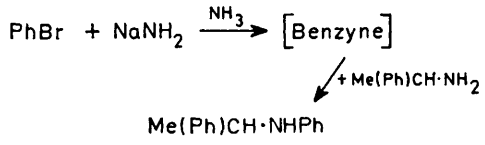
Experimental detail and results for the reaction:

PhBr + $NaNH_2$ ⟶ [Benzyne] + NH_2·CH(Me)Ph ⟶ PhNH·CH(Me)Ph

Liq·NH_3(ml)	Na(g)	PhBr(g)	NH_2·CH(Me)Ph (g)	PhNH·CH(Me)Ph B.p.	Yield (g; %)	$[\alpha]_D^{20}$ †
20	0.58	4.0	3.0 (±)	140 °C/1.3 mmHg (±)	3.2; 64	
20	0.58	4.0	3.0 (−) (−38.5° *)	142 °C/1.5 mmHg (−)	3.7; 74	−6.2°
20	0.58	4.0	3.0 (+) (+38.5° *)	142 °C/1.5 mmHg (+)	3.4; 68	+6.0°

* $[\alpha]^D_{20}$ of material supplied by E. Merck, Darmstadt. † In $CHCl_3$ at a concentration of 50%.

the optical purity of the *N*-(α-phenylethyl)aniline is estimated to be >95%. The maximum specific rotation obtained was −6.2°; this datum was used to calculate the stereoselectivity of the asymmetric reduction and gave a maximum of excess enantiomer of 23.6% (Table 3).



The three amines for which the configuration had not been determined previously are now assigned the *S*-configuration on the basis that in our laboratory the asymmetric reduction with this reagent of 40 compounds comprising ketones, oximes, *O*-alkyloximes, and now to give cyanoamines in good yield and these were converted into *N*-phenylazomethines with methanolic potassium hydroxide at room temperature.[9] In our hands the elimination of hydrogen cyanide from the α-cyanoamine (3) did not proceed in reasonable yield at room temperature but excellent yields were obtained when the reaction was carried out under reflux for 1 h. Eleven azomethines (5) were synthesised by this method and their structures confirmed by i.r., u.v., and n.m.r. spectroscopy and their elemental analyses (Table 4).

Both the u.v. and n.m.r. spectra of azomethines showed mesomeric participation of halogen substituent (X) in the *para*-position of a phenyl group of the imine (5; R = Me). The u.v. spectra show small but regular bathochromic shifts for *p*-bromo-, *p*-chloro-, and *p*-fluoro-substituents similar to those reported for *p*-

[5] A. W. Ingersoll, *Org. Synth.*, Coll. Col. II, 1943, 503.
[6] W. Leither, *Ber.*, 1931, 64, 2827.
[7] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.* (*C*), 1966, 1822, 2280; 1967, 197.
[8] R. W. Layer, *Chem. Rev.*, 1963, 63, 498, and references therein.
[9] J. S. Walia, L. Heindl, H. Lader, and P. S. Walia, *Chem. and Ind.*, 1968, 155.

halogen substituted ketones (1).[10] Considerable mesomeric shielding of the methyl (Δ τ 0.5) for all three halogens in the *para*-position was observed but the differences in chemical shift and, therefore, shielding between individual halogens is now more marked. Thus fluorine appears to be unable to make any contribution (the chemical shift is the same as for *para*-H) presumably because transfer of any substantial part of

TABLE 4

Physical constants and analytical data of α-cyanoamines RR'C(CN)NHPh and azomethines

α-Cyanoamine [RR'C(CN)·NHPh]										Azomethine (RR'C:NPh)							
				Found (%)			Required (%)					Found (%)			Required (%)		
R	R'	Yield %	M.p. (°C)	C	H	N	C	H	N	Yield %	M.p. (°C)	C	H	N	C	H	N
Ph	Me	82	155	81.0	6.15	12.4	81.08	6.31	12.61	82	38—39	86.0	6.55	7.1	86.16	6.67	7.17
p-BrC_6H_4	Me	80	140	59.9	4.45	9.2	59.80	4.32	9.30	88	78—80	60.7	4.4	5.25	60.80	4.38	5.11
p-ClC_6H_4	Me	78	147	70.15	5.0	11.0	70.17	5.06	10.92	83	84—85	67.1	4.55	5.6	67.32	4.87	5.62
p-FC_6H_4	Me	83	156	74.75	5.6	12.0	75.00	5.02	11.66	86	78—79	71.25	6.8	6.2	71.30	6.90	6.42
p-EtC_6H_4	Me	88	114	80.95	7.15	11.15	81.60	7.20	11.20	75	42—44	85.35	7.7	6.4	86.10	7.62	6.27
p-$Pr^iC_6H_4$	Me	75	136	81.7	7.55	9.8	81.81	7.57	10.01	76	66	86.0	8.05	5.85	86.08	8.02	5.90
p-$Bu^tC_6H_4$	Me	84	148	82.0	7.85	9.9	82.01	7.91	10.08	88	56	86.25	9.2	5.85	84.58	9.25	6.17
Ph	Et	86	139	81.05	6.7	12.2	81.36	6.78	11.86	81	49—51	86.2	7.1	6.5	86.14	7.18	6.68
Ph	Pr	84	160	81.85	7.25	10.8	81.60	7.20	11.20	72	26—28	86.1	7.5	6.35	86.10	7.62	6.28
Ph	Pr^i	83	137	81.75	77.25	11.2	81.60	7.20	11.20	75	28—29	86.1	7.45	6.15	86.10	7.62	6.28
Ph	Ph	80	150	85.25	5.7	9.0	84.51	5.61	9.86	82	116—117	88.1	6.0	5.3	88.37	6.20	5.43

TABLE 5

α-Cyanoamine [RR'C(CN)·NHPh]			Azomethine (RR'C:NPh)	
R	R'	R' τ	R' τ	$\lambda_{max.}$ * (ε) *
Ph	Me	8.14 (3H, s, Me)	7.38 (3H, s, Me)	310 (2 130)
p-BrC_6H_4	Me	8.17 (3H, s, Me)	7.98 (3H, s, Me)	317 (3 500)
p-ClC_6H_4	Me	8.19 (3H, s, Me)	7.90 (3H, s, Me)	315 (3 284)
p-C_6H_4	Me	8.13 (3H, s, Me)	7.85 (3H, s, Me)	312 (2 162)
Ph	Et	9.0 (3H, t, Me)	9.0 (3H, t, Me)	
		7.93 (1H, q, CH_2)	7.40 (2H, q, CH_2)	
		7.90 (1H, q, CH_2)		
Ph	Pr	9.15 (3H, t, Me)	9.08 (3H, t, Me)	
		8.55 (2H, m, $MeCH_2$)	8.55 (2H, m, $MeCH_2$–CH_2)	
		7.96 (2H, t, CH_2–CH_2)	8.00 (2H, t, CH_2–CH_2)	
Ph	Pr^i	9.08 (3H, d, Me)	8.80 (3H, d, Me)	
		8.86 (3H, d, Me)	8.60 (3H, d, Me)	
		7.80 (1H, m, CH)	7.05 (1H, m, CH)	
p-EtC_6H_4	Me	7.80 (3H, s, Me)	7.80 3(H, s, Me)	
p-$Pr^iC_6H_4$	Me	8.10 (3H, s, Me)		
p-$Bu^tC_6H_4$	Me			340 (4 204)
Ph	Ph			

* $\lambda_{max.}$ in nm and ε in mol cm^{-1} l^{-1}

between bromine and chlorine (Δ τ 0.08) and chlorine and fluorine (Δ τ 0.05) were small (Tables 5 and 6).

TABLE 6

Mesomeric shielding effects of *p*-halogen substituents on azomethines and protonated azomethine

R(Me)C:NPh R	$CDCl_3$ τ (Me)	Shielding Δτ	$CDCl_3$+ TFA * τ (Me)	TFA * τ (Me)	Shielding Δτ
Ph	7.38		7.08	7.07	
p-BrC_6H_4	7.98	0.6	7.58	7.56	0.49
p-ClC_6H_4	7.90	0.52	7.37	7.34	0.27
p-FC_6H_4	7.85	0.47	7.12	7.07	0.00

* TFA = trifluoroacetic acid.

The shielding was similar to that observed for a *para*-ethyl substituent which is mainly due to the inductive effect. Surprisingly, protonation of the halogen-substituted imine in trifluoroacetic acid resulted in smaller shielding effects by the halogens but the difference the positive charge to the fluorine destabilises the system to such an extent as to make any contribution minimal. Chlorine in the *para*-position shows only half the difference in chemical shift of the methyl for the protonated azomethine compared with the unprotonated compound which indicates that even positive chlorine destabilises the system. With a *para*-bromine substituent the shielding of the methyl protons and, therefore, electron donation to the protonated and unprotonated form is approximately the same. No splitting of the methyl protons due to the proton on the nitrogen of the protonated imine was observed or expected at 35 °C.* Sharma and Roels [11] found that protonated aldimines gave rise to splitting both of α-methylene and azomethine protons at −55 °C but coalescence was observed at temperatures from −45 to −33 °C.

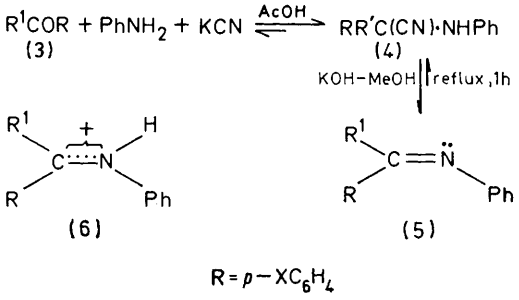
There appears to be no correlation between the chemical shifts of the methyl protons of *para*-substituted

* The normal temperature of the sample for n.m.r. determination.

[10] W. M. Schubert, J. M. Craven, and H. Steadly, *J. Amer. Chem. Soc.*, 1959, **81**, 2695; 1960, **82**, 1353, 1357.

[11] G. M. Sharma and O. A. Roels, *J. Org. Chem.*, 1973, **38**, 3648.

azomethines (5) or protonated azomethines (6) and Taft σ° parameters as shown by the ethynyl protons of *para*-substituted phenylacetylenes.[12] *para*-Substituents do not have any effect on the chemical shifts of methyls on sp^3 hybridised carbon of the cyanoamines (4; R = Me).



The α-cyanoamines (4; R = Et and Pr^{i}) show two signals for protons of methylene and methyls respectively due to diastereotopic non-equivalence. However the two signals of the methyls of the isopropyl group on the azomethine (5; R = Pr^{i}) can only be explained by conformational non-equivalence.

EXPERIMENTAL

N.m.r. spectra were obtained for solutions in deuteriochloroform with a Varian A60 and T60 spectrometers using tetramethylsilane as an internal reference. The u.v. spectra were recorded in ethanol using a Unicam SP 800 ultraviolet spectrophotometer and the absorbance obtained with a Unicam SP 500 Series 2 ultraviolet and visible spectrophotometer. 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 was repeatedly dried over sodium. The purity of the amines was established by g.l.c. on a 5-ft glass column of Carbowax 20M on Chromosorb (for the liquid amines), and by several recrystallisations until constant melting points were obtained (in the case of the solid amines). Optical rotations (0.01°) were determined for neat samples unless otherwise stated, with a Stanley photoelectric polarimeter and/or with a Perkin-Elmer 141 polarimeter at 20 °C.

Preparation of α-Cyanoamines.—The ketone (0.66 mol) and aniline (6.12 g, 0.06 mol) were dissolved in glacial acetic acid (25 ml). The mixture was gently stirred at 0 °C while portions of solid potassium cyanide (4.3 g, 0.66 mol) were cautiously added. Stirring was continued until a solid crystallised (*ca.* 1 h). The mixture was then cooled and filtered; the solid residue was washed with water (4 × 100 ml) and light petroleum (b.p. 40—60 °C; 4 × 50 ml) and then crystallised from methanol, yields 80—90% (see Table 4); $\nu_{max.}$ 2 230 (CN) and 3 400 cm^{-1} (NH).

Preparation of Azomethines.—The cyanoamine (0.03 mol) was dissolved in hot methanol (40 ml). To this a solution of potassium hydroxide (6.7 g, 0.12 mol) in methanol (50 ml) was carefully added and the reaction mixture heated under reflux for 1 h. Water (100 ml) was added to the cooled mixture and the organic material removed by extraction with light petroleum (b.p. 40—60 °C; 4 × 50 ml). The combined light petroleum extracts were washed with water (2 × 100 ml), dried ($MgSO_4$), and the solvent evaporated to give a light yellow oil which was refrigerated. The crude solid material was recrystallised from light petroleum (b.p. 40—60 °C) to give the pure azomethine (Table 4); $\nu_{max.}$ 1 640—1 650 cm^{-1} (CN).

Reduction of Azomethines with the Lithium Aluminium Hydride–3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose Complex.—A solution of the glucofuranose [7] (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 after which a solution of the azomethine (0.025 mol) in dry ether (20 ml) was added. Heating under reflux was continued for 2.5 h, after which the mixture was cooled, the complex was decomposed with water (15 ml) and the precipitated hydroxide was filtered off and washed with ether (2 × 40 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) and dried ($MgSO_4$); evaporation gave an oily product. The optically active secondary amine was isolated by fractional distillation under reduced pressure and characterised by i.r. and n.m.r. spectroscopy; its purity was checked by g.l.c. or by recrystallisation in the case of a solid product (Table 2).

Determination of the Absolute Configuration of N-(α-*phenylethyl*)*aniline.*—Metallic sodium (0.58 g, 0.025 mol) and an excess of liquid ammonia (20 ml) were stirred for 1 h and bromobenzene (4 g, 0.025 mol) was added to the mixture. The resultant dark violet product was further stirred for 1 h after which α-phenylethylamine (3.0 g, 0.025 mol) was added dropwise with stirring to the mixture. Stirring was continued for another 3 h, the reaction mixture was neutralised with dilute hydrochloric acid (3 × 10 ml), and the aqueous acid layer was basified (6M-NaOH). Work-up gave an oily product which was distilled under reduced pressure and then characterised by i.r. and n.m.r. spectroscopy; the optical rotation was determined.

[6/2173 *Received 25th November*, 1976]

[12] L. M. Jackmann and S. Sternhill, 'Applications of Nuclear Magnetic Resonance in Organic Chemistry', Pergamon Press, Oxford, 1969, p. 66; C. D. Cook and S. S. Danyluk, *Tetrahedron*, 1963, **19**, 177.