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HYDROXY SCHIFF BASE-OXAZOLIDINE TAUTOMERISM: APPARENT BREAKDOWN OF BALDWIN'S RULES

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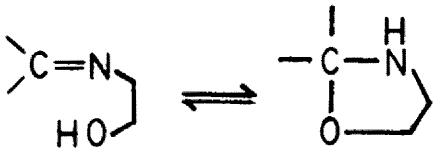
Abstract - The tautomerism between hydroxy Schiff bases, X-$C_6H_4CR{=}NCMe_2CH_2OH$ (R=H, Me, C_6H_5; X is a range of substituents) and X-$C_6H_4CR{=}NC_6H_4$(o-CH_2OH), and the corresponding ring closed systems, oxazolidines and dihydrobenzoxazines, has been investigated. In all cases where equilibria can be determined the process is shown to be extremely facile, despite the fact that Baldwin's rules are contravened. Information about the structure of some of these molecules in the crystalline state is provided by solid state NMR. Previous work on the equilibration of 1-methyl-1,3-oxazolidine and its iminium tautomer in trifluoroacetic acid is shown to be complicated by trifluoroacetate formation, but the overall conclusion that this 5-endo-trig process is also rapid, appears to be correct. Some mechanistic consequences of these deductions are discussed.

INTRODUCTION

It has been realized for some time that oxazolidines exist in equilibrium with hydroxy Schiff base open chain forms (1⇌2) in approximately equal amounts.



1 2

This 5-endo-trig process is formally disallowed,[1] and therefore attainment of equilibrium should be relatively very slow. An early, extensive, review[2] gave no evidence that such a process was measurably slow, however, and more recent reports[3,4] also appear to reveal a low energy barrier for the reaction. We have, therefore, synthesised a series of such compounds to see if systematic structure or solvent variation would alter the rate at which equilibrium was attained, and thus enable its measurement. The situation in the pure form of such compounds is also of interest - does the attainment of equilibrium in solution involve a slight variation of a tautomerism for which both species are present to a significant extent in the pure form, or does it involve equilibration from a solute existing initially predominantly in one form? Related problems are also of interest, in particular, the situation for ring closures to the iminium bond $C{=}\overset{+}{N}<$, and for the corresponding 6-endo-trig mode, where previous studies show that the character of the connecting chain between reacting centres may influence the "allowedness"

of a reaction.[5]

RESULTS and DISCUSSION

5-Endo-trig closures to imine bonds The following series of compounds were synthesised: 3a, X=p-NMe_2; b, p-OMe; c, p-Me, d, m-Me; e, H; f, p-F; g, p-Cl; h, m-F; i, m-Cl; j, m-Br; k, m-NO_2; l, p-NO_2.

3 4

^{13}C-high resolution solid state NMR were recorded for 3c and 3j. For 3c, the off resonance spectrum as well as the selection of quaternary carbons showed two non-equivalent methyls (20.3, 26.5 ppm), well resolved quaternary aliphatic (61.17) and hydroxymethyl (64.47), and five aromatic resonances, one corresponding to two carbons. The aromatic peak at highest frequency (133.69) was the quaternary carbon attached to the methyl group. The remaining peak corresponded to the -CH=N- carbon. Its chemical shift, (158.25), together with the absence of any peaks other than those listed above, showed the compound was at least 98% in the imine form. The interpretation of the spectra of 3j is similar, the only difference being in the aromatic region where the peaks were less well resolved and the quaternary selection experiment did not show the Br-bonded carbon, probably due to the quadrupolar ^{79}Br and ^{81}Br nuclei. We conclude that compounds 3 exist in the imine form in the solid state. This generalisation is supported by IR data, which in all cases show broad hydroxyl peaks ν(nujol and KBr discs) 3500-3000 cm^{-1}, and singlets corresponding to an imine band, 1640 cm^{-1}.

^1H NMR measurements on 3e in various solvents showed equilibration between imine and oxazolidine occurred very rapidly, within 18s, i.e. with a half-life of at most 6s. Since [ring closed]/[ring open] = (K) $\sim$1, and $k_{obs} > 0.11 s^{-1}$, the rate constant for unimolecular ring closure is greater than 0.06 s^{-1}.

This rapid equilibration was further confirmed over a wide range of substituents and solvents as follows. The equilibrium ratio for each compound was measured immediately on dissolution in a large number of solvents. In each case, the data gave good linear plots following eqn (1)[6] (Table 1).

$$\log K_X = \sigma^+\rho + \log K_{X=H} \qquad (1)$$

Any influence of a kinetic effect resulting in a slow equilibration on the NMR time scale would lead to a systematic variation in these plots. As Table 1 shows, none was detected. The accuracy of this technique is maximised by the fact that in nearly all correlations the "half-way" point was about K=1.

It is, perhaps, surprising that the better correlation should be found with σ^+ with such a small ρ value: the former argues for extensive delocalisation of the form 5, and the latter against it.

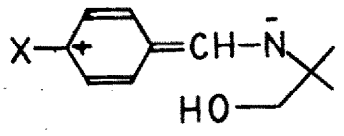


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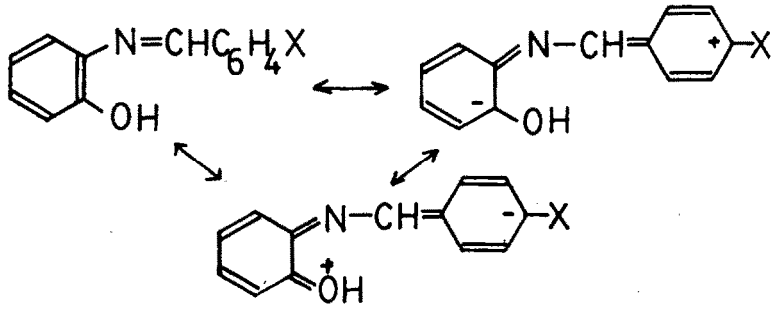
TABLE 1. Application of eqn (1) to tautomerism ratios 3 ⇌ 4 at 35°

Solvent	Substituent constant[a]	ρ	r[b]	$K_{X=H}$[c]
CCl_4	σ	0.63±0.08	0.968	2.26 (1.88)
	σ^+	0.50±0.03[d]	0.988[d]	
CS_2	σ	0.83±0.08	0.976	1.86)1.72)
	σ^+	0.50±0.02	0.992	
C_2HCl_3	σ	0.77±0.10	0.923	1.95
	σ^+	0.52±0.04	0.975	
$CDCl_3$	σ	0.69±0.07	0.952	1.59
	σ^+	0.47±0.02	0.993	
C_3D_6O	σ	0.61±0.08	0.922	0.45 (0.42)
	σ^+	0.42±0.03	0.980	
CD_3CN	σ	0.56±0.08	0.919	0.67
	σ^+	0.39±0.03	0.978	
CD_3OD	σ	0.60±0.07	0.939	0.39
	σ^+	0.41±0.02	0.989	
$(CD_3)_2SO$[e]	σ	0.68±0.11	0.913	0.11 (0.10)
	σ^+	0.48±0.09	0.877	

[a] Ref. 6. [b] Correlation coefficient. [c] [ring closed]/[ring open]; values in brackets are those given previously.[3] Values of K_H are, roughly, inversely proportional to ΔE,[8] in keeping with the suggestion[3] that hydrogen bond accepting solvents stabilise the open chain form. [d] Previous workers[4] give ρ = -0.54±0.01 (0.999); we found 3k and 3l too insoluble to measure in this solvent. [e] Correlations inaccurate because the ring open form was in large excess for all compounds.

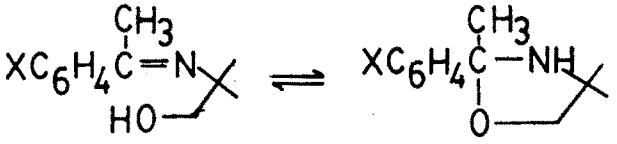
Such types of correlation are not however unprecedented.[7]

Presumably the substituent influence on the stability of 4 is negligible, the main effect being increasing stabilisation of 3 with electron donation by through conjugation. This stabilising effect on the open chain imine form was further exemplified by measurements on 3 a-l in trifluoroacetic acid(TFA), where the compounds were found to be entirely in iminium form, thereby enhancing through conjugation, and also by measurements on compounds 6, which proved to be in open form entirely in both $CDCl_3$ and TFA, as demonstrated clearly by ^1H NMR measurements.



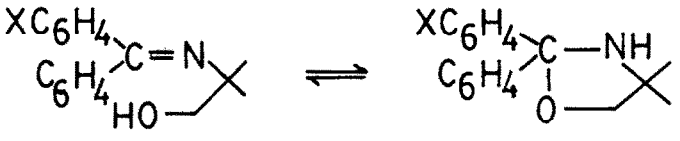
6 (X = NMe_2, OMe, Me, H, Cl, NO_2)

A number of acetophenone (7) and benzophenone (9) derivatives were also prepared in further structural modifications designed to slow down ring closure. These were generally liquids (even at -78°), difficult to prepare (presumably due to reduced electrophilicity of carbonyl and steric hindrance to approach of the nucleophilic nitrogen in Schiff base formation), and to purify (see EXPERIMENTAL).



7 8

a, X = m-OMe; b, p-Me; c, m-Me; d, H; e, p-F; f, p-Cl; g, p-Br; h, m-Br; i, m-NO_2; j, p-NO_2

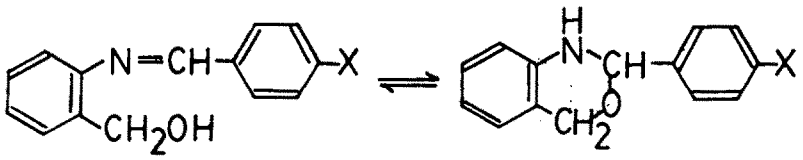


9 10

a, X=H; b, X=p-Me

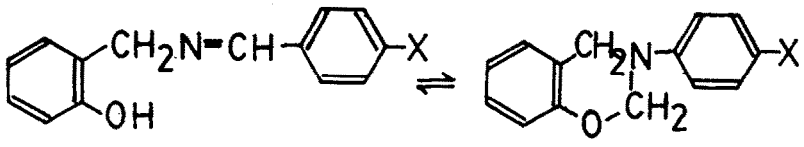
7i was a crystalline solid. ^{13}C NMR spectra in the solid state showed three non-equivalent methyls (27.41, 29.75, 33.05 ppm), a quarternary carbon at 59.74 (bound to two methyl groups), a methylene carbon at 77.80, and four aromatic resonances between 146.54 and 157.12. The remaining signal, that of the quarternary carbon bound to oxygen and nitrogen, was at 97.80, cf 158.25 for 3c, and the spectrum thus indicates that the compound is in the oxazolidine form 8i. ^{13}C and ^{1}H NMR spectra for compounds 7a-i in the solvents given in Table 1, and for compounds 7a-i as neat liquids, showed they existed as the ring closed form 8 in all cases: the distinctive features in the ^{1}H NMR spectra being the AB system for the geminal protons on the secondary carbon bound to oxygen, and the two non-equivalent signals from the methyl groups in the adjacent carbon atom. Confirmatory evidence was obtained from IR spectra, which showed no C=N absorption. More difficulty is experienced in analysing the ^{1}H NMR for system 9⇌10. For 10a the methyl and phenyl groups are equivalent, and while the spectrum displayed singlets for both CH_2 and $C(Me)_2$, showing the compound existed in only one form, it was not possible to say what that form was. In an attempt to release the limitations imposed by the symmetry of the molecule, 9b was synthesised, but the proton NMR showed the same features as the unsubstituted derivative. However, the ^{13}C NMR of both compounds ($CDCl_3$) showed the singlet for C-2 at 99.8 ppm, and this leads us to the conclusion that again these compounds are in the cyclic form 10.

6-Endo-trig closures to imine bonds Molecular models revealed that, by analogy with the hydroxy-chalcone flavanone equilibrium,[5] the 6-endo-trig mode in compounds 11 would be disallowed by virtue of the sp^2 bonding in the connecting side chain.



11 12

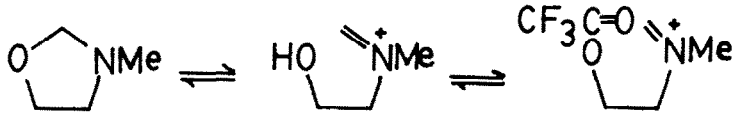
Proton NMR measurement showed compounds 11 to be predominantly in dihydrobenzoxazine 12 form (ca. 4:1 (11a), 20:1 (11d), $CDCl_3$), in an equilibrium whose rate of attainment was again immeasurably fast using NMR techniques. This matches the results of McDonagh,[9] who has demonstrated that equilibria 13⇌14 are also set up rapidly.



13 14

a, X=NMe_2, $CHMe_2$, H, Br, NO_2

5-Endo-trig closures to iminium bonds The non-applicability of Baldwin's rules for closure to the imine bond prompts questions with regard to closures to the iminium bond. Lambert[10] has shown for equilibrium 15⇌16 in TFA that the ring-closed compound appears to be in rapid equilibrium with a small amount of the ring open form.



15 16 17

Some doubt arises however over this interpretation, because it seems likely[11,12] that 16 would react with TFA to yield 17, and such an additional reaction might complicate interpretation of the situation. To check this possibility, 2-(methylamino)ethanol and 2-amino-2-methylpropanol, whose OH groups, in the protonated form of the compounds, should have a reactivity very similar to that of 16, were dissolved in TFA in an NMR tube, and the spectrum taken at appropriate intervals. These showed a decrease in intensity of the signals, together with concomitant appearance of corresponding signals, to an extent downfield proportional to the proximity of the OH group, and of an intensity proportional to the loss of intensity of the original peaks. The kinetics of this trifluoroacetylation were measured, and are recorded in Table 2.

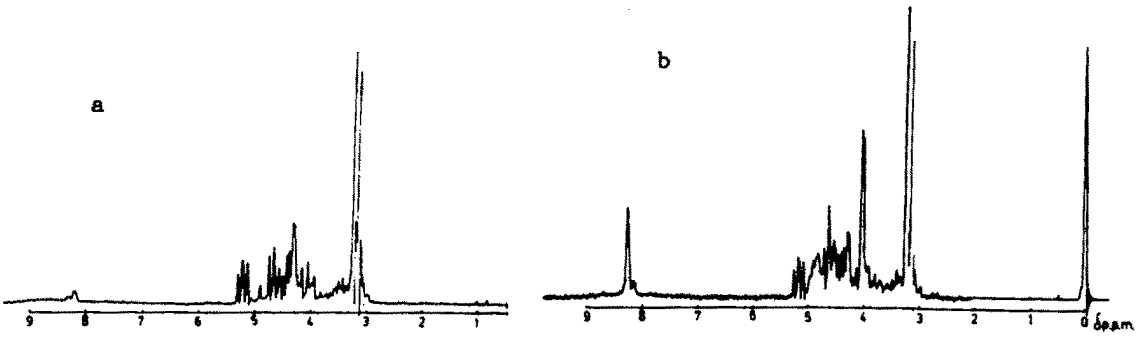
TABLE 2 Reaction of $NHMeCH_2CH_2OH$ and $Me_2CNH_2CH_2OH$ with TFA[a]

Compound[b]	[trifluoroacetate]/[alcohol][c]	$10^5k_f/s^{-1}$	$10^5k_r/s^{-1}$	$10^5k_{obs}/s^{-1}$
$NHMeCH_2CH_2OH$	2.36	17.4	7.4	24.8[d]±0.10(0.996)
$Me_2CNH_2CH_2OH$	6.60	8.98	1.36	10.3[e]±0.20(0.999)

[a]Temperature 34.5°. [b]Concn. 0.1 g in 1 ml TFA, conditions therefore pseudo first order. [c] At equilibrium. [d] Half life 46 min. [e] Half life 112 min.

Investigation of the time variant spectrum of 15 in TFA showed the same characteristics as previously reported.[10] However, on standing for several hours the low field broad signal at δ8.30 was augemented by a second at δ8.30, and this we believe is due to trifluoroacetylation to yield 17, which pulls the CH_2= resonance slightly downfield.[13,14] These spectral changes are illustrated in Fig. 1. The low field peaks in these spectra were so close together that accurate kinetics for the trifluoroacetylation reaction were unobtainable. However, the measurements given in Table 2, and time scale for conversion of spectrum a to spectrum b in Fig. 1 suggest that equilibrium 15 ⇌ 16 is set up more rapidly than can be measured by NMR change, while the equilibration of 16 and 17 takes several hours.

Figure 1. 60 mHz Spectra of 1-Methyl-1,3-oxazolidine in TFA. (a) 15 min after making up the solution (b) after standing for about 12 hr.



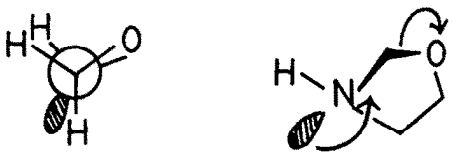
Thus, although we suggest that a modification of Lambert's interpretation[10] is required, we agree with his overall conclusion that the ring opening process between 15 and 16 is rapid. We find no evidence for attack of TFA on the iminium bond:

$$-\overset{|}{\underset{|}{\overset{+}{N}}}= \xrightarrow{\text{TFA}} -\overset{|}{\underset{|}{N}}-CH_2OCOCF_3$$

even though Norman has demonstrated such a reaction for C-C double bonds.[14] Examination of the NMR spectra of imines $XC_6H_4CH{=}N^tBu$ (X=H, p-Me, p-OMe, m-NO_2) in TFA also appeared to demonstrate absence of any significant amount of this reaction. Probably there would be a low energy barrier to this acetoxylation, but the reverse reaction, elimination, is even more facile.

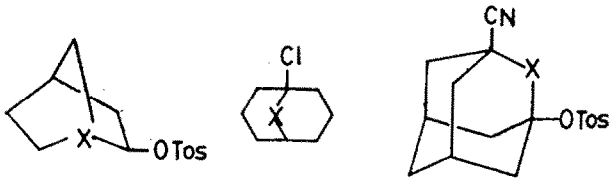
CONCLUSION

The observation of the large reaction window[15] for approach of the oxygen nucleophile to the imine bond concomitantly reveals for the reverse reaction (18) the ability of nitrogen atom lone pairs to interact with non-anti- or non-synperiplanar orbitals.



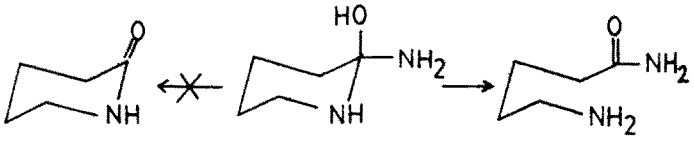
18

This ability has been remarked on previously:[16] rates of hydrolysis of compounds 19,[17] 20,[18] and 21[19] all reveal strong stabilisation of the carbenium ion intermediate for the nitrogen containing species, by comparison with the carbocyclic systems, and in the case of 20 and 21, the oxygen analogues.



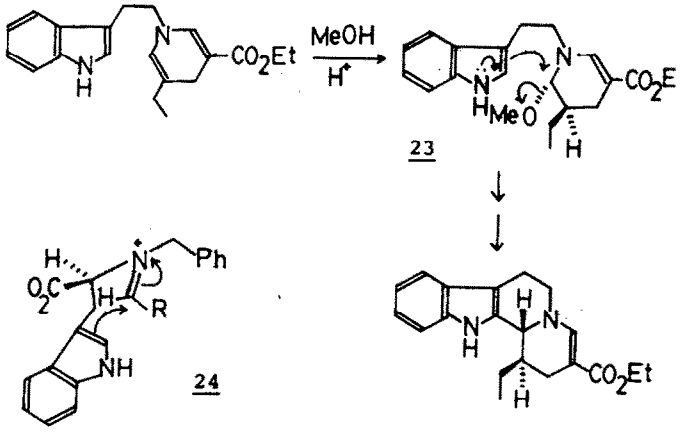
19 X = N, CH 20 X = O, CH_2, NMe 21 X = O, CH_2, NMe

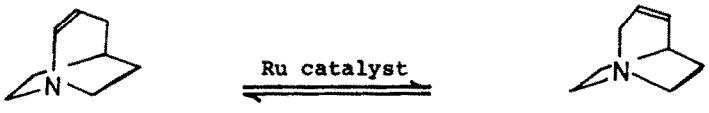
Moreover, mechanistic rationales that require non-availability of the nitrogen lone pairs for interaction with non-anti- or non-synperiplanar bonds might also perhaps be received with caution. For example, Perrins' suggestion,[20] that cyclic hemi-orthoamide 22 breaks down in the direction shown because the alternative mode would not be able to utilise the non-antiperiplanar lone pair on the ring nitrogen atom, may not be entirely justifiable. However, it would seem a reasonable assumption that an anti-periplanar nitrogen lone pair should be more available than a lone pair deviating from planarity, with a cleaving bond, if a choice was available.



22

Similarly, it might be wrong to assume that the Pictet-Spengler reaction goes via intermediate 23 in order to avoid the formally disallowed 5-endo-trig attack of the nucleophilic centre on the iminium bond.[21] In the case of the alternative direct 6-endo-trig ring closure process as suggested by other workers,[22] however, the attainment of the chair-like transition state 24 is facilitated by the sp^3 hybridised carbon atoms in the linking chain.





25 26

Finally, it may be noted that in the extreme case of equilibrium 25 26, no stabilisation of 25 over 26 is noted;[23] here the N lone pair in 23 is completely orthogonal to the double bond.

EXPERIMENTAL

Melting points are uncorrected and yields are not optimised. ^{1}H and ^{13}C NMR were recorded at 35° at 60 MHz and 25 MHz, respectively, using JEOL PMX 60SI and JEOL FX-100 FT spectrometers. Solid state ^{13}C high resolution NMR off resonance spectra (pulse programme CPSTXX-Cross polarization with flip-back) were measured by Professor K.J. Packer and his associates, to whom we record our thanks. Full details are given elsewhere.[24] IR spectra were obtained using Perkin Elmer 297 and 298 instruments. Standard reagents and solvents were used direct from bottle or purified by standard procedures as necessary. 1-Methyl-1,3-oxazolidine (15) was prepared as given previously.[10] Kinetics were determined by NMR procedures, previously detailed,[12] used to follow the disappearance of the methylene protons in the alcohol and their corresponding appearance in the trifluoroacetate for both compounds given in Table 2.

Substituted benzaldehyde derivatives 3

Appropriately substituted benzaldehydes (0.01 mol) and 2-amino-2-methyl-1-propanol (0.012 mol) in toluene (100 ml), containing a crystal of iodine, were left over freshly activated (600°C) 4A molecular sieves (20g) overnight at room temperature. The solvent was evaporated and the residue recrystallised from ethanol or ethyl acetate to constant m.p.

	Yield/%	m.p./°	Analysis
3a	76	111	Found: C, 70.68; H, 9.36; N, 12.66 $C_{13}H_{20}N_2O$ requires C, 70.90; H, 0.09; N, 12.73%.
3b	41	49	Found: C, 69.45; H, 8.22; N, 6.65. $C_{12}H_{17}NO_2$ requires C, 69.57; H, 8.21; N, 6.76%.
3c	50	55	Found: C, 75.42; H, 9.16; N, 7.30. $C_{12}H_{17}NO$ requires C, 75.39; H, 8.90; N, 7.33%
3d	59	50	Found: C, 75.26; H, 9.28; N, 7.35. $C_{12}H_{17}NO$ requires C, 75.39; H, 8.90; N, 7.33%.
3e	56	65	(lit. 66°)[2]
3f	56	75	Found: C, 67.57; H, 7.26; N, 7.15; F, 9.76. $C_{11}H_{14}NOF$ requires C, 67.69; H, 7.18; N, 7.18; F, 9.74%.
3g	61	66	Found: C, 62.04; H, 6.63; N, 6.57; Cl, 16.54. $C_{11}H_{14}NOCl$ requires C, 62.42; H, 6.62; N, 6.62; Cl, 16.77%.
3h	59	62	Found: C, 67.57; H, 7.26; N, 7.15; F, 9.76. $C_{11}H_{14}NOF$ requires C, 67.69; H, 7.18; N, 7.18; F, 9.74%.
3i	73	77	Found: C, 61.70; H, 6.77; N, 6.51. $C_{11}H_{14}NOCl$ requires C, 62.42; H, 6.62; N, 6.62%.
3j	65	91	Found: C, 51.52; H, 5.49; N, 5.45; Br, 31.29. $C_{11}H_{14}NOBr$ requires C, 51.58; H, 5.47; N, 5.47; Br, 31.23%.
3k	75	126	Found: C, 59.17; H, 6.35; N, 12.47; $C_{11}H_{14}N_2O_3$ requires C, 59.46; H, 6.31; N, 12.61%.
3l	48	60	Found: C, 59.20; H, 6.40; N, 12.51. $C_{11}H_{14}N_2O_3$ requires C, 59.46; H, 6.31; N, 12.61%.

^{1}H NMR (90 MHz). Peak positions varied slightly with structure and solvent, but assignments common to all benzaldehyde derivatives were approximately as follows: 3, δ 3.5 (CH_2, s), 0.9-1.4 (CH_3, s), 8.3 (CH, s, invariably below aromatic peaks); 4, 3.5 (CH_2m dd), 0.9-1.4 (CH_3, two separate peaks), 5.5 (CH, s), 5.5 (CH, s). Equilibrium ratios were readily determined from multiple integrations of the CH peaks.

Substituted acetophenones and benzophenone derivatives 7 & 9

Appropriately substituted acetophenones and benzophenones (0.05 mol) were refluxed with 2-amino-2-methyl-1-propanol (0.25 mol) and iodine (0.05 g) in toluene or xylene under a Dean Stark water separator. Reaction progress was monitored by TLC, and the reaction invariably required many days (generally about 10) for completion. The solvent was evaporated and the product distilled under reduced pressure, or, in the case of 7j recrystallised from ethyl acetate.

	Yield/%	b.p. (mm Hg)	Analysis
7a	47	112(2)	Found: C, 70.44; H, 8.53; N, 6.33. $C_{13}H_{19}NO_2$ requires C, 70.59; H, 8.60; N, 6.33%.
7e	56	116(4)	Found: C, 68.86, H, 7.98; N, 6.74. $C_{12}H_{16}NOF$ requires C, 68.90; H, 7.66; N, 6.70%.
7f	56	116(3.5)	Found: C, 63.90; H, 7.21; N, 6.34; Cl, 15.64. $C_{12}H_{16}NOCl$ requires C, 63.87; H, 7.10; N, 6.21; Cl, 15.72%.
7g	54	121(5)	Found: C, 53.65; H, 5.77; N, 4.96; Br, 29.38. $C_{12}H_{16}NOBr$ requires C, 53.35; H, 5.93; N, 5.19; Br, 29.61%.
7b	38	132(12)	Found: C, 53.66; H, 5.84; N, 4.88; Br, 29.52. $C_{12}H_{16}NOBr$ requires C, 53.35; H, 5.93; N, 5.19; Br, 29.61%.
7j	59	m.p 83	Found: C, 61.01; H, 6.85; N, 11.82. $C_{12}H_{16}N_2O_3$ requires C, 61.02; H, 6.80; N, 11.86%.
9a	73	m.p.67	Found: C, 80.39; H, 7.63; N, 5.54. $C_{17}H_{19}NO$ requires C, 80.63; H, 7.51; N, 5.53%.
9b	66	142(0.5)	Found: C, 80.61; H, 7.98; N, 5.71. $C_{18}H_{21}NO$ requires C, 80.90; H, 7.87; N, 5.24%.

For 7b,c,d,i, yields and b.p's (mm Hg) were respectively 51, 135(20); 63, 104(3.5); 45, 102(3.5); 48, 138(1.5); however, analyses were repeatedly just outside accepted error limits. NMR (see RESULTS and DISCUSSION) showed compounds to be reasonably pure.

Substituted N-benzylidene-o-aminophenols (6)

Prepared by the same procedure as given above for benzaldehyde derivatives 3. M.p's agreed with those previously reported.[25-28]

Substituted N-benzylidene-o-amino benzyl alcohols (11) dihydrobenzoxazines (12)

Equimolar amounts of o-amino benzyl alcohol and the appropriately substituted benzaldehyde were dissolved in toluene (except 11d, where toluene-dichloromethane (1:1) was used) and allowed to stand overnight over freshly activated (600°) 4Å molecular sieves. The solution was filtered, evaporated and the residue recrystallised. 11a m.p. 147-150°C (lit.[29] 147-151°C); ^{1}H NMR ($CDCl_3$) δ 3.8 (3H, 2s, CH_3O ring and chain forms), 3.7-4.4 (br s -NH), 4.6-5.1 (2H, m, CH_2 ring and chain forms), 5.5 (s, N-CH, ring form), 6.6-8.0 (8H, m, arom), 8.45 (s, N=CH). 11b recrystallised from hexane (64%), m.p. 115-116°C; ^{1}H NMR 2.36 (s, CH_3 ring form), 2.40 (s, CH_3 chain form), 3.7-4.2 (br s -NH), 4.6-5.2 (2H, m, CH_2, ring and chain forms), 5.45 (s, N-CH, ring form), 6.5-7.8 (8H, m, arom), 8.40 (s, N=CH chain form). Found: C, 79.71; H, 6.67; N, 6.16. $C_{15}H_{15}NO$ requires C, 79.96; H, 6.72; N, 6.21%. 11c m.p. 119-121°C; (lit.[29] 121-124°C); ^{1}H NMR δ 4.5-5.2 (2H, m, CH_2 ring and chain forms), 3.6-5.3 (br s NH), 5.6 (s, N-CH ring form), 6.5-8.1 (9H, m, arom), 8.5 (br s N=CH chain form). 11d recrystallised from hexane (78%), m.p. 116-118°C; H NMR δ 3.8-4.3 (br s -NH), 4.6-5.2 (2H, m, CH_2, ring and chain forms), 5.6 (s, N-CH ring form), 6.8-8.3 (8H, m, arom), 8.5 (s, N=CH). Found: C, 65.53; H, 4.71; N, 10.8.3. $C_{14}H_{12}N_2O_3$ requires C, 65.61; H, 4.73; N, 10.93%.

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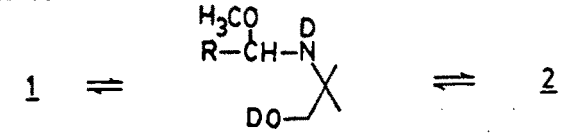

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