Stereoselective Reduction of Indoline Nitroxide Radicals

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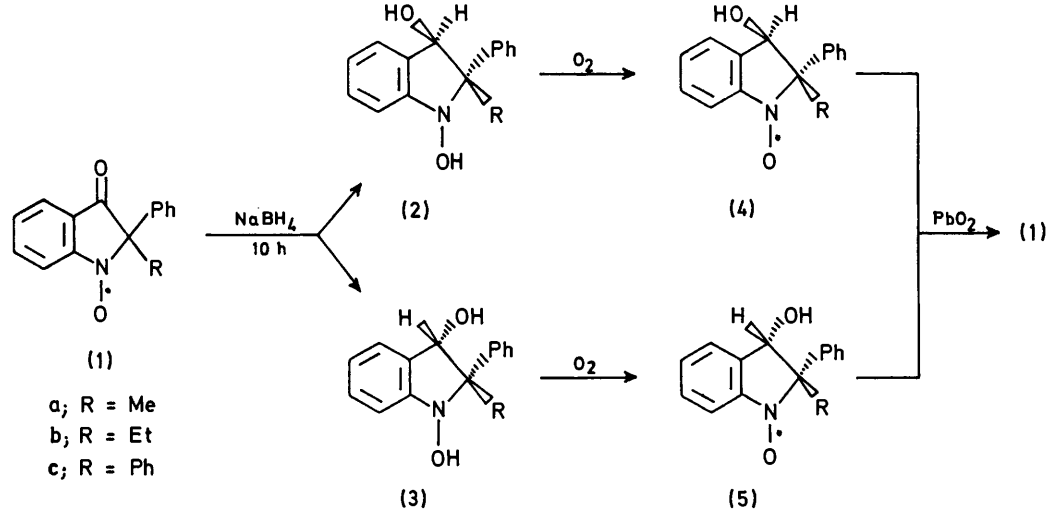
1,2-Dihydro-2-alkyl-2-phenyl-3*H*-indol-3-one 1-oxyls (1) and the corresponding amines (6) undergo stereoselective reduction with $NaBH_4$ giving respectively a pair of diastereoisomeric hydroxylamines (2),(3) and the corresponding amines (7),(8) Both lead to nitroxide radicals (4) and (5), by oxidation; the quantitative ratio of diastereoisomers was determined by means of liquid–liquid chromatography. The configurations of the isomers are tentatively assigned on the basis of ^1H n.m.r. and e.s.r. data, as well as on the stereochemistry of the reaction.

THE reduction with $NaBH_4$, KBH_4, and $LiAlH_4$ of nitroxide radicals having a carbonyl group in the molecule has been extensively studied.[1,2] It has been demonstrated that these compounds undergo reduction at the carbonyl group, while the reduction of the nitroxide group depends either on the reagent or on the type of nitroxide. Here we describe the behaviour of the nitroxide radicals (1) when treated with $NaBH_4$; the interest of this reaction centres of the presence of the asymmetric C-2 atom in the nitroxide radicals (1a) and (1b).

RESULTS

Reduction of the nitroxide radicals (1a—c) was carried out in methanol at room temperature with $NaBH_4$ (Scheme 1). For (1a) and (1c), the hydroxylamine derivatives (2a) and (3a), and (2c) = (3c), which are easily oxidized in solution by air to the corresponding nitroxide radicals (4a) and (5a), and (4c)/(5c), were isolated and analysed (Table 1). The hydroxylamines (2) and (3) when treated with PbO_2, undergo initial oxidation of the hydroxylamino-group; subsequently the OH group in position 3 is oxidized, and the nitroxide (1) (Scheme 1) is generated again.



SCHEME 1

Compounds (6a—c) [3] also undergo reduction of the carbonyl group with $NaBH_4$ giving the corresponding alcohols (Scheme 2). For (6a) and (6c), products (7a) and (8a), and (7c) = (8c) were isolated and analysed (Table 1), while for (6b) only compound (7b) was readily isolated (Table 1). The corresponding diastereoisomer (8b), although the major product, is difficult to purify. Compounds (7) and (8) gave the corresponding radicals (4) and (5) by oxidation with *m*-chloroperbenzoic acid.

Structure and Spectroscopic Data.—I.r. spectra of compounds (2), (3), (7), and (8) show a typical band in the range of 1 605—1 610 cm^{-1}, due to Ph–N–C– group; [4,5] furthermore the carbonyl band at *ca.* 1 680 cm^{-1}, typical of the starting compounds (1) and (6), is absent. I.r. data for the pairs of the isolated diastereoisomers (2a),(3a) and (7a),(8a) are quite similar, but interesting differences are found in the ^1H n.m.r. spectra. The diastereoisomers (7a) and (8a) show very similar spectra for the aromatic hydrogens; however for the coupled hydrogens (J = 8.9 Hz) of OH and 3-H, the signals are significantly different. In the case of (7a) the doublet due to the OH appears at δ 1.97 † and the doublet due to the CH at δ 5.10: in contrast, for the corresponding diastereoisomer (8a) the signals for the same group were found at δ 1.28 † and 4.95, respectively The assignment of these values has been performed using the scaled molecular models of the pair of the two diastereoisomers. In (7a), the 3-H *cis* to the phenyl on C-2 lies in the range associated with the hydrogens of the phenyl group.

This could explain the higher chemical shift (δ 5.10) with respect to that observed for the diastereoisomer (8a) (δ 4.95), in which the hydrogen atom on C-3 is not influenced by the phenyl group on C-2. Analogous considerations can be made for the chemical shifts values of 3-OH group;

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† The chemical shifts of the OH group do not change on changing the concentration of the $CDCl_3$ solution.

TABLE 1

Analytical and spectroscopic data

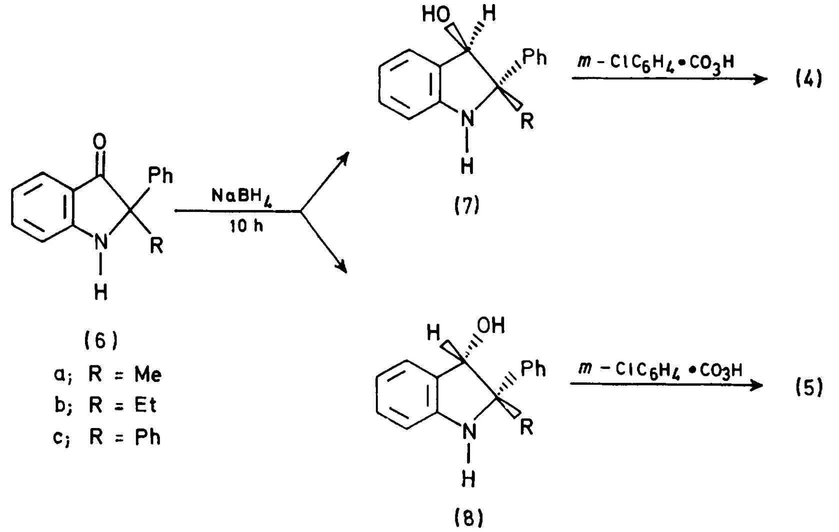
Compound	M.p. (°C)	Formula	% Found *			I.r. ($\nu_{max.}$/cm^{-1})	^{1}H N.m.r. (δ)
(2a)	84 [a]	$C_{15}H_{15}NO_2$	C 74.4 (74.66)	H 6.15 (6.26)	N 5.85 (5.80)	1 610 [b] 3 330 [c]	1.46 (3 H, s, CH$_3$), 2.31 (1 H, d, OH, J = 8.3 Hz), 4.95 (1 H, d, CH, J = 8.3 Hz), 5.40 (1 H, s, NOH), 6.67—7.70 (9 H, m, arom.)
(2c) = (3c)	136 [a]	$C_{20}H_{17}NO_2$	C 79.35 (79.18)	H 5.85 (4.61)	N 4.9 (4.61)	1 610 [b] 3 350 [c]†	1.86 (1 H, d, OH, J = 8.0 Hz), 4.79 (1 H, s, NOH), 5.62 (1 H, d, CH, J = 8.0 Hz), 6.85—7.64 (14 H, m, arom.)
(3a)	130 [a]	$C_{15}H_{15}NO_2$	C 74.45 (74.66)	H 6.05 (6.26)	N 5.95 (5.80)	1 610 [b] 3 360 [c]†	1.52 (3 H, s, CH$_3$), 1.74 (1 H,d, OH, J = 6.3 Hz), 4.83 (1 H, d, CH, J = 6.3 Hz), 5.34 (1 H, s, NOH), 6.73—7.66 (9 H, m, arom.)
(4b)	129 [a]	$C_{16}H_{15}NO_2$	C 74.55 (74.08)	H 6.35 (6.06)	N 5.2 (5.08)	1 600 [b] 3 300 [c]†	
(7a)	130 [a]	$C_{15}H_{16}NO$	C 80.3 (79.96)	H 6.65 (6.71)	N 6.20 (6.21)	1 610 [b] 3 250 [d]†	1.63 (3 H, s, CH$_3$), 1.97 (1 H, d, OH, J = 8.9 Hz), 4.06 (1 H, broad NH), 5.10 (1 H, d, CH, J = 8.9 Hz), 6.72—7.71 (9 H, m, arom.)
(7b)	153 [a]	$C_{16}H_{17}NO$	C 80.0 (80.30)	H 7.1 (7.16)	N 5.8 5.85)	1 610 [b] 3 300 [c,e]†	0.71 (3 H, t, CH$_2$CH$_3$), 2.06 (3 H, m, CH$_2$CH$_3$ + OH), 4.29 (1 H, broad, NH), 5.03 (1 H, s, CH), 6.59—7.56 (9 H, m, arom.)
(7c) = (8c)	186 [a]	$C_{20}H_{17}NO$	C 83.9 (83.59)	H 5.9 (5.96)	N 4.95 (4.87)	1 610 [b] 3 370 [e] 3 400 [c]‡	1.52 (1 H, d, OH, J = 9.0 Hz), 4.55 (1 H, broad, NH), 5.82 (1 H, d, CH, J = 9.0 Hz), 6.72—7.53 (14 H, m, arom.)
(8a)	150 [a]	$C_{15}H_{15}NO$	C 80.85 (79.96)	H 6.65 (6.71)	N 6.25 (6.21)	1 622 [b] 3 230 [c,e]†	1.23 (1 H, d, OH, J = 7.3 Hz), 1.61 (3 H, s CH$_3$), 4.06 (1 H, broad, NH), 4.95 (1 H, d, CH, J = 7.3 Hz), 6.76—7.77 (9 H, m, arom.)
(8b)						1 612 [b] 3 390 [c,e]‡	0.71 (3 H, t, CH$_2$CH$_3$), 1.94 (3 H, m, CH$_2$CH$_3$ + OH), 4.20 (1 H, broad, NH), 4.90 (1 H, broad, CH), 6.61—7.64 (9 H, m, arom.)

* Calc. values in parentheses. † KBr. ‡ Nujol.

[a] Benzene–light petroleum. [b] Ph–N–C–. [c] OH. [d] Benzene. [e] NH.

indeed in the diastereoisomer (8a), 3-H *trans* to phenyl on C-2, the OH group lies in the shielding zone above the phenyl ring bonded to C-2. This might justify the lower chemical-shift value (δ 1.23) with respect to that observed in the diastereoisomer (7a) (δ 1.97), where the OH group is not influenced by the phenyl group bonded to C-2. The OH doublet of (8a), is exchangeable with D_2O whilst the CH doublet collapses to a singlet. Similar deductions are possible for the pair of diastereoisomers (7b),(8b).

The configurations of the diastereoisomers (2a) and (3a) corresponded to those of (7a) and (8a), respectively; by oxidation of (7a) with *m*-chloroperbenzoic acid, we obtained the same nitroxide radical (4a) formed by oxidation of (2a). Similarly, (5a) was obtained from (3a) and (8a) (Schemes 1 and 2). The e.s.r. spectra of the nitroxide radicals (4a—c) and (5a—c) feature a 1 : 1 : 1 nitrogen triplet with a coupling constant a^N = 10.48—10.75 (Table 2). Also observed was the interaction of the unpaired electron with two pairs of hydrogens, having a^H *ca.* 3 G and a^H *ca.* 1 G; these were assigned to hydrogens 5-H,7-H, and 4-H,6-H respectively, on the basis of previous results.[4,6,7] The most interesting point in the e.s.r. spectra is the different hyperfine coupling values of hydrogen bonding to C-3 (Table 2). It is well known that the coupling constant of such a hydrogen depends on the angle between the CH bond and the axis of the p_z orbital of the unpaired electron; the a^H value decreases as this angle increases.[8] Now, let us to consider the scaled molecular models of the two diastereoisomers (4a) and (5a), and note that the more stable conformation for each diastereoisomer is that with the bulky phenyl group in a ψ-axial position. We observe, in the conformation of (4a), where 3-H is *cis* to the 2-phenyl, that the CH bond is almost

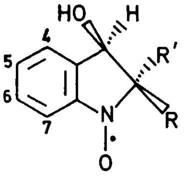


SCHEME 2

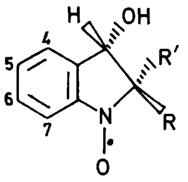
in the same plane as the indolic ring and strongly influenced by the 2-phenyl group; the lower value for a^H (1.68 G; Table 2) is thus justified. In the conformation of (5a), where 3-H is *trans* to the 2-phenyl, the 3-H bond is in a more axial position, thus justifying the higher value of a^H (2.38 G; Table 2). Similar arguments can be advanced for the diastereoisomer pair (4b), (5b), even if, in this case, the differences are less significant (Table 2).

TABLE 2

Hyperfine coupling constants in gauss of nitroxide radicals (4) and (5)



(4)



(5)

Compd.	R	R′	a^N	$a^{H-5} = a^{H-7}$	$a^{H-4} = a^{H-6}$	a^{H-3}
(4a)	Me	Ph	10.63	3.35 (2 H)	1.00 (2 H)	1.68 (1 H)
(4b)	Et	Ph	10.58	3.30 (2 H)	1.00 (2 H)	2.20 (1 H)
(4c) = (5c)	Ph	Ph	10.75	3.26 (2 H)	0.98 (2 H)	1.80 (1 H)
(5a)	Me	Ph	10.65	3.39 (2 H)	0.98 (2 H)	2.38 (1 H)
(5b)	Et	Ph	10.48	3.38 (2 H)	1.01 (2 H)	2.43 (1 H)

DISCUSSION

In the reduction of nitroxide radicals (1a, b) we observe that the red-orange solution immediately turns yellow owing to the formation of the corresponding hydroxylamines,[4] whereas in 10 h we obtain complete reduction of carbonyl group. Nitroxides (1a, b) and indolines (6a, b), having an asymmetric carbon atom at C-2, undergo stereoselective reduction the diastereoisomeric products being formed in the ratio *ca.* 1 : 2.

In recent years there has been much discussion of the factors influencing the stereoselectivity of reduction and nucleophilic addition to a carbonyl group.[9] We believe that the main parameter controlling the present reaction is a steric factor.[10] The hydride ion approaches the carbon atom of the carbonyl group more readily from the side of the smaller alkyl group;[11] the major product is, therefore, the diastereoisomer having a *trans*-configuration with respect to 3-H and the 2-phenyl group. The major product in the reduction of (6a) (see Experimental section) is, in fact, (8a). Both the stereochemistry of the reaction and the spectroscopic considerations support the assignment of configurations we have suggested, although they could not be confirmed by *X*-ray analysis, suitable crystals not having been obtained.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 257 apparatus. ^{1}H N.m.r. spectra were recorded on a Varian C.F.T. 20 spectrometer in $CDCl_3$ solution using $SiMe_4$ as internal standard. E.s.r. spectra were recorded on a Varian E4 spectrometer in $CHCl_3$ solution. The liquid–liquid chromatograph used was a Perkin-Elmer 601 with column ODS-HC-X-1 (0.26 by 25 cm). Compounds (1a—c)[4] and (6a—c)[3] were prepared as described in the literature.

(A) *Reaction of* (1a—c) *with* $NaBH_4$.—Solid $NaBH_4$ (50 mmol) was added to a solution of (1a—c) (5 mmol) in MeOH (100 ml) during 7 h, with stirring at room temperature. After 10 h the reaction mixture was poured into 10% aq. NH_4Cl (200 ml) and extracted with benzene. The benzene layer was dried (Na_2SO_4) and evaporated to dryness. The residue was taken up with benzene and chromatographed on a SiO_2 column using benzene as the eluant. The yields were quantitative but the tendency of products towards autoxidation only permitted the separation of small quantities of the two diastereoisomers (2a) and (3a) from (1a), and (2c),(3c) from (1c); from (1b) it was impossible to isolate (2b) and (3b), for which only the corresponding nitroxide radicals (4b) and (5b) were isolated. The separation of the two diastereoisomers (2a) and (3a) was effected by preparative t.l.c. on SiO_2 with benzene–acetone (95 : 5) as the eluant; compound (2c) = (3c) was purified by column chromatography (on SiO_2) with benzene as the eluant: analytical and spectroscopic data are set out in Table 1. The two diastereoisomeric nitroxide radicals (4b) and (5b) were separated by preparative t.l.c. [SiO_2/light petroleum–ethyl acetate (8 : 2)]; analytical and spectroscopic data are set out in Tables 1 and 2.

(B) *Oxidation of* (2a), (2c), (3c), *and* (3a) *with* PbO_2.—Compound (2a) (100 mg) in $CHCl_3$ (20 ml) and PbO_2 (500 mg) were stirred at room temperature for 12 h; after 10 min the e.s.r. signal of nitroxide radical (4a) was detected in the reaction solution. After 12 h the inorganic salts were filtered off and the filtrate evaporated to dryness to give (1a) in quantitative yield. Working as described for (2a), from (3a) the e.s.r. signal of the nitroxide radical (5a) was detected after 10 min and after 12 h (1a) was isolated in quantitative yield; in this way from (2c) = (3c), the nitroxide radical (4c) = (5c) was identified and compound (1c) was obtained in quantitative yield.

(C) *Reaction of* (6a—c) *with* $NaBH_4$.—The reactions were carried out as described in (A). The mixture of two diastereoisomers (7a),(8a) and (7b),(8b) were isolated from (6a) and (6b) respectively; from (6c) only (7c) = (8c) was isolated; in all cases the yields were 85—95%. The diastereoisomers were partly separated by preparative t.l.c. (on SiO_2) or column chromatography (on SiO_2) with light petroleum–ethyl acetate (9 : 1) as the eluant: analytical and spectroscopic data of isolated compounds are set out in Table 1.

(D) *Oxidation of* (7a), (7b),(7c), (8c), *and* (8a) *with* m-*Chloroperbenzoic Acid*.—Compound (7a) (100 mg) in $CHCl_3$ (20 ml) were treated with an equimolar quantity of *m*-chloroperbenzoic acid, with stirring at room temperature. After 30 min the reaction solution was subjected to preparative t.l.c. on SiO_2 with benzene–acetone (95 : 5) as the eluant. The yellow fraction corresponded to the nitroxide radical (4a), which was extracted with $CHCl_3$ and identified by its e.s.r. signal. In this way the radicals (4b), (4c) = (5c), and (5a) were identified: the hyperfine coupling constants are given in Table 2.

(E) *Percentage Determination of two Diastereoisomers* (7a) *and* (8a) *in the Reaction Mixture*.—The reaction mixture obtained from (6a) by reduction with $NaBH_4$ as described above was analysed by liquid–liquid chromatography, working with a detector L.C. 55 at 250 nm and with a mixture $MeCN-H_2O$ in the ratio of 35 : 65. Two well separated peaks were obtained and identified by comparison with authentic samples; the areas ratio gave 36% of (7a) and 64% of (8a), having the two diastereoisomers the same extinction coefficients at 250 nm: (7a) ($\log \varepsilon = 3.96$); (8a) ($\log \varepsilon = 3.98$).

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