# Acid-catalysed Rearrangements. Specific Syntheses of 2,3-Disubstituted Indoles and N-Hydroxyindoles

By **Corrado Berti, Lucedio Greci,*** and **Marino Poloni,** Istituto Chimico, Facoltà di Ingegneria, Università di Bologna, Viale Risorgimento 2, 40136 Bologna, Italy

Diastereoisomeric 2-alkyl-(or phenyl)-2-phenyl-3-hydroxy-2,3-dihydroindoles in an acid medium undergo elimination of water and transposition of the group having the major migratory power from C-2 to C-3. The stereochemistry of these compounds and the substituent at the nitrogen atom does not affect the final products, which are the same for the two diastereoisomeric indolines. The migratory power follows the sequence benzyl > phenyl > alkyl. The resulting 2,3-disubstituted indoles and N-hydroxyindoles were obtained in quantitative yield.

DURING the last thirty years many papers concerning the Wagner–Meerwein transposition in indole and indoline systems have appeared in the literature.[1-4] Nevertheless, having synthesized a significant series of diastereoisomeric indoline pairs, we considered it would be interesting to study these compounds in acidic media for the following reasons: (*i*) these reactions are specific and alternative syntheses of 2,3-disubstituted indoles and N-hydroxyindoles, which are difficult to prepare;[5] (*ii*) there is the possibility of verifying the migratory

always observed the formation of indoles (3a) and (3b), respectively, whether starting from the *cis*- or *trans*-isomer. Indole (3a) was identified by comparison with an authentic sample prepared by an independent synthesis,[8] and by its u.v. spectrum. The u.v. spectra of the 2-alkyl-3-phenyl-indoles are different from those of the corresponding 3-alkyl-2-phenyl indoles; the first have $\lambda_{max.}$ at 225 and 280 nm, the second have $\lambda_{max.}$ at 225 and 300 nm (Table). On the basis of this difference indole (3b) was identified, and analysed as the picrate. The diastereoisomeric indolines (1c) and (2c)[9] quantitatively yielded 3-benzyl-2-phenyl-
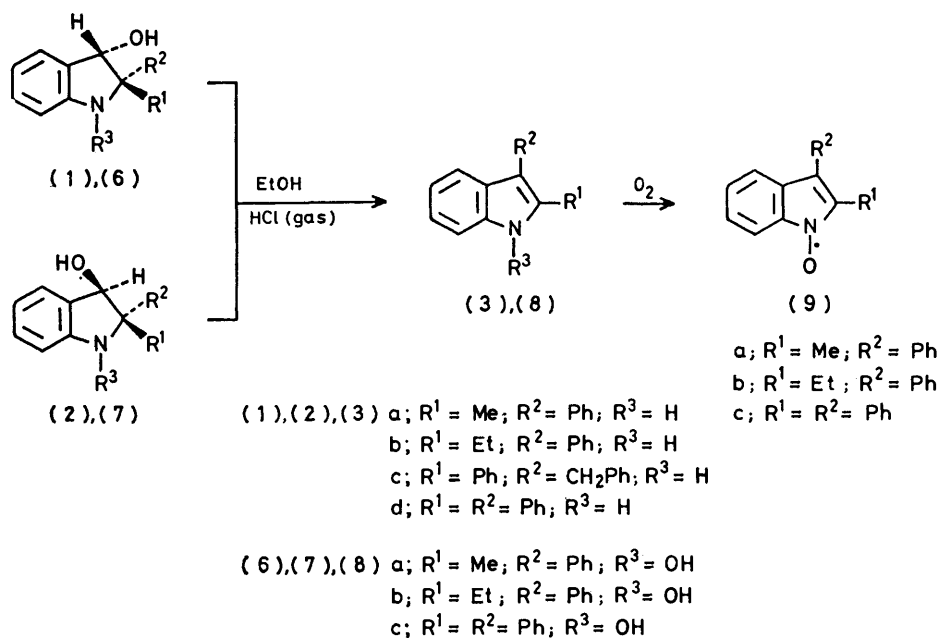
SCHEME 1

ability[6] of the groups considered on the basis of the stereochemistry of the starting compounds, and also the influence of substituents at the indoline nitrogen in the elimination–transposition process.

RESULTS

When the diastereoisomeric indolines (1a—c) and (2a—c),[7] in ethanolic solution at room temperature, were treated with gaseous hydrogen chloride they gave the indoles (3a—c) in almost quantitative yield. In the case of the diastereoisomeric 2-methyl-(1a, 2a) and 2-ethyl-(1b, 2b) indolines we

indole (3c), which is formed by transposition of the benzyl group from C-2 to C-3. The indole (3c) was identified by comparison with authentic samples of the two possible isomers, *i.e.* 2-benzyl-3-phenylindole, prepared as described in the literature,[10] and 3-benzyl-2-phenylindole (3c). Compound (3c), though described in the literature,[5] was prepared by iron–acetic acid reduction of compound (4) (Scheme 2). This specific synthesis unequivocally confirmed the transposition of the benzyl group.

The u.v. spectrum of (3c) had $\lambda_{max.}$ at 213 and 308 nm; the isomeric 2-benzyl-3-phenylindole had $\lambda_{max.}$ at 225 and 285
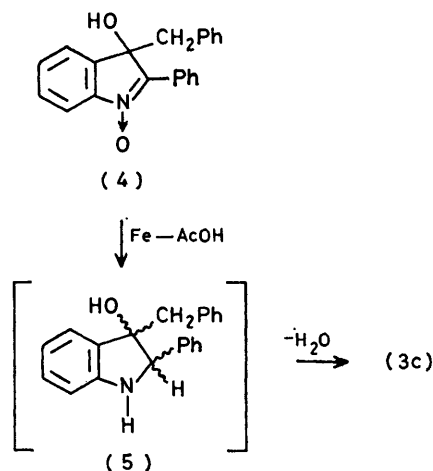
nm. The indoline (1d, 2d) yielded 2,3-diphenylindole (3d) quantitatively, which was identified by comparison with an authentic sample. The pairs of diastereoisomeric hydroxyl-amines, (6a, 7a)[7] and (6b, 7b),[7] treated with gaseous

Spectroscopic data

| Compound	$\lambda_{max.}$/nm (log ϵ)	$\nu_{max.}$/cm^{-1}	^{1}H N.m.r. (δ, J/Hz)
(3a) [a]	225 (4.55) 278 (4.21)	1 605 [c] 3 400 [d]	2.27 (3 H, s, Me); 6.98—7.74 (9 H, m, aromatic + NH)
(3b)	227 (4.61), 283 (4.25)	1 605 [c] 3 400 [d]	1.22 (3 H, t, CH$_2$Me, J 7.0); 2.90 (2 H, q, CH_2Me, J 7.0); 7.04—7.66 (9 H, m, aromatic); 7.96 (1 H, br, NH)
(3c)	213 (4.44), 308 (4.29)	1 600 [c] 3 400 [d]	4.26 (2 H, s, CH_2Ph); 6.6 (9 H, m, aromatic); 8.04 (1 H, br, NH)
(13) [g]		1 610 [e]	1.28 (3 H, s, Me); 2.45 (3 H, s, NMe); 4.5 (1 H, d, CH, J 6.8); 6.25—7.45 (9 H, m, aromatic + OH)
(14) [g]		3 400 [f]	1.22 (3 H, s, Me); 2.41 (3 H, s, Me); 4.73 (1 H, d, CH, J 6.8); 6.25—7.45 (9 H, m, aromatic + OH)
(15) [b]	228 (4.56) 285 (4.17)	1 600 [c]	2.38 (3 H, s, Me); 3.59 (3 H, s, NMe); 7.0—7.87 (9 H, m, aromatic)
(16)	2.28 (4.49) 300 (4.14)	1 600 [c]	2.30 (3 H, s, Me); 3.5 (3 H, s, NMe); 7.1—7.80 (9 H, m, aromatic)

[a] M. Nakazaki, *Bull. Chem. Soc. Jpn.*, 1960, **33**, 461. [b] Ref. 13. [c] Ph–NH–C=C. [d] NH. [e] Ph–N–C. [f] OH. [g] I.r. and n.m.r. spectra were recorded for the mixture of diastereoisomers (13) and (14).

hydrogen chloride, gave the 2,3-disubstituted-1-hydroxy-indoles (8a) and (8b), respectively. Because of their susceptibility to autoxidation,[3] compounds (8a) and (8b) were not isolated, but their formation was verified by the e.s.r. spectra of the corresponding nitroxides, (9a) and (9b),

with intensity 1 : 1 : 1 relative to the nitrogen atom. The coupling constant (a_N 5.88 G) is in agreement with the nitr-oxide indole structure.[11] The e.s.r. spectrum of nitroxide (9b)

(4)

$\downarrow$ Fe—AcOH

(5)

$\xrightarrow{-H_2O}$ (3c)

SCHEME 2

showed only three bands relative to the nitrogen atom (a_N 6.0 G). Thus the phenyl group transposition is confirmed by the e.s.r. spectra of (9a) and (9b), which differ completely

(10)   (11)
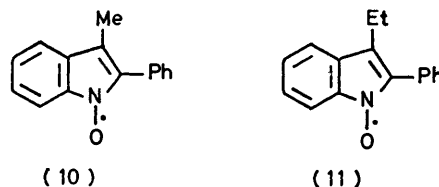
from those of the corresponding isomers, (10) and (11), previously described by us.[12] The hydroxylamine (6c, 7c)[7] quantitatively yielded 1-hydroxy-2,3-diphenylindole (8c),
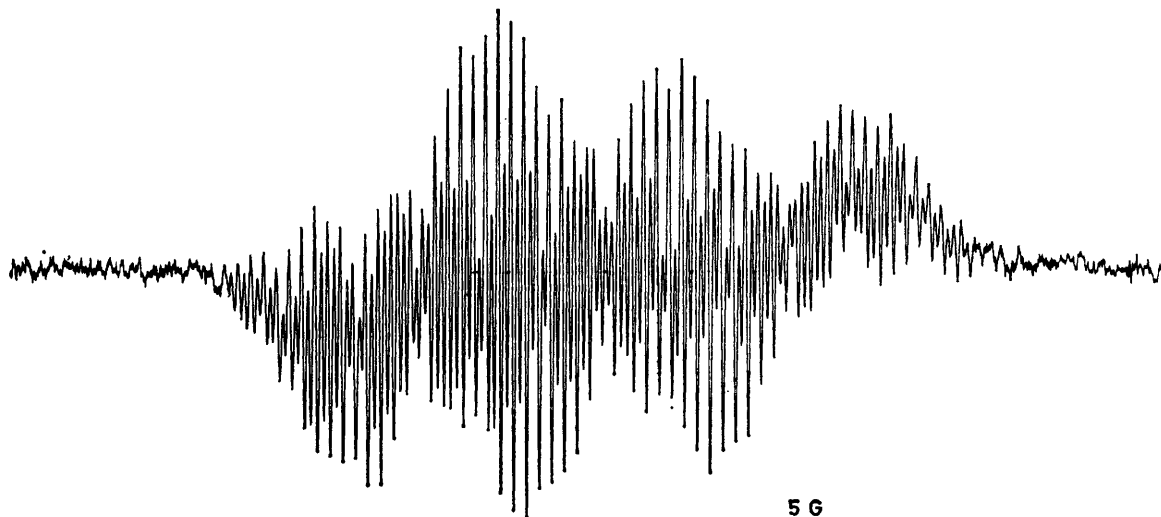

E.s.r. spectrum of (9a) in CHCl$_3$

respectively. The e.s.r. spectrum of (9a) (Figure) was well resolved but because of the large number of different spins, its computer simulation was impossible. The same spectrum recorded with high amplitude modulation showed three bands

which was also obtained by a different route,[12] and the e.s.r. spectrum of the corresponding nitroxide (9c) was the same as that described previously.[12] The mixture of the two diastereoisomers (13) and (14), under the same conditions,

quantitatively formed 1,2-dimethyl-3-phenylindole (15) by phenyl migration from C-2 to C-3.

Indole (15) was identified by comparison with the two possible isomeric indoles (15) and (16) which although

spectrometer (SiMe$_4$ as internal standard). E.s.r. spectra were recorded on solutions in CHCl$_3$ with a Varian E4 spectrometer. U.v. spectra were recorded on solutions in 95% EtOH with a Perkin-Elmer 402 spectrophotometer.
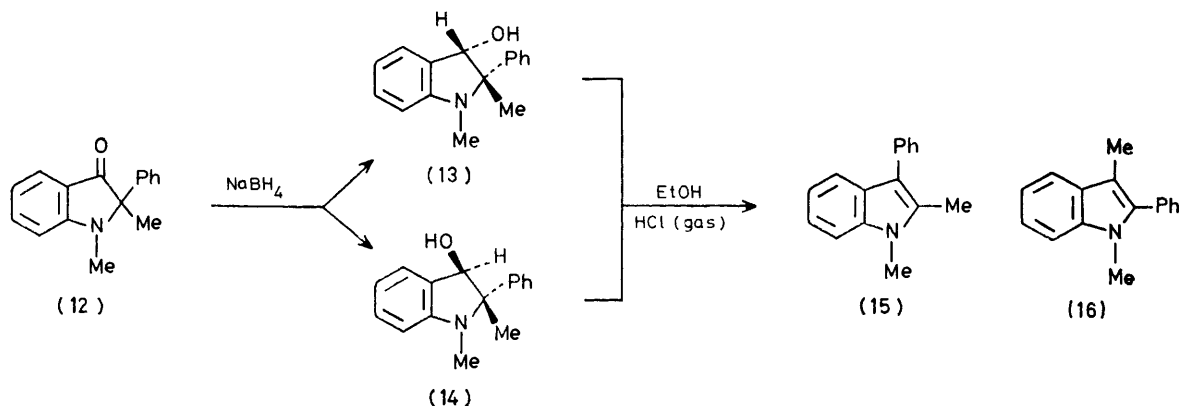

SCHEME 3

known,[13] were prepared by methylation of the corresponding NH-indoles (see Experimental section).

DISCUSSION

These results show clearly the migratory aptitude of the phenyl group relative to alkyl groups, irrespective of the stereochemistry of the starting compounds.

The behaviour of the two diastereoisomers (1c) and (2c) different, because there is competition between the phenyl and benzyl groups; in this case, it is the latter which migrates. Thus the sequence is benzyl > phenyl > alkyl.[6] Since the indole obtained from the diastereoisomeric indolines is always the same, we believe that these experimental results indirectly confirm that the reaction intermediate is the carbo-cation (17),[14,15] which then undergoes attack on the C-2 substituent having the highest migratory aptitude. We
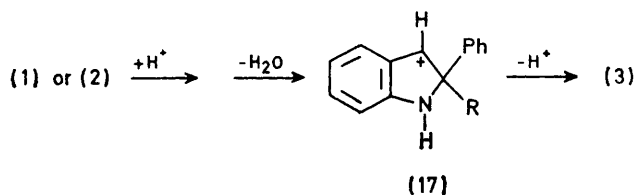
carried out a study on a mixture of the two diastereoisomers (13) and (14), to verify the role of the substituent at the indoline nitrogen on intermediate carbo-cation formation. Since, in this case also, the isolated product was in agreement with the results for indolines (1), (2), (6), and (7), we conclude that the substituent at the nitrogen atom does not influence the transposition mechanism.

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls on a Perkin-Elmer 257 spectrophotometer. N.m.r. spectra were recorded on solutions in CDCl$_3$ with a Perkin-Elmer R12B

Indoles (3a—d) *from Indolines* (1a—d) *and* (2a—d).— Ethanol (20 ml) saturated with gaseous HCl was added to a solution of the indoline (1 mmol) in EtOH (20 ml) with stirring at room temperature. After 2 h the solvent was evaporated and the residue was dissolved in benzene (30 ml). The benzene solution was washed with 10% aqueous NaHCO$_3$ (50 ml), and then with H$_2$O (2 × 30 ml), and dried on Na$_2$SO$_4$. The removal of the solvent gave indoles (3a—d) >95% yield. Indole (3b), an oil, was analysed as the *picrate*: m.p. 138 °C from EtOH (Found: C, 58.35; H, 4.05; N, 12.15. C$_{22}$H$_{18}$N$_4$O$_7$ requires C, 58.66; H, 4.03; N, 12.44%).

Nitroxide (9a—c) *from* N-*hydroxyindolines* (6a—c) *and* (7a—c).—As described above, nitroxide radicals (9a—c) were obtained in chloroform solution and identified by e.s.r. All attempts to isolate the corresponding 1-hydroxyindoles (8a—c) failed; in fact these compounds undergo facile autoxidation to nitroxides (9a—c) in air.[12]

Indoles (3c).—Compound (4)[16] (0.5 g) in acetic acid (10 ml) and iron powder (1 g) were refluxed for 10 min. The reaction mixture, after cooling, was filtered, and the insoluble salts were washed with benzene. The combined filtrates were evaporated to dryness and the residue dissolved in benzene. The benzene solution was washed with 10% aqueous NaHCO$_3$, and dried (Na$_2$SO$_4$). Evaporation of solvent gave indole (3c)[5] in quantitative yield.

1,2-Dimethyl-2-phenylindolin-3-one (12).—2-Methyl-2-phenylindolin-3-one (1 mmol) in THF (50 ml) and MeI (2 g) were added to a stirred solution of MeMgI (1.2 mmol) in Et$_2$O (50 ml) at room temperature with a stream of nitrogen. After 20 h the reaction mixture was poured into 10% aqueous NH$_4$Cl (100 ml) and extracted with benzene (100 ml). The benzene solution was dried (Na$_2$SO$_4$), and evaporated to dryness. The residue was taken up in benzene and chromatographed [SiO$_2$; light petroleum–ethyl acetate (9 : 1)] to give *compound* (12) in 70% yield, m.p. 110 °C (from n-heptane) (Found: C, 81.55; H, 6.65; N, 6.14. C$_{16}$H$_{15}$NO requires C, 80.98; H, 6.37; N, 5.90%).

Indolines (13) *and* (14).—A mixture of the two diastereoisomeric indolines (13) and (14) was prepared following the method previously described by us.[7] The percentages of the two diastereoisomers, obtained in quantitative yield,

were 65% for (14) and 35% for (13) (by n.m.r.). The relative structures were assigned as described previously.[7]

1,2-*Dimethyl*-3-*phenylindole* (15) *from Indolines* (13) *and* (14).—A mixture of (13) and (14) (0.5 g) in EtOH (20 ml), treated as described above, gave indole (15) quantitatively.

Synthesis of Indoles (15) *and* (16).[13]—Sodium hydride (4 mmol) was added to a solution of 2-methyl-3-phenylindole (1 mmol) in THF (40 ml), at room temperature, with a stream of nitrogen, and stirred for 3 h. Methyl iodide (3 g) was then added to the reaction solution, and after 4 h the reaction mixture was poured into 10% NH_4Cl (100 ml). By extraction with benzene, indole (15) was obtained in quantitative yield. Indole (16) was obtained in the same way from 2-phenyl-3-methylindole.

[0/1092 *Received*, 10*th July*, 1980]

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