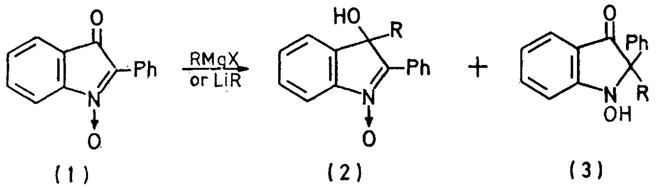
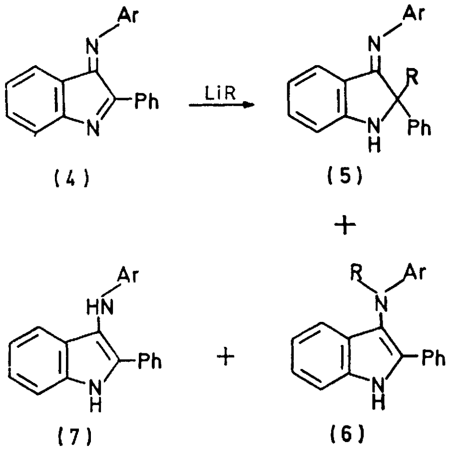
Competition between Single Electron Transfer and Nucleophilic Attack. Part 2.† Reaction of 2-Phenyl-3*H*-indol-3-one with Grignard Reagents

By **Covido Berti, Lucedio Greci, and Leonardo Marchetti,*** Istituto Chimico, Facolta di Ingegneria, viale Risorgimento 2, 40136 Bologna, Italy

2-Phenyl-3*H*-indol-3-one reacts with Grignard reagents leading both to 2,3-dihydro-2-alkyl(or phenyl)-2-phenylindol-3-ones and to 2-phenyl-3-alkyl(or phenyl)-3*H*-indol-3-ols; the ratio of the yields of these compounds depends on the Grignard reagent used and, to a small extent, on the reaction medium. The results are discussed in terms of competition between single electron transfer and nucleophilic attack.

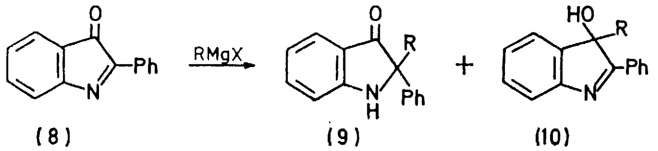
2-PHENYL-3*H*-INDOL-3-ONE 1-OXIDE (1) has been shown to react with organomagnesium and organolithium compounds to give both products (2) and (3);[1] similarly, 2-phenyl-3-arylimino-3*H*-indoles (4) react with lithium derivatives, giving 1,2-addition (5), 1-4-addition (6), and reduction products (7).[2] In this paper we report on the reaction between 2-phenyl-3*H*-indol-3-one (8) and Grignard reagents, which proved to be an interesting process involving attack on both the carbonyl carbon and the azomethine group carbon.





RESULTS

The reactions of 2-phenyl-3*H*-indol-3-one (8) with Grignard reagents were carried out in tetrahydrofuran (THF) at room temperature; the yields of 2,3-dihydro-2-alkyl(or phenyl)-2-phenylindol-3-ones (9a—f) and of 2-phenyl-3-alkyl(or phenyl)-3*H*-indol-3-ols (10a—f) are set out in Table 1. Compounds (9) and (10) were assigned the reported structures by comparison with the same compounds obtained by different and independent routes and on the basis of analytical and spectroscopic data (Tables 2 and 3). In fact, compounds (9a, b, and e) were also obtained both by iron–acetic acid reduction of the corresponding compounds (11)[1] and by hydrolysis of the corresponding compounds (12).[2] On the other hand, compounds (9) react with organic peracids to give nitroxide radicals (11).[3]

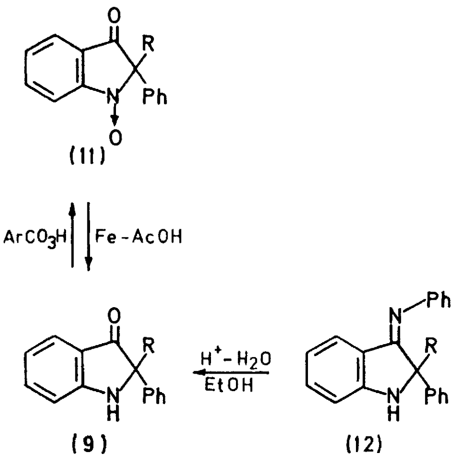


a; R = Me
b; R = Et
c; R = Pr^i
d; R = Bu^t
e; R = Ph
f; R = CH$_2$Ph

TABLE 1

Average yields of compounds (9a—f) and (10a—f) calculated on the isolated products

Compounds	R Me	R Et	R Pr^i	R Bu^t	R Ph	R CH$_2$Ph
			Yield (%)			
(9)	6	8	12	55	0	93
(10)	59	51	25	14	92	0



The i.r. spectra of (9a—f) show bands at *ca.* 3 340, 1 650, and 1 620 cm^{-1} corresponding to the NH, PhN–C, and –C=O groups,[1,4] respectively. The n.m.r. spectra are in agreement with those of the corresponding arylimines (12), the structures of which have been demonstrated.[2] In particular, the n.m.r. spectrum of (9c) exhibits two doublets at δ 0.83 and 0.86, respectively, attributable to the two non-equivalent methyls of the isopropyl group, coupled with the hydrogen atom of the same group which in turn appears

---

† Part 1, C. Berti, L. Greci, and L. Marchetti, *J.C.S. Perkin II*, 1977, 1032.

TABLE 2

Analytical and spectroscopic data of compounds (9a—f)

Compound	M.p. (°C) ^{a}	Formula	Found (%) *			$\nu_{max.}$/cm^{-1}	Chemical shift (δ)
(9a)	See ref. 6					1 620 ^{b}—1 673 ^{c} 3 340 ^{d}	1.6 (3 H, s, CH_3), 5.1br (1 H, NH), 6.6—7.7 (9 H, m, ArH)
(9b)	173	$C_{16}H_{15}NO$	C 80.8 (81.0)	H 6.2 (6.35)	N 6.0 (5.9)	1 620 ^{b}—1 677 ^{c} 3 300 ^{d}	0.83 (3 H, t, CH_2CH_3), 2.18 (2 H, q, CH_2CH_3), 5.2br (1 H, NH), 6.7—7.8 (9 H, m, ArH)
(9c)	190	$C_{17}H_{17}NO$	C 81.1 (81.25)	H 6.8 (6.8)	N 5.45 (5.55)	1 620 ^{b}—1 678 ^{c} 3 330 ^{d}	0.83 (3 H, d, CH_3, J 7 Hz), 0.86 (3 H, d, CH_3, J 7Hz), 2.85 (1 H, sept, $CHMe_2$, J 7 Hz), 5.45br (1 H, NH), 6.7—7.9 (9 H, m, ArH)
(9d)	210	$C_{18}H_{19}NO$	C 81.2 (81.45)	H 7.1 (7.2)	N 5.15 (5.3)	1 620 ^{b}—1 650 ^{c} 3 335 ^{d}	1.0 [9 H, s, $C(CH_3)_3$], 5.67br (1 H, NH), 6.7—8.0 (9 H, m, ArH)
(9e)	See ref. 7					1 622 ^{b}—1 675 ^{c} 3 340 ^{d}	5.35br (1 H, NH), 6.8—7.8 (14 H, m, ArH)
(9f)	185	$C_{21}H_{17}NO$	C 84.32 (84.25)	H 5.73 (5.72)	N 4.77 (4.68)	1 627 ^{b}—1 678 ^{c} 3 310 ^{d}	3.28 (1 H, d, CH_2Ph, J 14 Hz), 3.54 (1 H, d, CH_2Ph, J 14 Hz), 5.15br (1 H, NH), 6.6—7.8 (14 H, m, ArH)

* Required values in parentheses.

^{a} From EtOH. ^{b} PhNH–C. ^{c} >C=O. ^{d} >NH.

TABLE 3

Analytical and spectroscopic data of compounds (10a—e)

Compound	M.p. (°C)	Formula	Found (%) *			$\nu_{max.}$/cm^{-1}	Chemical shift (δ)
(10a)	See ref. 6					1 535 ^{c} 3 290 ^{d}	1.55 (3 H, s, CH_3), 3.78 (1 H, s, NH), 7.1—7.6 (7 H, m, ArH), 8.05—8.3 (2 H, m, ArH)
(10b)	88 ^{a}	$C_{16}H_{15}NO$	C 80.05 (81.0)	H 6.5 (6.35)	N 6.05 (5.9)	1 545 ^{c} 3 280 ^{d}	0.37 (3 H, t, CH_2CH_3), 2.1 (2 H, dq, CH_3CH_3), 3.53br (1 H, NH), 7.02—7.55 (7 H, m, ArH), 8.07—8.28 (2 H, m, ArH)
(10c)	140 ^{b}	$C_{17}H_{17}NO$	C 81.3 (81.25)	H 6.75 (6.8)	N 5.65 (5.55)	1 537 ^{c} 3 270 ^{d}	0.23 (3 H, d, CH_3, J 7 Hz), 1.25 (3 H, d, CH_3, J 7 Hz), 2.4 (s, 1 H, septet, $CHMe_2$, J 7 Hz), 3.3br (1 H, NH), 7.1—7.65 (7 H, m, ArH), 8.2—8.45 (2 H, m, ArH)
(10d)	135 ^{b}	$C_{18}H_{19}NO$	C 81.55 (81.45)	H 7.0 (7.2)	N 5.2 (5.3))	1 545 ^{c} 3 160 ^{d}	1.83 [9 H, s, $C(CH_3)_3$], 3.22br (1 H, NH), 7.15—7.57 (7 H, m, ArH), 8.02—8.28 (2 H, m, ArH)
(10e)	See ref. 7					1 540 ^{c} 3 160 ^{d}	3.21 (1 H, s, NH), 7.1—7.7 (7 H, m, ArH), 7.9—8.2 (2 H, m, ArH)

* Required values in parentheses.

^{a} n-Heptane. ^{b} Benzene–light petroleum. ^{c} OH. ^{d} PhN=C.

as a septet at δ 2.85 (J 7 Hz). This slight non-equivalence of the methyl groups is due to the presence of a chiral carbon (C-2 of the ring) bonded to the isopropyl group. Examples of this type of chirality in n.m.r. spectroscopy are well known,[5] and a very similar case was reported and discussed by us in ref. 1. The same phenomenon is present in the n.m.r. spectrum of (9f) in which the CH_2Ph protons give rise to an AB system appearing as a pseudo-quartet at δ 3.28 and 3.54, respectively, because of the presence of the neighbouring chiral carbon, C-2 of the ring. On the other hand, magnetic non-equivalence could not be proved for the two methylene protons of the ethyl group in (9b), even though the corresponding n.m.r. signal, which appears as a quartet owing to the presence of the neighbouring methyl group, is somewhat broadened.

Finally, compounds (9a and e) have already been described,[6,7] and the physical data for our compounds agree with the literature values.

As far as compounds (10) are concerned, we were not able to isolate the benzyl derivative (10f), even though it was carefully sought among the products. Compounds (10a and e) have already been described,[6-8] and the physical data of our compounds agree with those reported. Compounds (10b—d), previously unknown, were assigned the reported structures on the basis of analytical and spectroscopic data (Table 3) and by analogy with (10a and e).

In the aromatic hydrogen atoms region all the n.m.r. spectra of (10a—e) have a signal at δ *ca.* 8.3, corresponding to two protons, which is also present in the spectrum of phenylisatogen and in various other cases in which the $\mathrm{O}\leftarrow\overset{|}{\mathrm{N}}=\overset{|}{\mathrm{C}}\mathrm{Ph}$ or the $\overset{|}{\mathrm{N}}=\overset{|}{\mathrm{C}}\mathrm{Ph}$ groupings are present;[9] this this signal, which confirms the reported structure (10), is attributable to the two *o*-protons of the phenyl group deshielded by the N=C double bond.

The n.m.r. spectrum of (10d) does not show any other particular features, whereas the spectra of (10b and c) are more interesting. The former exhibits a double quartet at δ 2.1, corresponding to the two non-equivalent methylene protons of the ethyl group bonded to the chiral C-3, and a triplet, corresponding to the methyl hydrogens of the same group at δ 0.37, *i.e.* at unusually high field. This unexpected position can be accounted for by the peculiar geometry of (10c), in which, as can be verified by using scaled molecular models, the methyl group lies in the shielding zone above the indole ring. A similar phenomenon was reported by us in a similar case.[9]

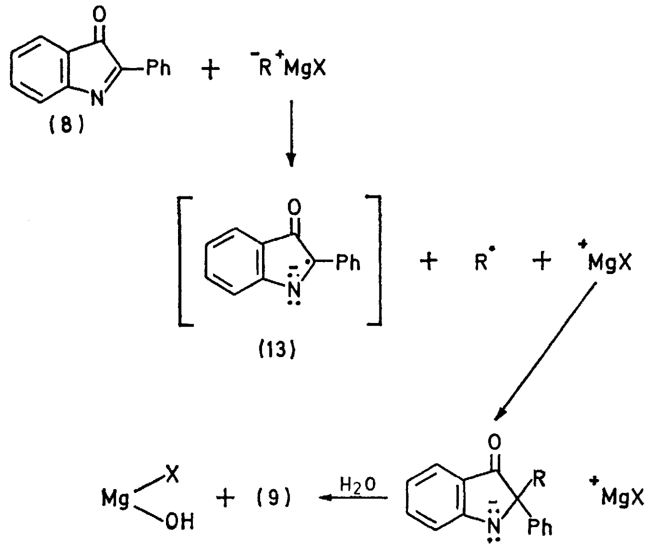
Finally, the n.m.r. spectrum of (10c) exhibits a signal at δ 2.42 attributable to the methine proton of the isopropyl group, which appear as a septet (J 7 Hz), and two well separated doublets for the two magnetically non-equivalent methyls of the isopropyl group, at δ 0.25 and 1.25, respectively, this sharp non-equivalence being due to the peculiar geometry of the molecule, as indicated for (10b); in this case, too, scaled molecular models show that one, and only one, methyl group lies at a given time in the shielding zone above the indole ring.

Finally, the i.r. spectra of all compounds (10a—e) show a standard pattern for the OH (*ca.* 3 160 cm^{-1}) and PhN=C groups (*ca.* 1 540 cm^{-1}), and are in agreement with the assigned structures.

DISCUSSION

Table 1 shows that the reaction of 2-phenyl-3*H*-indol-3-one with Grignard reagents gives addition both to the N=C and the C=O double bonds depending on the organic part of the organometallic derivative. In particular, the reaction with PhMgBr gave only (and in practically quantitative yields) compound (10e), *i.e.* addition to the carbonyl group. The total electron density of the carbonyl carbon, according to HMO calculations (see Experimental section), is 0.762 0, whilst that of C-2 of the ring is 0.890 2; therefore, the behaviour of PhMgBr can easily be explained by nucleophilic attack of the reagent molecule on the carbon atom which appears to the most electron-deficient position of the whole molecule.

The same mechanism, however, cannot explain the reaction of the benzylmagnesium derivative which specifically attacks C-2 of the ring, giving only compound (9f) in quantitative yield without any trace of (10f). In our opinion, the formation of compounds (9) can be accounted for only by a single electron transfer mechanism which passes through the intermediate radical anion (13). A similar reaction path was proposed by us in an analogous case[2] and some experimental evidence was obtained at that time. The radical anion (13) was also obtained by one of us by electrochemical reduction of (8)[10] and HMO calculations, carried out according to MacLachlan, showed that the greatest spin density in the radical anion is at C-2 of the ring (0.308 8 *versus* a spin density of 0.142 6 for C-3), *i.e.* at the position attacked by the R group of the Grignard reagents.



As far as the other Grignard reagents are concerned, both compounds (9) and (10) were obtained, the yields for compounds (9) increasing in the order Me $\leqslant$ Et $<$ CHMe$_2$ $<$ CMe$_3$, and the yields for compounds (10) decreasing in the same order. This sequence is in agreement with the donor power of organomagnesium compounds which increases in the order Ph $\ll$ Me $\leqslant$ Et $<$ CHMe$_2$ $<$ CMe$_3$ $<$ CH$_2$Ph, as established from the decomposition potential of alkylmagnesium halides[11] and from their electrochemical oxidation potentials.[12] Moreover, it is known[12] than an important condition for the occurrence of a single electron transfer from an anion to a neutral molecule is a sufficiently great difference between the values of the electron affinity of the donor and the acceptor. The electron acceptor characteristics of compound (8) have been studied both chemically[13] and polarographically,[10] and the half-wave reduction potential of (8) ($E_{\frac{1}{2}}$ 0.724 V[10]) proved lower than that of the corresponding 3-arylimino derivatives ($E_{\frac{1}{2}}$ 0.914 V[14]), which react with organolithium compounds to give different products *via* a single electron transfer process.[2] The greater reactivity of the carbonyl derivative (8) compared with the arylimino derivatives (4) is also demonstrated by the fact that the latter do not react with Grignard reagents, whilst (8) does.

All these data support the hypothesis of a single electron transfer mechanism to account for the formation of compounds (9). Other experimental evidence was sought to confirm this reaction path; unfortunately, whilst in the reaction of 3-arylimino-2-phenyl-3*H*-indoles with organolithium compounds an e.s.r. signal could be observed (when the reaction was carried out in the e.s.r. spectrometer cavity) emanating from a radical intermediate, in the present case no e.s.r. signal could be recorded, perhaps owing to the greater reactivity of (8) *versus* the 3-arylimino derivatives. However, when the reaction of (8) with PhMgBr, which usually gave only (10e), was carried out in hexamethylphosphoramide (HMPA) as a solvent, which is known to promote single electron transfer processes, compound (9e) was also obtained, although in small quantities.

EXPERIMENTAL

M.p.s are uncorrected. I.r. spectra were recorded in Nujol on a Perkin-Elmer 257 instrument. N.m.r. spectra were recorded for CDCl$_3$ solutions on a Perkin-Elmer R12 B instrument (Me$_4$Si as internal standard). Compound (8)[15] and compounds (12)[2] were prepared as described in the literature. Grignard reagents were prepared by the usual method starting from MeI, EtBr, Me$_2$CHCl, Me$_3$CCl, PhBr, and PhCH$_2$Cl in THF under nitrogen.

Reaction of Compound (8) *with Grignard Reagents*.—Grignard reagent (3 mmol) was added to (8) (2.5 mmol) in THF or HMPA (20 ml), dropwise, at room temperature and in a stream of nitrogen. The mixture was stirred for 2 h, then poured into aqueous 5% NH$_4$Cl and extracted with CHCl$_3$. The CHCl$_3$ layer was dried and evaporated to dryness; compounds (9) and (10) were isolated by chromatography on silica using benzene or light petroleum–ethyl acetate (9 : 1) as eluant. The yields are set out in Table 1; analytical and spectroscopic data are set out in Tables 2 [compounds (9)] and 3 [compounds (10)].

Reaction of Compounds (11a, b, *and* e).—Compounds (11a, b, and e) (2 mmol) and iron powder (1g) in AcOH (25 ml) were refluxed for 10 min. After cooling, the inorganic precipitate was filtered off and solid Na_2CO_3 was added until a solid mixture was obtained. This mixture was extracted with benzene; the extract, when evaporated to dryness, gave (9a, b, and e) in over 90% yield.

Acid Hydrolysis of Compounds (12a, b, *and* e).—Compounds (12a, b, and e) (5 mmol) and 10% HCl (5 ml) in EtOH (70 ml) were refluxed for 7 h. The mixture was evaporated to dryness and the residue was taken up with $CHCl_3$; the $CHCl_3$ layer, washed with aqueous Na_2CO_3 and water, was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on a silica column using benzene as eluant. Compounds (9a, b, and e) were isolated in 65—80% yield.

HMO Calculations.—The calculations were carried out with the aid of an automatic calculation program, using the parameter set:[16,17] $h_{\dot{N}} = 0.44$, $h_{\dot{O}} = 0.84$, $k_{CC} = 1.0$, $k_{C-C} = 0.9$, $k_{C=N} = 1.06$, $k_{C=O} = 1.23$, $k_{C-N} = 0.8$.

[8/582 *Received*, 29*th March*, 1978]

REFERENCES

[1] C. Berti, M. Colonna, L. Greci, and L. Marchetti, *Tetrahedron*, 1975, **31**, 1745.

[2] C. Berti, L. Greci, and L. Marchetti, *J.C.S. Perkin II*, 1977, 1032.

[3] C. Berti, M. Colonna, L. Greci, and L. Marchetti, *Tetrahedron*, 1977, **33**, 2321.

[4] B. Witkop, *Bull. Soc. chim. France*, 1954, 423.

[5] M. L. Martin and G. J. Martin, *Bull. Soc. chim. France*, 1966, 2117; M. Gorkom and G. E. Hell, *Quart. Rev.*, 1968, **22**, 14.

[6] J. W. Kershaw and A. Taylor, *J. Chem. Soc.*, 1964, 4320.

[7] L. J. Dolby and R. M. Rodia, *J. Org. Chem.*, 1970, **35**, 1493.

[8] D. Lednicer and E. Emmert, *J. Heterocyclic Chem.*, 1970, **7**, 575.

[9] See ref. 1, footnote, p. 1746.

[10] R. Andruzzi, A. Trazza, P. Bruni, and L. Greci, *Tetrahedron*, 1977, **33**, 665.

[11] W. V. Evans, *J. Amer. Chem. Soc.*, 1942, **64**, 2865.

[12] K. A. Bilevitch and O. Yu. Okhlobystin, *Russian Chem. Rev.*, 1968, **37**, 12.

[13] M. Colonna and L. Greci, *Gazzetta*, 1969, **99**, 940.

[14] R. Andruzzi, T. Carelli, A. Trazza, P. Bruni, and M. Colonna, *Tetrahedron*, 1974, **30**, 3741.

[15] L. Kalb and J. Bayer, *Ber.*, 1912, **45**, 2157.

[16] H. P. Figeys and P. Dedieu, *Theor. Chim. Acta*, 1967, **9**, 82.

[17] A. Streitwieser, jun., ' Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1961.