Competition between Single Electron Transfer and Nucleophilic Attack: Reaction of 3-Arylimino-2-phenyl-3*H*-indoles with Organolithium Compounds

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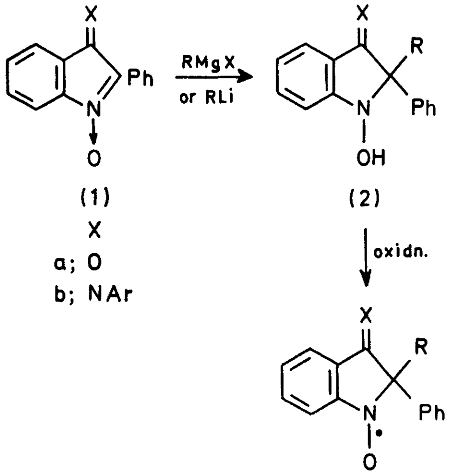
3-Arylimino-2-phenyl-3*H*-indoles react with organo-lithium compounds giving 1,2-addition, 1,4-addition, and reduction products; the extents of formation of these compounds depend on the substituent *para* with respect to the arylimino-group. Competition between single electron transfer and nucleophilic attack is discussed.

2-PHENYL-3*H*-INDOL-3-ONE 1-OXIDE (1a) and related 3-arylimino-derivatives (1b) have been shown to react with organomagnesium and organolithium compounds to give hydroxylamines (2) which easily undergo autoxidation to nitroxide radicals (3).[1] The purpose of this work was to prepare 2-phenyl-2-alkyl- (or -phenyl-)3-aryliminoindolines (5) (which are difficult to prepare in other ways) by 1,2-addition of organometallic reagents to 3-arylimino-2-phenyl-3*H*-indoles (4). The reaction with organo-lithium compounds proved to be complex, involving 1,2-addition, 1,4-addition, and reduction; Grignard reagents gave no reaction.



(1)

X
a; O
b; NAr

(2)

(3)

RESULTS

Reactions were carried out in benzene–tetrahydrofuran (1 : 1) at room temperature, and compounds (5)—(7) were isolated (Scheme 1). Table 1 gives average yields of 1,2-addition, 1,4-addition, and reduction products. In a number of experiments carried out at −40 °C, lower yields were obtained, but the ratios of products were not affected significantly; moreover a change in solvent composition had little influence, at least in the narrow range of variation allowed by the solubility of the reagents.

Compounds (5a—i) were identified by their reactions and their analytical and spectroscopic data; when oxidized with peroxy-acids, *e.g.* *p*-nitro- or *m*-chloro-perbenzoic acid, they gave the corresponding nitroxide radicals (3b).[1] The structures were confirmed by reduction of the nitroxides (3b) with iron–acetic acid.

The i.r. spectra of compounds (5a—i) (Table 2) show bands at *ca.* 3 400, 1 650, and 1 600 cm^{-1}, corresponding to NH, PhN–C, and $>$C=N–,[1,2] respectively. The n.m.r. spectra of compounds (5a, d, and g) show methyl signals at δ 1.93, 1.77, and 1.88, respectively; comparison with the corresponding values for compounds (8),[3,4] (9),[4-7] (10),[8] (11),[9] and (12) [1] (Scheme 2) indicates that the methyl group is bonded to a saturated carbon atom rather than an unsaturated one or a nitrogen atom. The same argument can be applied to the ethyl group (Table 2). Moreover, the ethyl group bonded to the C-2 of the ring in (5b, e, and h) always exhibits two quartets for $CH_2{\cdot}CH_3$, the two hydrogen atoms giving rise to an AB system because of the presence of a neighbouring chiral carbon atom. A similar phenomenon has been shown for compounds (2) (R = Et or CH_2Ph).[1]

Compound (6c) was identified by comparison with an authentic sample obtained by direct methylation of 3-(*p*-methoxyphenylamino)-2-phenylindole.[9] Compounds (6a, b, d, and e) were identified on the basis of their i.r. and n.m.r. spectra (Table 3), the e.s.r. spectra of the derived radical cations, and comparison with (6c). The i.r. spectra exhibit NH band at 3 370—3 390 cm^{-1}; i.r. spectra of (7a—c), on the other hand, exhibit two bands in the NH region, at *ca.* 3 420 and *ca.* 3 380 cm^{-1}, corresponding to the amine NH and the indolic NH, respectively;[10] the spectrum of (6c) shows only one band, at 3 390 cm^{-1} (indolic NH).[9] The n.m.r. spectra of all compounds (6) exhibit a signal at δ 8.1—8.2 corresponding to one NH group; this chemical shift value is characteristic of the indolic NH group, as can be shown by comparison of the spectra of compounds (7a—e) (two NH signals, δ 8.1 and 5.3, respectively) (Table 4) (6c) [9] (one indolic NH signal, at δ 8.2), and (13) [5,11] (one amine NH signal at δ 5.25—5.45).

The chemical shift of the alkyl group R^2 in (6a—e), unlike that of the NH group, cannot be used to determine

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

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

[3] M. Colonna, L. Greci, L. Marchetti, E. Foresti-Serantoni, and R. Mongiorgi, *Gazzetta*, 1974, **104**, 385.

[4] M. Colonna, L. Greci, L. Marchetti, G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *J.C.S. Perkin II*, 1976, 309.

[5] M. Colonna, L. Greci, and L. Marchetti, *Ann. Chim. (Italy)*, 1973, **63**, 785.

[6] M. Colonna, L. Greci, and L. Marchetti, *Gazzetta*, 1974, **104**, 395.

[7] M. Colonna, L. Greci, L. Marchetti, G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *J.C.S. Perkin II*, 1976, 317.

[8] M. Mousseron-Canet and J. P. Boca, *Bull. Soc. chim. France*, 1967, 1296.

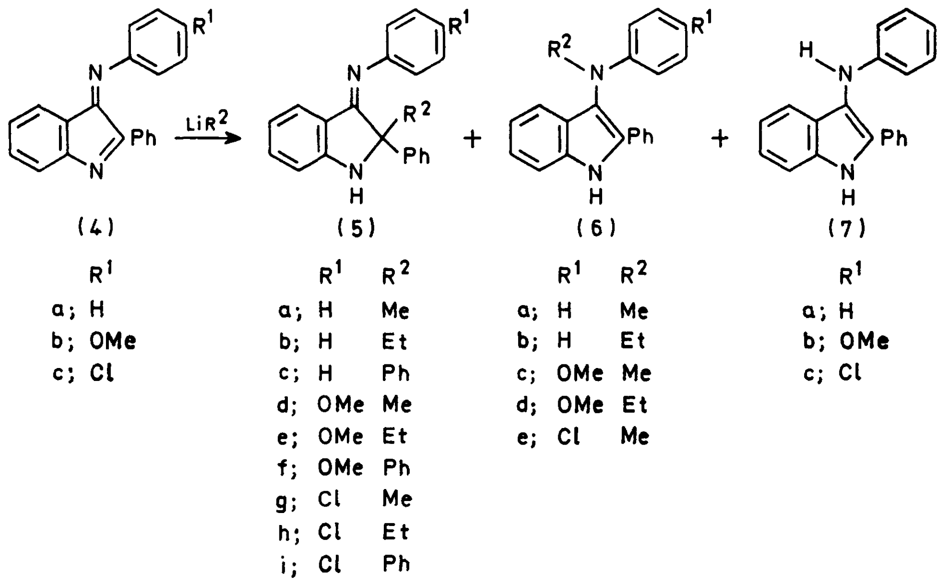
[9] Compounds (11) were prepared by P. Bruni, M. Colonna, and L. Greci, (*Tetrahedron*, 1971, **27**, 5893); they, however, did not report the n.m.r. spectrum, which we have recorded.

[10] L. Marchetti, L. Greci, and G. Tosi, *Gazzetta*, 1970, **100**, 770.

[11] This assignment is confirmed by a similar case: M. Colonna, L. Greci, and L. Marchetti, *Gazzetta*, 1975, **105**, 665.

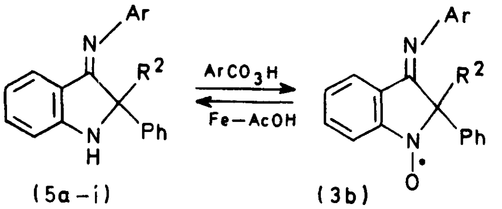
whether this group is bonded to the endocyclic or the exocyclic nitrogen atom; in fact, the chemical shift values set out in Scheme 2 indicate that the NMe group always absorbs at the same field, independent of which of the two nitrogen atoms it is bonded to. E.s.r. spectra gave a further proof of structure (6). It was known [9] that (6c), when oxidized with Gomberg's reagent (I_2–$AgClO_4$), gives (6), and is similar to that discussed for the di-indolylamines.[5] Finally, to confirm their structure, compounds (6) were prepared independently by alkylation of the corresponding 3-arylamino-2-phenylindoles, according to ref. 9.

Compounds (7a—c) were identified by comparison with authentic samples obtained *via* an independent synthesis.[10]



SCHEME 1

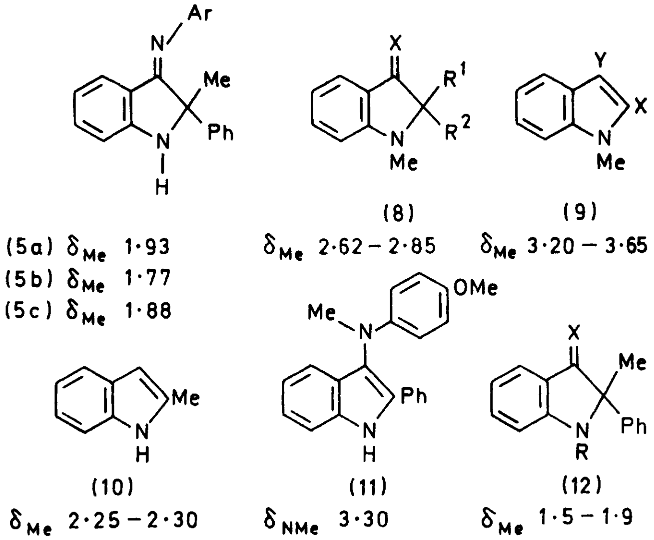
the corresponding radical cation (14c), which shows a six-line spectrum with relative intensities 1 : 4 : 7 : 7 : 4 : 1, attributed to coupling of the unpaired electron with one nitrogen and three hydrogen nuclei ($a^{\mathrm{N}}_{\mathrm{NMe}} = a^{\mathrm{H}}_{\mathrm{NMe}} =$ 8.5 G). The same spectrum is shown by the radical cations (14a) and (14e) obtained in the oxidation of (6a) and (6e), whereas the radical cations (14b and d) exhibit five-line e.s.r. spectra with relative intensities 1 : 3 : 4 : 3 : 1, attributable to coupling of the unpaired electron with one nitrogen and two hydrogen nuclei ($a^{\mathrm{N}}_{\mathrm{NEt}} = a^{\mathrm{H}}_{\mathrm{NC}H_2\mathrm{CH}_3}$ = 7.3—8.1 G). All the e.s.r. spectra show only the hyperfine structure due to the exocyclic nitrogen atom and to the protons attached to the carbon atom directly bonded to nitrogen.



Compounds (6a—e) undergo spontaneous oxidation to the radical cations (14a—e) in deuteriochloroform solution; as a consequence, the n.m.r. signals of the alkyl groups bonded to the exocyclic nitrogen atom are considerably broadened, and in some cases the signal practically disappears; addition of a little *NN'*-diphenylhydrazine (DPH) to the oxidized solution causes reduction of the radical cation (14) and the reappearance of the alkyl group signals. This phenomenon is due to an electron exchange reaction between the radical cation (14) and the reduction product

DISCUSSION

As is shown in Table 1, compounds (5) were obtained in high yields from all reactions, whereas the formation of compounds (6) and (7) seemed to depend upon the organolithium derivative used and the substituent R *para* with respect to the imino-group in the starting materials (4). In the reactions with phenyl-lithium we were not able to obtain experimental evidence for 1,4-addition or for reduction.



SCHEME 2

1,2-Addition of the organolithium compounds giving compounds (5a—i) can be easily explained by a nucleophilic process, involving either a cyclic transition state with simultaneous shift of electron pairs, or direct attack of the reagent molecule polarised by solvation at C-2 of the substrate (4) which, from HMO calculations, appears to be one of the more electron-deficient positions.[12] However, against this ionic or quasi-ionic [13] mechanism is that C-3 has exactly the same electron density as C-2,* but compounds derived from attack at C-3 were never isolated. From a molecular model of the planar molecule (4), it seems unlikely that steric hindrance can explain this specificity.

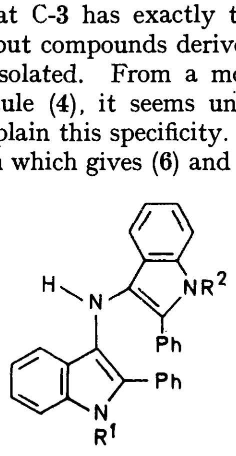
TABLE 1

Yields (%) of products of 1,2-addition (5), 1,4-addition (6), and reduction (7)

Substrate	Reagent	(5)	(6)	(7)
(4a)	LiMe	72	*a*	*a*
	LiEt	68	*a*	*a*
	LiPh	80		
(4b)	LiMe	65	10	*b*
	LiEt	70	8	*b*
	LiPh	75		
(4c)	LiMe	68	*a*	4
	LiEt	72		4.5
	LiPh	80		

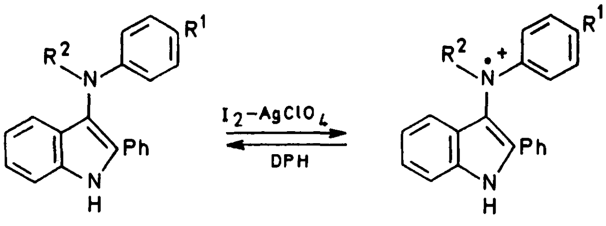
[a] Small quantities of products isolated and identified by comparison with authentic samples. [b] Traces of products identified by t.l.c. comparison with authentic samples.

The mechanism which gives (6) and (7) is less difficult to envisage. An ionic reaction pathway can hardly explain the formation of the 1,4-addition products (6), which would require nucleophilic attack of the reagent at the exocyclic nitrogen atom, *i.e.* one of the more negative positions of the molecule. As far as the formation of the reduction compounds (7) is concerned, a single electron transfer mechanism can be proposed. The aptitude of organometallic reagents to bring about reduction in competition with addition is known, and a mechanism involving electron transfer is firmly established [14] in this case. In our reactions we observed an e.s.r. signal that was conclusively shown to emanate from species produced during the reaction and was not due to the reagents. The signal is transient, not well resolved, and difficult to observe, but its observation was reproducible.



(13)

In our opinion, a single electron transfer mechanism could explain the formation of all products, and in particular could account for the lack of products deriving from nucleophilic attack at C-3 of the ring. However, we have at present insufficient experimental evidence to decide between an ionic and an electron transfer process as far as the formation of compounds (5) is concerned. Further studies are under way to clarify this point.



(6a—e) (14a—e)

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 257 spectrometer. N.m.r. spectra were recorded for solutions in $CDCl_3$ with a Perkin-Elmer R12 B spectrometer (Me_4Si as internal standard). E.s.r. spectra were recorded for solutions in acetonitrile with a Varian E4 spectrometer.

3-Arylimino-2-phenyl-3*H*-indoles (4a—c) were synthesized as reported in ref. 10. Methyl-, ethyl-, and phenyl-lithium were commercial products (Fluka).

Reaction of 3-*Arylimino*-2-*phenyl*-3H-*indoles* (4a—c) *with Organolithium Derivatives*.—The organolithium derivative (6 mmol) was mixed with compound (4) (5 mmol) in benzene–tetrahydrofuran (1 : 1) (60 ml) at room temperature. A deep violet colour appeared and after 3 h the mixture was poured into aqueous 5% ammonium chloride, then extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated; the residue was taken up with benzene and chromatographed on silica gel. Elution with benzene gave first a mixture of compounds (6) and (7), then compounds (5) were obtained. Compounds (6) and (7) were separated by t.l.c. (silica gel; light petroleum–ethyl acetate, 9 : 1); the separation was made easier by the intense fluorescence of all compounds. Yields are reported in Table 1; analytical and spectroscopic data are set out in Tables 2—4.

Radicals (3b) *by Oxidation of the Indolines* (5) *with Peroxy-acids*.—The radicals (3b) were obtained directly in the e.s.r. spectrometer cavity by using an inverted U cell as described by Russel.[15] The experiments were carried out with 1.5 mmol each of (5) and peroxy-acid (*m*-Cl- or *p*-NO_2–C_6H_4·CO_3H) in chloroform solution; these were mixed in the cell after effective degassing with pure nitrogen, so obtaining the e.s.r. spectrum of (5) [1] in a few minutes.

Compounds (5) *by Reduction of the Radicals* (3b).—The nitroxide (3b) (2 mmol) and iron powder (1g) in acetic acid (25 ml) were refluxed for 10 min. After cooling the inorganic precipitate was filtered off and solid sodium

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* This is true for HMO calculations; it is possible that more sophisticated calculation methods would reveal a slight difference, but it seems unlikely, because of the symmetry of the molecule, that this would be large enough to explain the specificity of the reaction.

[12] J. Honzl and M. Metalovà, *Tetrahedron*, **1969**, **25**, 3641.

[13] T. Holm and I. Crossland, *Acta Chem. Scand.*, 1971, **25**, 59.

[14] B. Uchytil, J. Honzl, and V. Kubelka, *Coll. Czech. Chem. Comm.*, 1975, **40**, 462, and references quoted therein.

[15] G. A. Russel, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, 1964, **86**, 1807.

carbonate was added to the filtrate to give a solid mixture. This mixture was then extracted with benzene and the extract, evaporated to dryness, gave compound (5) in over 90% yield.

TABLE 2

Analytical and spectroscopic data of compounds (5a—i)

Compound	Recryst. solvent[a]	M.p./°C	Formula	% Found * C	H	N	I.r. $\nu_{max.}$/cm^{-1}	N.m.r. (δ)
(5a)	A	133	$C_{21}H_{18}N_2$	85.05 (85.55)	6.05 (6.1)	9.1 (9.4)	3 370,[b] 1 652,[c] 1 580,[d]	1.72 (3 H, s, CH_3), 4.52br (1 H, NH), 6.3—7.8 (14 H, m, ArH)
(5b)	A	154	$C_{22}H_{20}N_2$	84.75 (84.6)	6.3 (6.45)	8.8 (8.95)	3 410,[b] 1 655,[c] 1 592 [d]	0.98 (3 H, t, $CH_2{\cdot}C\mathit{H}_3$), 2.28 (2 H, two q, $C\mathit{H}_2{\cdot}CH_3$), 4.72br (1 H, NH), 6.3—8.0 (14 H, m, ArH)
(5c)	A	193	$C_{26}H_{20}N_2$	86.05 (86.65)	5.95 (5.6)	7.85 (7.75)	3 410,[b] 1 660,[c] 1 595 [d]	6.4—7.8 (m, ArH)
(5d)		†	$C_{22}H_{20}N_2O$	80.25 (80.45)	6.05 (6.15)	8.2 (8.4)	3 435,[b] 1 655,[c]‡ 1 610 [d]	1.77 (3 H, s, CH_3), 3.67 (3 H, s, OCH_3), 4.95br (1 H, NH), 6.2—7.8 (13 H, m, ArH)
(5e)	B	143	$C_{23}H_{22}N_2O$	80.4 (80.65)	6.35 (6.5)	8.2 (8.2)	3 390,[b] 1 635,[c] 1 600 [d]	0.94 (3 H, t, $CH_2{\cdot}C\mathit{H}_3$), 2.28 (2 H, two q, $C\mathit{H}_2{\cdot}CH_3$), 3.82 (3 H, s, OCH_3), 4.82br (1 H, NH), 6.3—7.9 (13 H, m, ArH)
(5f)	C	216	$C_{27}H_{22}N_2O$	83.1 (83.05)	5.65 (5.67)	6.85 (7.2)	3 361,[b] 1 648,[c] 1 603 [d]	3.85 (3 H, s, OCH_3), 4.95br (1 H, NH), 6.4—7.8 (18 H, m, ArH)
(5g)	B	124	$C_{21}H_{17}ClN_2$	75.5 (75.8)	4.8 (5.15)	8.7 (8.4)	3 410,[b] 1 660,[c] 1 610 [d]	1.88 (3 H, s, CH_3), 4.65br (1 H, NH), 6.4—7.8 (13 H, m, ArH)
(5h)	A	150	$C_{22}H_{19}ClN_2$	76.25 (76.2)	5.8 (5.5)	8.5 (8.1)	3 390,[b] 1 655,[c] 1 605 [d]	1.05 (3 H, t, $CH_2{\cdot}C\mathit{H}_3$), 2.37 (2 H, two q, $C\mathit{H}_2{\cdot}CH_3$), 4.75br (1 H, NH), 6.5—7.9 (13 H, m, ArH)
(5i)	B	162	$C_{26}H_{19}ClN_2$	79.6 (79.1)	4.95 (4.85)	6.85 (7.1)	3 408,[b] 1 650,[c] 1 600 [d]	4.8br (1 H, NH), 6.3—7.7 (18 H, m, ArH)

* Required values in parentheses. † Oil. ‡ In CCl_4.

[a] A, n-heptane; B, light petroleum (b.p. 80—100 °C); C, light petroleum (b.p. 100—130 °C). [b] NH. [c] C=NAr. [d] PhN–C.

TABLE 3

Analytical and spectroscopic data of compounds (6a—e)

Compound	Recryst.[a] solvent	M.p. (°C)	Formula	% Found * C	H	N	I.r. $\nu_{max.}$/cm^{-1}	N.m.r. (δ)
(6a)	A	105	$C_{21}H_{18}N_2$	84.65 (84.55)	6.0 (6.1)	9.5 (9.4)	3 390	3.32 (3 H, s, NCH_3), 6.8—7.9 (14 H, m, ArH), 8.23br (1 H, NH)
(6b) [b]			$C_{22}H_{20}N_2$	84.3 (84.6)	6.2 (6.45)	9.3 (8.95)	3 475 [c]	1.1 (3 H, t, $CH_2{\cdot}C\mathit{H}_3$), 3.66 (2 H, q, $C\mathit{H}_2{\cdot}CH_3$), 6.6—8.0 (15 H, m, ArH), 8.12br (1 H, NH)
(6c) [d]								3.3 (3 H, s, NCH_3), 3.8 (3 H, s, OCH_3), 6.8—7.9 (13 H, m, ArH), 8.22br (1 H, NH)
(6d)	B	152	$C_{23}H_{22}N_2O$	80.05 (80.65)	6.5 (6.45)	8.05 (8.2)	3 370	1.1 (3 H, t, $NCH_2{\cdot}C\mathit{H}_3$), 3.68 (2 H, q, $NC\mathit{H}_2{\cdot}CH_3$), 3.79 (3 H, s, OCH_3), 6.8—7.9 (13 H, m, ArH), 8.25br (1 H, NH)
(6e)								3.13 (3 H, s, NCH_3), 6.5—7.7 (13 H, m, ArH), 8.05br (1 H, NH)

* Required values in parentheses.

[a] A, light petroleum; B, light petroleum (b.p. 80—100 °C). [b] Oil. [c] In CCl_4. [d] See refs. 9 and 17.

3-(N-*Alkylanilino*)-2-*phenylindoles* (6) *by Direct Alkylation of the Anilinoindoles* (7a—c).—The indole (7) (10 mmol) and ethyl bromide (6 ml) in ethanol (20 ml) were heated at 140 °C in a small autoclave for 3 h. After cooling, the mixture was treated with dilute aqueous ammonia and extracted with benzene. The extract was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (light petroleum–ethyl acetate, 9 : 1). Compounds (6b and d) were thus obtained in 40—50% yield. Compounds (6a, c, and e) were synthesized in the same way from (7a—c) with methyl iodide and methanol. Analytical and spectroscopic data are in Table 3.

TABLE 4

N.m.r. spectra of compounds (7a—c) (δ values)

(7a)	5.25br (1 H, NH), 6.65—7.8 (14 H, m, ArH), 8.1br (1 H, NH)
(7b)	3.7 (3 H, s, OCH_3), 5.02br (1 H, NH), 6.5—7.8 (13 H, m, ArH), 8.04br (1 H, NH)
(7c)	5.2br (1 H, NH), 6.5—7.8 (13 H, m, ArH), 8.1br (1 H, NH)

Radical Cations (14a—f).—The radical cations (14a—f) were obtained in acetonitrile solution by oxidation of compounds (6a—f) with Gomberg's reagent and work-up as reported in ref. 16.

HMO Calculations.—The calculations were carried out with the aid of an automatic calculation program, using the parameter set:[17,18] $h_{\dot{N}} = 0.44$, $K_{CC} = 1.0$, $K_{C-C} = 0.9$, $K_{C=N} = 1.06$, $K_{C-N} = 0.8$. Calculated electron densities for C-2 and -3 of the heterocycle were 0.901 and 0.906, respectively.

[6/1409 *Received*, 19*th July*, 1976]

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[16] M. Colonna, P. Bruni, and L. Greci, *Tetrahedron*, 1973, **29**, 185.

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

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