Tetrahedron Vol. 38, No. 1, pp. 173 to 182, 1982
Printed in Great Britain.

0040-4020/82/010173-10$03.00/0
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SELECTIVITY IN CYCLOADDITIONS—IX[1]

CYCLOADDITIONS OF NITRILE OXIDES TO INDOLES. REACTIVITY AND REGIOCHEMISTRY

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(*Received in U.K. 28 May* 1981)

Abstract—Cycloadditions of benzonitrile oxide and mesitonitrile oxide to N-methylindole and indole yield the acid sensitive cycloadducts **1 a-d** with high regioselectivity. With N-carbethoxyindole the stable cycloadducts **1 e,f** and minor amounts of the regioisomeric **2 e,f** are isolated. The electron withdrawing substituent reduces both the regioselectivity and the reactivity of the cycloadditions.

Frontier orbital considerations, based on MINDO/3 calculations, allow elucidation of the observed changes in reactivity and regiochemistry.

Previous papers of this series dealt with the dipolarophilic reactivity of heteroaromatic compounds in the 1,3-dipolar cycloaddition of nitrile oxides. Despite the reluctance of aromatic systems toward addition reactions and their preference for substitution, only in the case of furan a competition between the concerted cycloaddition and a minor substitution pathway could be detected.[3] Thiophene,[4] benzofuran[5] and benzothiophene[4] behave as regular π_s^2 components in the 1,3-dipolar cycloadditions with nitrile oxides. The reactivity of these heteroaromatic dipolarophiles is however sharply decreased because of the loss of aromaticity in the cycloaddition transition states. Both the regioisomeric cycloadducts could be isolated or evidenced in all cases and the regiochemistry fits well the simple frontier molecular orbital (FMO) model.[6]

The following is a study of the cycloadditions of benzo and mesitonitrile oxides to N-methylindole. The results of the cycloadditions with indole and N-carbethoxyindole are also discussed. The dipolarophilic reactivity of indole derivatives[7] in Diels Alder reactions with tetrazines[8] and 1,3-dipolar cycloadditions with nitrile imines,[9] azides[10] and ozone[11] has recently been reported.

RESULTS

N-methylindole is slightly reactive with benzonitrile oxide (BNO). Its dipolarophilic activity is 7 times less than that of the carbocyclic analog, indene, as determined by competition experiments. Generation of BNO *in situ* in ether in the presence of 2 equiv. of N-methylindole afforded, along with the dimerization products of BNO, a 19% yield of cycloadduct **1a** (Scheme 1), which was isolated by fractional crystallization of the reaction mixture.

The structure of the cycloadduct **1a** is based on chemical and NMR evidence (Table 1). With respect to the corresponding cycloadduct of BNO to indene,[12] the isoxazoline C-5 proton is deshielded by the adjacent nitrogen by 0.73 ppm and occurs as a doublet at low field, δ 6.27, whereas the doublet of the isoxazoline C-4 proton at δ 5.16 is almost unaffected.

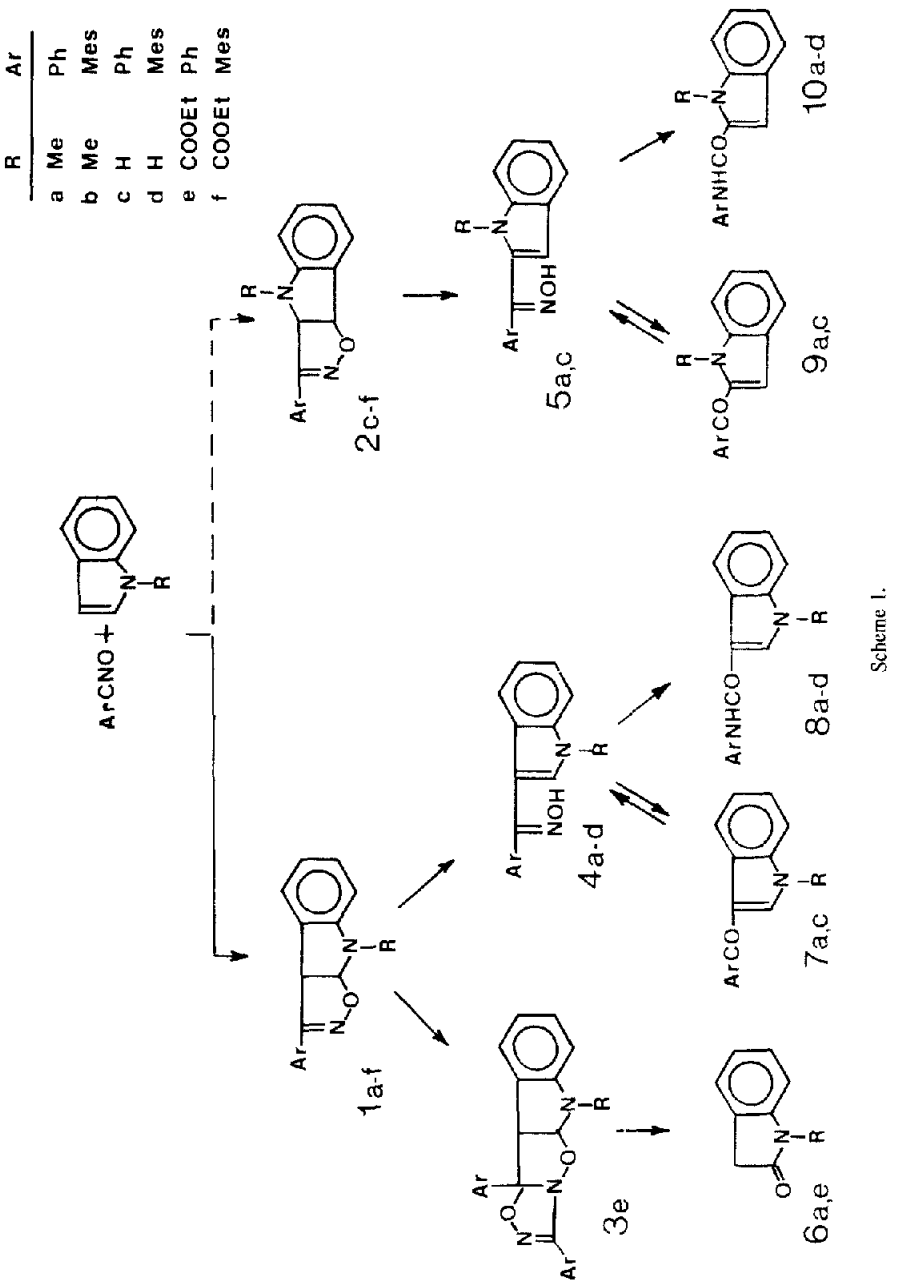
Compound **1a** is thermally stable. It could be recovered unchanged by boiling in benzene, even in the presence of triethylamine. It is however very sensitive to acids. Addition of *p*-toluensulphonic acid to the benzene solution of **1a** at r.t. caused cleavage of the isoxazoline ring, yielding the *Z*-oxime **4**. On silicagel the stability of **1a** is only moderate. It can be recovered almost unchanged by a rapid chromatographic elution but a slow elution affords the oxime **4**.

A minor product with lower *Rf* was isolated in a 3% yield by column chromatography of the mixture and identified as N-methyloxindole **6a**. **6a** is a secondary product since it forms by exposure of the cycloadduct **1a** to BNO. Its formation can be attributed to the slow addition of BNO to the isoxazolinic C=N bond of **1a** yielding **3a**, whose fragmentation affords 3,5-diphenyl-1,2,4-oxadiazole and the lactam **6a**. A similar facile fragmentation yielding a lactone has been already observed.[3]

No other products could be detected in the reaction mixture. The oximes **4** and **5** which are the formal products of a 1,3-addition of BNO to the β and α position of N-methylindole, have been obtained by oximation of the ketones **7a** and **9a**, with a *Z*/*E* ratio of 9:1 and 2:1 resp. The *Z*-configuration of the major stereoisomer of the oximes has been established by Beckmann rearrangement to anilide **8a** and to a chlorine containing anilide derived from **10a**, resp. The oximes are stable under the conditions of the cycloaddition reactions and of the separation, and could not be detected by tlc or NMR in the original cycloaddition mixtures.

Mesitonitrile oxide, a stable nitrile oxide, which does not dimerize at r.t., reacted with excess N-methylindole (2 equiv) in benzene very slowly. After 1 month at r.t. cycloadduct **1b** was isolated in a 62% yield. The isoxazolinic ring of **1b** is cleaved at r.t. in EtOH in the presence of HCl yielding the *Z*-oxime **4b**. On standing in solvent this oxime slowly equilibrates with the more stable *E*-form. At the equilibrium the ratio *Z*/*E* can be estimated by tlc at 1:4. The configuration of the *Z*-oxime follows from **1b** and from the Beckmann rearrangement to **8b**.

The larger stability of the mesityl *E*-oxime **4b** con-


R Ar
a Me Ph
b Me Mes
c H Ph
d H Mes
e COOEt Ph
f COOEt Mes
ArCNO +
1a-f
2c-f
3e
4a-d
5a,c
6a,e
7a,c
8a-d
9a,c
10a-d

Scheme 1.

Table 1. Chemical shifts[a] and coupling constants[b] of cycloadducts[c]

Compound	4-H[d]	5-H[d]	$J_{4,5}$	Other
1a	5.16 d	6.27 d	8.3	N-CH_3 3.07
1b	4.93 d	6.28 d	8.0	N-CH_3 3.07
1c[e]	5.45 d	6.52 dd	8.6 (2.6)[f]	N-H 7.1[g]
1d[h]	4.49 d	6.01 dd	8.3 (2.7)[f]	N-H 4.50[g]
1e	5.25 d	6.85 d	9.0	N-$COOCH_2$ 4.4, CH_3 1.3
1f	5.05 d	6.89 d	9.0	N-$COOCH_2$ 4.4, CH_3 1.4
2c[e]	5.89 dd	6.32 d	9.3 (2.6)[f]	N-H 6.9[g]
2d	5.43 dd	6.30 d	9.3 (2.6)[f]	N-H 4.01[g]
2e	6.28 d	6.45 d	8.7	N-$COOCH_2$ 4.2, CH_3 1.2
2f	6.11 d	6.31 d	9.9	N-$COOCH_2$ 3.8, CH_3 0.9
3e[e]	5.05 d[i]	6.05 d[i]	6.6	N-$COOCH_2$ 4.3, CH_3 1.2

(a) In parts for million (δ) from internal Me_4Si. Multiplicity: d, doublet; t, triplet; q, quartet; m, multiplet. Solvent: $CDCl_3$, unless otherwise stated.

(b) In Hz

(c) Satisfactory combustion analytical data C,H,N (± 0.4%) have been obtained for these compounds.

(d) Numbering refers to the isoxazoline ring.

(e) Acetone-d_6

(f) $J_{CH,NH}$

(g) Exchanges with D_2O

(h) Benzene-d_6

(i) Isoxazolidine ring protons

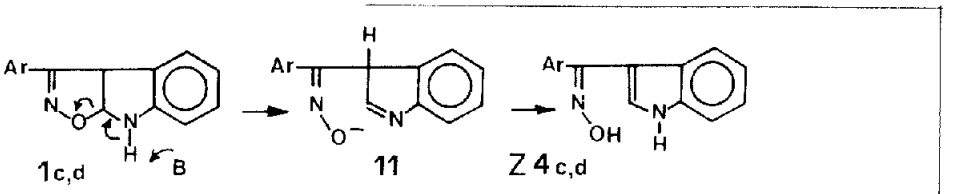
Analytical Data for Compounds of Table 1

Compound	Formula	Found %			Required %		
		C	H	N	C	H	N
1a	$C_{16}H_{14}N_2O$	76.52	5.67	11.21	76.78	5.64	11.19
1b	$C_{19}H_{20}N_2O$	78.44	7.08	9.62	78.05	6.90	9.58
1c	$C_{15}H_{12}N_2O$	76.65	5.26	11.87	76.25	5.12	11.86
1d	$C_{18}H_{18}N_2O$	77.34	6.32	10.23	77.67	6.52	10.07
1e	$C_{18}H_{16}N_2O_3$	70.01	5.51	9.20	70.11	5.23	9.09
1f	$C_{21}H_{22}N_2O_3$	71.70	6.30	7.97	71.98	6.33	8.00
2c	$C_{15}H_{12}N_2O$	76.21	5.02	11.75	76.25	5.12	11.86
2d	$C_{18}H_{18}N_2O$	77.87	6.65	10.10	77.67	6.52	10.07
2e	$C_{18}H_{16}N_2O_3$	70.30	5.12	9.19	70.11	5.23	9.09
2f	$C_{21}H_{22}N_2O_3$	71.77	6.30	8.11	71.98	6.33	8.00
3e	$C_{25}H_{21}N_3O_4$	70.42	5.15	9.52	70.24	4.95	9.83

trasts with the opposite preference of the *Z*-oxime **4a** observed in the phenyl series. The trend finds, however, ample precedent in the conformational studies of the imines of mesityl and phenyl alkyl ketones,[13] which show that the substituent at nitrogen prefers to reside *anti* to the phenyl and *syn* to the mesityl. The bulky *ortho* substituents twist the mesityl ring out of the imino plane and the substituent at nitrogen finds more room on the side of mesityl.

In the cycloadditions to indole itself similar results have been obtained. The cycloadducts of BNO and mesitonitrile oxide **1c** and **1d** could be isolated in a 15% and 28% yield, resp. by crystallization. These cycloadditions are, however, very delicate and sensitive to the experimental conditions, owing to the instability of **1c,d** in the presence of acids and even bases (NEt_3). Addition of a drop of NEt_3 to the benzene solution of **1c,d** causes cleavage of the isoxazolinic ring in a few hours at r.t., yielding the *Z*-oximes **4c,d**. Cycloadduct **1c** could indeed be obtained only in the absence of bases, by adding indole to an ethereal solution of BNO. Under normal conditions, i.e. generating BNO *in situ* from benzhydroximic acid chloride and triethylamine, the *Z*-oxime **4c** is isolated as the principal product.

Since the N-Me cycloadducts **1a,b** are stable in the presence of bases, a reasonable mechanism for the base-catalysed cleavage of the NH cycloadduct **1c,d** requires the intermediacy of the indolenine **11**, as depicted below.



With the aim of avoiding the high sensitivity of these reactions to acids and to get more tractable reaction mixtures, we have extended the investigation to the cycloadditions of N-carbethoxyindole. The electron withdrawing substituent at nitrogen does indeed stabilize the cycloadducts, which can be separated by column chromatography but affects the reactivity and regioselectivity of the cycloadditions too.

With BNO and N-carbethoxyindole (5 equiv) in ether only a 6% yield of cycloadducts **1e** (4%), **2e** (0.3%) and **3e** (1.4%) could be isolated along with the dimerization products of BNO. A better yield of cycloadducts **1e** and **2e** (14%) in a ratio 96:4 was obtained using the dipolarophile as the solvent. The reactivity of N-carbethoxyindole toward BNO is 15 times less than that of N-methylindole.

With the stable mesitonitrile oxide and N-carbethoxyindole (2 equiv) fair yields of adducts **1f** (53%) and **2f** (3%) could be achieved after 2 months at r.t. Only a 2-fold decrease of rate with respect to N-methyl indole shows up here.

The structure of the cycloadducts **1e,f** and **2e,f** rely upon NMR data (Table 1) and chemical transformations. The N-COOEt group deshields the adjacent isoxazoline protons by 1.5 ppm relative to the indene adducts. This strong deshielding causes the isoxazoline doublets of the minor adduct **2e,f** to occur as a closely spaced AB system centered at 6.3–6.2 δ.

Acidic hydrolysis of the major adducts **1e** and **1f** yielded ketone **7c** and amide **8d**, resp.; similarly, hydrolysis of the minor adducts **2e** and **2f** afforded ketone **9c** and amide **10d**, resp. The different behaviour of 3-phenyl and 3-mesityl isoxazolines in the hydrolytic cleavage has been already noticed[4] and attributed to the high migratory aptitude of the mesityl group which causes a facile Beckmann rearrangement of the intermediate oximes.

The isolation of bisadduct **3e** in the cycloaddition of BNO to N-carbethoxyindole supports the view that the ease of fragmentation of the isoxazolidine ring depends upon the availability of a lone pair adjacent to the C-5 of the ring. **3e** has been obtained from **1e** by exposure to BNO. On heating above the m.p., **3e** breaks down, yielding 3,5-diphenyl-1,2,4-oxadiazole and N-carbethoxyoxindole **6e** (Scheme 1) as well as the cycloreversion fragments, 3,5-diphenyl-1,2,4-oxadiazole-4-oxide and N-carbethoxyindole.

Treatment of the minor cycloadducts **2e,f** with NaOH/EtOH at r.t. afforded the missing NH adducts **2c,d**. No traces of cycloadducts **2c,d** could be evidenced by tlc in the cycloaddition mixtures, thus confirming the high regioselectivity of the cycloadditions of nitrile oxides to indole.

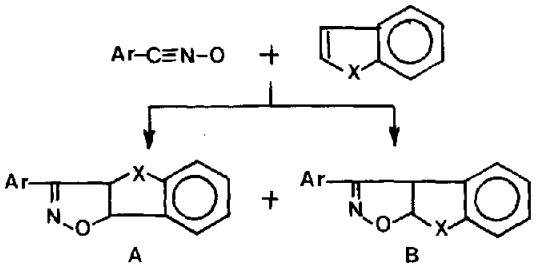
DISCUSSION

The indole derivatives examined so far enter 1,3-dipolar cycloadditions with BNO and mesitonitrile oxide as regular π^2 components. The high propensity to ring opening of the cycloadducts to N-methylindole and especially indole complicates somewhat the experimental study. Under controlled conditions, however, the cycloadducts are the only detectable primary products. The results are therefore fully compatible with a concerted mechanism.[14] If real dipolar or zwitterionic intermediates were involved, the gain of aromaticity should provide a noteworthy driving force to substitution products. No such a driving force shows up here.

The cycloadditions to indole and N-methylindole are highly regioselective, yielding only cycloadducts **1a–d**. With the less reactive N-carbethoxyindole the cycloadditions become less regioselective and small amounts of cycloadducts **2** could be isolated, a result which does not meet the reactivity selectivity principle.[15] When viewed in the series of indene analogs (Table 2), indole and N-methylindole represent the case of complete reversal of regioselectivity. With the parent styrene only adducts of type A have been isolated.[16] Bridging causes a shift toward adducts B, following the order of the donor ability of the added ring element: $H,H \ll CH_2$[12] $< O$[5], S[4] $<$ N–COOEt $\ll$ NH, NMe. Moreover, as shown in Table 2, the regiochemical change on going from BNO to mesitonitrile oxide observed with indene, benzofuran and benzothiophene vanishes with N-carbethoxyindole.

The observed regiochemistry is satisfactorily accounted for by a frontier molecular orbital (FMO) treatment. The shapes of the FMOs of styrene, indole

Table 2. Regioisomer distribution in the cycloadditions of nitrile oxides to indene analogs



X	A/B Ph[c]	A/B Mes[d]	$\Delta\Delta G^{\ddagger}_{A/B}$ Ph	$\Delta\Delta G^{\ddagger}_{A/B}$ Mes	Change[a,b]
H,H	100:0	100:0			
CH_2	96:4	76:24	1.72	0.68	1.0
O	70:30	26:74	0.46	-0.62	1.1
S	78:22	26:74	0.68	-0.62	1.3
NCOOEt	4:96	5:95	-1.72	-1.74	0.0
NH	0:100	0:100			
NCH_3	0:100	0:100			

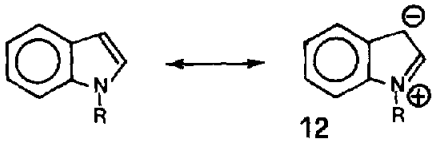
a Kcal/mole

b $\Delta\Delta G^{\ddagger}_{A/B}(Ph) - \Delta\Delta G^{\ddagger}_{A/B}(Mes)$

c 0°, ether

d 25°, benzene

and N-carbethoxyindole are shown in Fig. 1. The MINDO/3[17] eigenvectors and eigenvalues of the FMOs are given in Table 3, along with the ionization potentials[18] and electron affinities[19] for these dipolarophiles. Also in the Table is the polarization of the FMOs, defined as the difference between the squares of the coefficients on the C=C double bond of the heterocyclic ring. The shapes of the LUMOs of the indoles correspond essentially to the familiar LUMOs of butadiene and styrene, whose FMOs are polarized toward the terminal carbon of the alkene double bond as a consequence of conjugation. Noteworthy changes occur in the HOMOs whose polarization is reversed with respect to butadiene and styrene. Interestingly enough, the shape of the N-CH=CH fragment looks like an enamine and the C=C polarization toward the β-position follows the donor ability of the substituent, NCOOEt < NH < NMe. In an alternate way of viewing, this corresponds to an increase of the weight of the VB representation **12** with donor substituents.



12

The changes of the shapes of the HOMO in these dipolarophiles can be understood by deriving the FMOs from those of styrene by perturbation theory.[20] Upon interaction of the styrene orbitals with the orbital of an X perturber as shown in Fig. 2, the familiar repulsion of the levels and the change of their shape in second order occur. According to the mixing rules,[21] the π mixes in some π^* in a negative fashion at the site of substitution and π^* mixes in some π in a positive fashion, albeit at lower degree ($\lambda' < \lambda$) because of the large difference between the X and π^* energies. As a result the HOMO polarization decreases and eventually switches, whereas the LUMO polarization is expected to increase slightly. For C, O and N X perturbers, which have comparable overlaps with the styrene orbitals, the degree of mixing is inversely proportional to the energy difference between the X orbital and the styrene orbital to be polarized, i.e. the raising of the X orbital affects the HOMO polarization. On going from styrene to indene and benzofuran the HOMO polarization decreases and finally, with the high lying N perturbers, is reversed, the degree of reversal in the indoles being quite sensitive to the donor ability of the N substituent. In the simplified model no allowance is made for other orbitals than FMOs or for electronegativity effects,[22] the effect of low lying vacant orbitals of X[21] and even for the changes in the geometry of the dipolarophiles. The crude model retains, however, in its simplicity the essential interactions involved in determining at least the shapes of the FMOs and reproduces well the trends shown in the actual calculations and observed in the regioselectivity experiments. The change of the FMO energies can be similarly accounted for but allowance has to be made for the electronegativity effect of the X fragment, which lowers the HOMOs of benzofuran and carbethoxyindole.

In the cycloadditions with nitrile oxides to indole and N-methylindole the two frontier interactions favor the

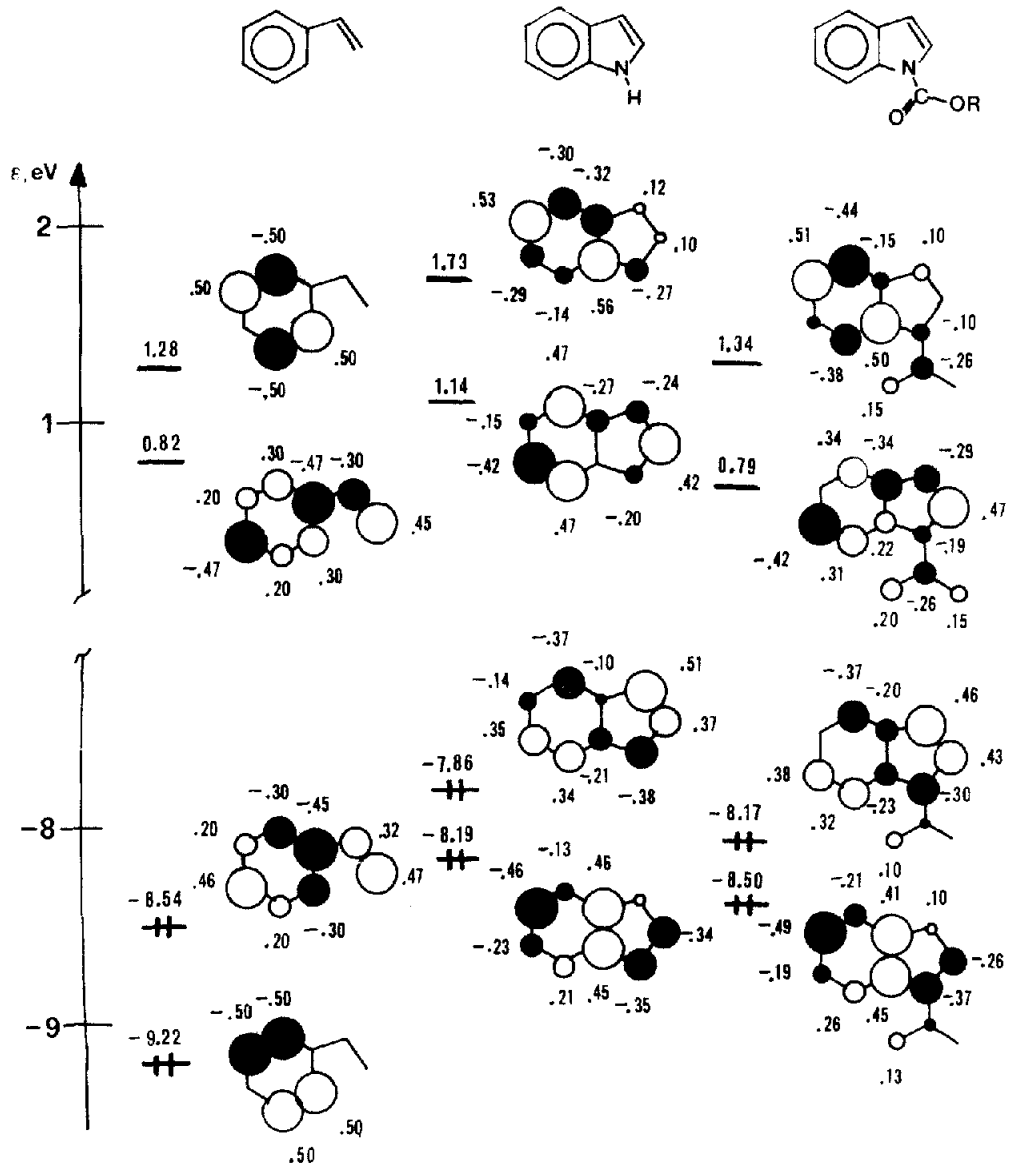


Fig. 1. Frontier molecular orbitals of styrene, indole and N-carbethoxyindole (MINDO/3).

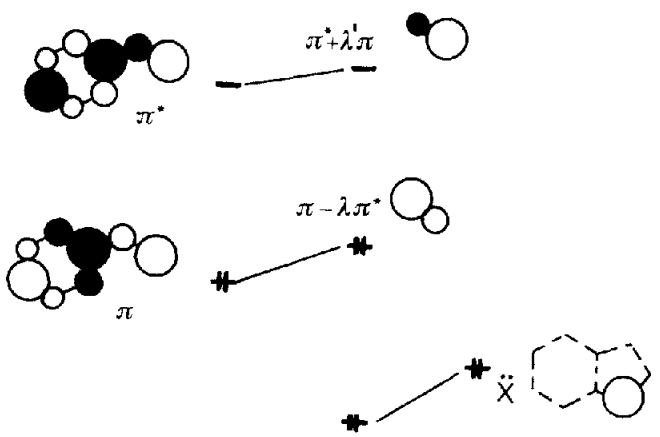
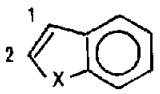


Fig. 2. Derivation of the FMOs of indoles from styrene orbitals.

Table 3. MINDO/3 eigenvectors and eigenvalues for the frontier orbitals



	HOMO						LUMO					
	C_1	C_2	X	ε,eV	IP,eV	P[b]	C_1	C_2	X	ε,eV	EA,eV	P[b]
N-methylindole	.51	.30	-.45	-7.77	7.71[d]	-0.17	.24	-.43	.20	1.15	-0.47[g]	0.13
Indole	.51	.37	-.38	-7.86	7.79[e]	-0.12	.24	-.42	.20	1.14	-0.53[g]	0.12
N-carbethoxyindole[c]	.46	.43	-.30	-8.17	8.20[f]	-0.03	.29	-.47	.19	0.79	-	0.14
Styrene	.32	.47	-	-8.53	8.55[e]	+0.11	.30	-.44	-	0.82	-0.25[h]	0.11

(a) Geometries have been taken from ref. 18a

(b) Polarization defined as $C_2^2 - C_1^2$

(c) Calculations were run for N-carbomethoxy

(d) Ref. 18b (e) Ref. 18a (f) Ref. 18c (g) Ref. 19a (h) Ref. 19d

same isomer **1**, since the nucleophilic and electrophilic centers in nitrile oxides are on oxygen and carbon, resp.[23] and in the indoles on the β- and α-carbon, resp. The regioselectivity effects of the interactions are proportional to the dipolarophile polarizations, and inversely proportional to the energy separations.[6c] Since the polarizations of the FMOs are high, a high regioselectivity results.

On going to N-carbethoxyindole, the regioselectivity effect of the HOMO (dipole)– LUMO (dipolarophile) interaction remains almost unchanged since the polarization of the N-carbethoxyindole LUMO and the HOMO (dipole)–LUMO (dipolarophile) energy separations are only slightly altered. The effect of the other frontier interaction, however, drops considerably, mainly because of the large decrease of the HOMO polarization, which precipitates to a 1/4 of the value of indole. The isolation of small amounts of the regioisomers **2e,f** suggests therefore that the regioselectivity effect of the HOMO (dipole)–LUMO (dipolarophile) interaction is relatively weak and cannot exceed the 1.7 kcal/mole observed in the experiments (Table 2). This feeble control on regioselectivity is easily overcome by the more powerful directive effect of the LUMO (dipole)-HOMO (dipolarophile) interaction as the results with styrene show. The behaviour harmonizes with the small and large polarizations of nitrile oxides HOMO and LUMO, resp. in the bent geometry calculated for the cycloaddition transition state.[24,25]

On going from BNO to the more nucleophilic mesitonitrile oxide, the HOMO (dipole)–LUMO (dipolarophile) strengthens and the other interaction weakens.[26] When the two interactions favor different isomers, a large shift of regioselectivity results, as observed with indene, benzofuran and benzothiophene. When the two interactions favor the same isomer the final effect depends upon the relative increase of one and the relative decrease of the other and a small change is predicted, as the result with N-carbethoxyindole shows.

The reactivity trends fit the FMO approach. BNO behaves mainly as an electrophile as inferred from the low reactivity of N-carbethoxyindole, which is 15 times less reactive than N-methylindole, as well as from a comparison of the frontier orbital separations. Mesitonitrile oxide still behaves as an electrophile, but its reactivity with N-carbethoxyindole is only 2 times less than with N-methylindole. The attenuation of the reactivity difference between the two dipolarophiles on going from BNO to mesitonitrile oxide agrees with the higher HOMO and LUMO energies of the latter dipole.

The aromatic character of indoles manifests in reduced 1,3 dipolar reactivity. Despite its lower IP (7.97 ev), N-methylindole is 7 times less reactive toward BNO than the carbocyclic analog indene (IP = 8.20 ev)[18a]. With N-carbethoxyindole, which has the same IP of indene, the decrease of reactivity is larger (10^2). The drop of reactivity corresponds to an increase of the barrier of 1.0 and 2.5 Kcal/mole, resp. The effect of aromaticity in reducing the 1,3 dipolar reactivity can then be estimated around 2 kcal/mole, a value which compares well to those observed with other heteroaromatics. The sacrifice of aromaticity in the cycloadditions is only a small fraction of the resonance energy of indole, which is estimated at 41.8 kcal/mole.[27] This behaviour supports the idea of an early transition state for the nitrile oxides cycloadditions which allows for applicability of the FMO approach.

CONCLUSIONS

In the cycloadditions with nitrile oxides, the 1,3-dipolar reactivity of indole is reduced but apparently no adequate stabilization is provided to diradical or zwitterionic intermediates. Moreover the alignment for 1,3 addition is not assisted by significant secondary orbital interactions between the enamine-looking HOMO of indoles and the nitrile oxide LUMO.

Similar results have been reported for the cycloadditions of N-methylindole with diarylnitrilimines.[9c] Along with the cycloadducts, small amounts of a 1,3-addition product have been isolated by column chromatography. More consistent yields of 1,3-addition products have been obtained in the cycloadditions of C-acylnitrilimines.[9a,b] The efficient dispersal of negative charge provided by the carbonyl group may facilitate the formation of a zwitterionic intermediate. The dispersal of negative charge over the C=O in the zwitterions could even result in favorable coulombic effects assisting the proper alignment for 1,3-additions.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra: "Perkin–Elmer" Model 197 spectrophotometer, nujol mulls. NMR spectra: "Perkin–Elmer" R12 spectrometer, 60 MHz. Microanalyses were performed by Dr. L. Maggi Dacrema. Satisfactory analytical data (±0.4% for C, H, N) were obtained for all the compounds listed in Table 1. Column chromatography and tlc: silicagel H and GF_{254} (Merck), respectively, eluant cyclohexane: EtOAc 9:1 to 7:3 unless otherwise specified. The identification of samples from different experiments was secured by mixed m.ps and superimposable IR spectra.

Cycloadditions of benzonitrile oxide

(a) N-*methylindole.* To a stirred ice-cooled soln of benzhydroximic acid chloride (1.55 g, 10 mmoles) and N-methylindole (2.62 g, 20 mmoles) in anhyd ether (50 ml), a stoichiometric amount of Et_3N (10 mmoles) in ether (20 ml) was added over a 2 hr period. After keeping 2 days at r.t. the $Et_3N.HCl$ was filtered off and the filtrate was evaporated under reduced pressure, leaving a residue. Cystallization from benzene/hexane afforded 0.48 g (19%) of **1a**, colorless crystals m.p. 140° from EtOH. Column chromatography of the mother liquors afforded unreacted N-methylindole, 3,4-diphenylfuroxane (5%), **Z-4a** (0.12 g, 5%), colorless crystals m.p. 208–9° from EtOAc (Found: C, 77.01; H, 5.74; N, 11.14. $C_{16}H_{14}N_2O$ requires: C, 76.78; H, 5.64; N, 11.19%) and 0.04 g (3%) of **6a**, m.p. 89° from hexane, identical with an authentic specimen.[28] The oxime **Z-4a** was absent in the cycloaddition mixture (tlc) and derives by cleavage of **1a** on kieselgel. **6a** was obtained by exposure of **1a** (0.5 mmoles) to BNO (3 mmoles) in ether. Column chromatography gave 15 mg (20%) of **6a** along with diphenylfuroxane and **Z-4a**.

(b) *Indole.* To a soln of BNO in ether, prepared from benzhydroximic acid chloride (10 mmoles) and NaOH 14%,[29] indole (2.34 g, 20 mmoles) was added. After keeping 1 day, the solvent was evaporated under reduced pressure. The oily residue afforded upon crystallization from benzene/hexane **1c** (0.35 g, 15%), colorless crystals m.p. 143–4°. Operating as under (a) crystallization of the residue from benzene yielded oxime **Z-4c** (0.3 g, 13%) colorless crystals m.p. 193–4° for benzene, ν_{NH} 3395 cm^{-1} (Found: C, 76.13; H, 5.22; N, 11.81. $C_{15}H_{12}N_2O$ requires: C, 76.25; H, 5.12; N, 11.86%).

(c) N-*carbethoxyindole.* Benzhydroximic acid chloride (1.55 g, 10 mmoles) and N-carbethoxyindole[30] (9.5 g, 50 mmoles) were reacted as under (a). Column chromatography of the residue afforded (i) **3e** (0.03 g, 1.4%), colorless crystals m.p. 136–7° from EtOH, ν_{CO} 1703 cm^{-1}; (ii) **2e** (0.01 g, 0.3%), colorless crystals m.p. 121° from EtOH, ν_{CO} 1695 cm^{-1}; (iii) **1e** (0.12 g, 4%), colorless crystals m.p. 143–4° from EtOH, ν_{CO} 1714 cm^{-1}.

In a duplicate experiment BNO (10 mmoles) was generated *in situ* in N-carbethoxyindole (40 g) as solvent. Column chromatography yielded **3e** (0.05 g, 2.3%), **2e** (0.03 g, 0.8%) and **1e** (0.39 g, 13%). **3e** was obtained by exposure of **1e** (0.5 mmoles) to BNO (3 mmoles) in ether. Column chromatography gave 10 mg (12%) of **3e** along with diphenyl-furoxane and unreacted **1e**.

The relative rate constants for the cycloaddition of BNO to indene, N-methylindole and N-carbethoxyindole were estimated by the competition method.[31] BNO (0.1 mmole) was generated *in situ* in anhyd ether in the presence of indene (1 mmole) and N-methylindole (10 mmoles) or N-methylindole (0.5 mmoles) and N-carbethoxyindole (30 mmoles). The ratios of adducts have been estimated by tlc comparison with mixtures of known compositions.

Cycloadditions of mesitonitrile oxide

(a) N-*methylindole.* A soln of 0.8 g (5 mmoles) mesitonitrile oxide and 1.31 g (10 mmoles) N-methylindole in anhyd benzene (50 ml) was kept at r.t. for 1 month. After evaporation of the solvent under reduced pressure, crystallization from EtOH afforded 0.90 g (62%) of **1b**, colorless crystals m.p. 159–160°. A similar result has been obtained by running the reaction in the presence of NEt_3 (1 equiv).

(b) *Indole.* A soln of 1.6 g (10 mmoles) mesitonitrile oxide and 1.5 g (12.8 mmoles) indole in anhyd benzene (50 ml) was kept 1 month at r.t. The solvent was evaporated under vacuum and the residue was crystallized from isopropyl ether (30 ml) affording 0.8 g (28%) of **1d**, colorless crystals m.p. 144–5°.

Oxime **4d** was not detected by tlc in this reaction or in similar reactions with excess (3 equiv) mesitonitrile oxide. Oximes were detected when reacting mesitonitrile oxide with excess indole (3-5 equiv). In such a case oxime **E-4d** began to crystallize out after 2 weeks in fair yields (30–40%), colorless crystals m.p. 199–201° from chloroform, ν_{NH} 3415, 3395 cm^{-1} (Found C 77.29, H 6.57, N 10.02. $C_{18}H_{18}N_2O$ requires C 77.67, H 6.52, N 10.07%).

(c) N-*carbethoxyindole.* A soln of 1.6 g (10 mmoles) mesitonitrile oxide and 3.8 g (20 mmoles) N-carbethoxyindole[30] in anhyd benzene (50 ml) was kept at r.t. for 2 months. After evaporation of the solvent, grinding the oily residue with EtOH yielded 1.51 g (43%) of **1f**, colorless crystals m.p. 124–5° from EtOH. Column chromatography of the mother liquors afforded 0.11 g (3%) of **2f**, colorless crystals m.p. 169–70° from EtOH and 0.35 g (10%) of **1f**.

Oximes **4a,c** *and* **5a,c**

The oximes have been prepared by refluxing for 1–3 days a suspension of the benzoyl derivatives **7a**,[32] **7c**,[33] **9a**[34] or **9c**[34] (0.5 g), $NH_2OH.HCl$ (0.5 g) and KOH (0.3 g) in EtOH (50 ml). After concentration under vacuum, dilution with water and bubbling of CO_2, the oximes were filtered. Crystallization from a suitable solvent, yielded the pure *Z*-oximes in fair yields (50–60%). Samples of the minor *E*-oximes **4**, which have higher R_f values, have been isolated by column chromatography, eluant cyclohexane: ethyl acetate 7:3 or $CHCl_3$. The minor *E*-oximes **5** are also formed and are detectable in TLC, eluant benzene where they have a slightly higher R_f than the *Z*-isomers.

Oximes **Z-4A**, colorless crystals m.p. 208–9° from EtOAc and **Z-4c**, colorless crystals m.p. 193–4° from benzene are identical with the samples isolated from the cycloaddition mixtures. **E-4a**: colorless crystals m.p. 197–9° from EtOAc (Found: C, 76.96; H, 5.75; N, 11.30. $C_{16}H_{14}N_2O$ requires: C, 76.78; H, 5.64; N, 11.19%). **E-4c**: colorless crystals m.p. 145–6° from EtOH/H_2O, ν_{NH} 3320 cm^{-1} (Found: C, 76.31; H, 5.20; N, 11.90. $C_{15}H_{12}N_2O$ requires: C, 76.25; H, 5.12; N, 11.86%). **Z-5a**: colorless crystals m.p. 152–3° from hexane (Found: C, 76.50; H, 5.70; N, 11.36: $C_{16}H_{14}N_2O$ requires: C, 76.78; H, 5.64; N, 11.19%). **Z-5c**: colorless crystals m.p. 177–9° from hexane, ν_{NH} 3460 cm^{-1} (Found: C, 76.55; H, 5.21; N, 12.04. $C_{15}H_{12}N_2O$ requires: C, 76.25, H, 5.12; N, 11.86%).

Beckmann rearrangement of the *Z*-oximes **4a**, **4c** and **5c** with PCl_5 in ether, 0°, 24 hr yielded quantitatively the anilides **8a**, colorless crystals m.p. 172–3° from benzene, ν_{NH} 3290 cm^{-1}, ν_{CO} 1638 cm^{-1} (Found: C, 76.51; H, 5.86; N, 11.45. $C_{16}H_{14}N_2O$ requires: C, 76.78; H, 5.64; N, 11.19%), **8c**, colorless crystals m.p. 173–4° from benzene (lit.[35] m.p. 175.5–6.2°) and **10c**, colorless crystals m.p. 200–2° from benzene/hexane (lit.[35] m.p. 202–3°). Anilides **8c** and **10c** are identical with samples obtained according to the literature.[35] Anilide **8a** was similarly obtained, by conversion of 1-methylindole-3-carboxylic acid[36] to the acid chloride ($SOCl_2$, 0.5 hr reflux, evaporation under reduced pressure) followed by treatment with aniline in benzene. Beckmann rearrangement of the *Z*-oxime **5a** yielded a chlorine containing product, colorless crystals m.p. 169–70° from isopropyl ether, ν_{NH} 3320 cm^{-1}, ν_{CO} 1652 cm^{-1} (Found: C, 67.58; H, 4.88; N, 9.65, Cl, 12.81. $C_{16}H_{13}N_2OCl$ requires: C, 67.48; H, 4.60; N, 9.83; Cl, 12.45%), which has been independently obtained by exposure of anilide **10a**[37] to the same conditions of the Beckmann rearrangement. The structure of the chlorine containing anilide can be formulated as 1-methyl-3-chloroindol-2-carboxanilide, by analogy to the behaviour of indole-2-carboxylic acid derivatives in the presence of PCl_5.[38]

Cleavage of cycloadducts **1a-d**

To a soln of **1a** or **1c** in EtOH a drop of conc HCl was added. After keeping 1 hr at r.t. and evaporation of the solvent under reduced pressure, crystallization of the residue afforded the *Z*-oxime **4a**, m.p. 208–9° from EtOAc and the *Z*-oxime **4c**, m.p. 193–4° from benzene, resp. Cleavage occurred also by adding a few crystals of *p*-toluenesulphonic acid to a benzene soln of **1a**. Under similar conditions **1b** and **1d** yielded the *Z*-oximes **4b**, colorless crystals m.p. 211–13° from EtOH (Found:

C, 77.75; H, 7.05; N, 9.76. $C_{19}H_{20}N_2O$ requires: C, 78.05; H, 6.90; N, 9.58%) and **Z-4d**, colorless crystals m.p. 175–6° from benzene, ν_{NH} 3360 cm^{-1} (Found: C, 77.47; H, 6.76; N, 9.91. $C_{18}H_{18}N_2O$ requires: C, 77.67; H, 6.52; N, 10.07%), resp. On standing in solvents ($CHCl_3$, benzene) the *Z*-oximes equilibrate in a few weeks at r.t. with the more stable *E*-isomers, which have higher R_f. Column chromatography afforded samples of **E-4b**, colorless crystals m.p. 211–215° from EtOH (Found: C, 77.67; H, 6.98; N, 9.61. $C_{19}H_{20}N_2O$ requires: C, 78.05; H, 6.90; N, 9.58%) and **E-4d**, colorless crystals m.p. 199–201° from $CHCl_3$, identical with the sample obtained from the cycloaddition.

Beckmann rearrangement of the *Z*-oximes **4b** and **4d** yielded carboxamides **8b**, colorless crystals m.p. 249–50° from EtOH, ν_{NH} 3200 cm^{-1}, ν_{CO} 1628 cm^{-1} (Found: C, 77.52; H, 6.97; N, 9.72. $C_{19}H_{20}N_2O$ requires: C, 78.05; H, 6.90; N, 9.56%) and **8d**, colorless crystals m.p. 264° from EtOH, ν_{NH} 3440, 3140, 3120 cm^{-1}, ν_{CO} 1640 cm^{-1} (Found: C, 77.57; H, 6.56; N, 9.93. $C_{18}H_{18}N_2O$ requires: C, 77.67; H, 6.52; N, 10.07%). Carboxamides **8b** ad **8d** were independently obtained from the carboxylic acid, $SOCl_2$ and 2,4,6-trimethylaniline, as described above for the anilides.

By adding a few drops of NEt_3 to the benzene soln of **1c** and **1d**, the cycloadducts were cleaved in a few hrs at r.t. yielding the *Z*-oximes **4c** and **4d**, resp.

Cleavage of cycloadducts **1e,f**, **2e,f** *and* **3e**

A soln of **1e** in HOAc (3 ml) and 50% H_2SO_4 (3 ml) was refluxed for 6 hrs. After cooling, the mixture was poured on ice and extracted with $CHCl_3$. The extracts were washed with 5% NaOH and dried on Na_2SO_4. The solvent was evaporated giving ketone **7c**, m.p. 234–5° from acetone, identical with an authentic sample.[33] Similarly **1f** yielded carboxamide **8d**, m.p. 264° from EtOH, identical with the sample obtained by Beckmann rearrangement of oxime **Z-4d**. Under similar conditions, adduct **2e** yielded ketone **9c**, m.p. 144–5° from EtOH, identical with an authentic sample,[34] and adduct **2f** yielded carboxamide **10d**, colorless crystals m.p. 255–7° from EtOH, ν_{NH} 3390, 3255 cm^{-1}, ν_{CO} cm^{-1} (Found: C, 77.31; H, 6.52; N, 10.28. $C_{18}N_{18}N_2O$ requires: C, 77.67; H, 6.52; N, 10.07%). The carboxamide was independently obtained from indole-2-carbonyl chloride[35] and 2,4,6-trimethylaniline.

Adduct **3e** was kept at 140° for 5 min, yielding a mixture of N-carbethoxyindole and **6e** in a 3:1 ratio (NMR) as well as 3,5-diphenyl-1,2,4-oxadiazole-4-oxide and 3,5-diphenyl-1,2,4-oxadiazole (tlc). **6e** was independently obtained from oxindole, NaH and ethyl chloroformiate (1 equiv) in tetrahydrofuran (r.t., 1 hr). Column chromatography yielded **6e** (20%), colorless crystals m.p. 80–1° from hexane, ν_{CO} 1760, 1715 cm^{-1}, NMR ($CDCl_3$): δ 1.40 t (J = 7Hz, 3H), δ 3.60 s (2H), δ 4.46, q (J = 7Hz, 2H), δ 7.2–8 m (4H). (Found: C, 64.01; H, 5.40; N, 6.80. $C_{11}H_{11}NO_3$ requires: C, 64.38; H, 5.40; N, 6.38%).

Alkaline hydrolysis of adduct **2e,f**

A soln of **2e** and NaOH in 95% EtOH was kept at r.t. 1 day. After dilution with water and extraction with $CHCl_3$, the extracts were dried on Na_2SO_4 and evaporated to give **2c**, colorless crystals m.p. 176–7° from EtOH, ν_{NH} 3320 cm^{-1}. Under similar conditions adduct **2f** yielded **2d**, colorless crystals m.p. 170–1° from EtOH, ν_{NH} 3360 cm^{-1}.

Calculations. The computations were executed with the MINDO/3 program on a CDC 6600 computer available at the University of Catania.

Acknowledgements—We would like to thank Prof. G. Buemi for making available an enlarged version of MINDO/3 and Prof. P. Grünanger and Prof. G. Purrello for stimulating discussions. Financial support of the Italian CNR and MPI is gratefully acknowledged.

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