# CYCLOADDITION OF 1,3-DIPOLES TO BULLVALENE

A. Gamba Invernizzi, R. Gandolfi* and M. Strigazzi

Istituto di Chimica Organica, Università di Pavia, Italy.

Abstract—The dipolarophilic reactivity of bullvalene toward several nitrile oxides and other 1,3-dipoles (diphenylnitrilimine, 3,4-dihydroisoquinoline-N-oxide and diazoethane) has been studied. The $3 + 2 \to 5$ cycloaddition is perispecific. Valence tautomerism of the cycloadducts is evaluated and the influence of the substituents in the isoxazoline ring is briefly discussed.

Orbital symmetry analysis shows that 1,3-dipoles may react with bullvalene through two different thermally-allowed competing modes of concerted cycloaddition: a normal $[\pi^2 s + \pi^4 s]^1$ or $3 + 2 \to 5^2$ cycloaddition to a double bond leading to $3 \rightleftharpoons 4$, and an unprecedented $[(\pi^2 s + \sigma^2 s + \pi^2 s) + \pi^4 s]$ or $7 + 3 \to 10$ cycloaddition leading to 5 (Scheme 1).

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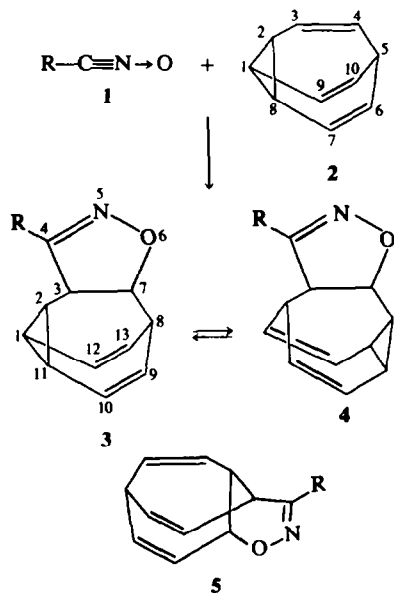
a: R = Me
b: R = t-Butyl
c: R = Ph
d: R = p-NO$_2$C$_6$H$_4$-
e: R = p-MeOC$_6$H$_4$-
f: R = 2,6Cl$_2$C$_6$H$_3$-
g: R = 2,4,6-Me$_3$C$_6$H$_2$-
h: R = 2,4,6-(MeO)$_3$C$_6$H$_2$-
i: R = 2,4,6-Me$_3$-3,5-Cl$_2$C$_6$-

SCHEME 1

*The signals corresponding to protons of **3f** and **4f** are superimposed and do not allow us to evaluate the **3f/4f** ratio at − 70°. This ratio is expected to be different from that at + 36° because of the temperature dependence of the equilibrium constant.

Recent interest in the steric and electronic factors which induce periselectivity in 1,3-dipolar cycloaddition[3-5] as well as interest in substituent effects on equilibria of bridged homotropolidenes[6] led us to investigate the reaction of some 1,3-dipoles with bullvalene.

Admixture of several nitrile oxides (1) with an excess of bullvalene (2) at room temperature, followed by column chromatography, afforded only one monoadduct in each case. Small amounts of by-products with lower R_f have also been evidenced, and in the case of **1f** two other products could be isolated and identified as bis-adducts.

Structural assignments for the monoadducts relied on NMR spectroscopy. All NMR spectra were temperature dependent and the exchange process was fast at 36°. These properties are typical for *cis* fused bicyclo[5,1,0]octa - 2,5 - diene system,[7-9] being thus in complete accordance with structures $3 \rightleftharpoons 4$, whereas they are not consistent with a blocked structure 5. The temperature dependence of the NMR spectra of $3f \rightleftharpoons 4f$ is shown in Fig 1. The ratio value 3:1:2:4 for the areas of the signals centered resp. at $\delta 1·83$ (cyclopropyl protons), $\delta 3·05$ (bridgehead protons), $\delta 4·68$ (isoxazoline protons), $\delta 6·03$ (vinyl protons), in the − 70° spectrum is good evidence that the exchange was very slow at such a temperature and that this spectrum is the sum of the signals corresponding to the protons of the blocked structures **3f** and **4f**.*

Furthermore by a NMR study it was possible to evaluate the proportion of the two tautomers 3 and 4, which are not structurally identical, present in the equilibrium mixture at 36°.

As a matter of fact in the NMR spectrum of $3b \rightleftharpoons 4b$ at + 36° (Fig 2) the two signals (dd) centered at $\delta 3·68$ and $\delta 4·52$ were assigned to H–3 and H–7 respectively, since the proton in isoxazoline 5-position is well-known to resonate at lower field than the proton in 4-position, owing to paramagnetic shift caused by the adjacent O atom.[10] Moreover decoupling experiments established that H–2 (td at $\delta 2·24$) is spin coupled with H–1, H–11 (multiplet centered at $\delta 3·14$) and H–3, whereas H–8 (td at $\delta 2·53$) is spin coupled with H–9, H–13 (multiplet
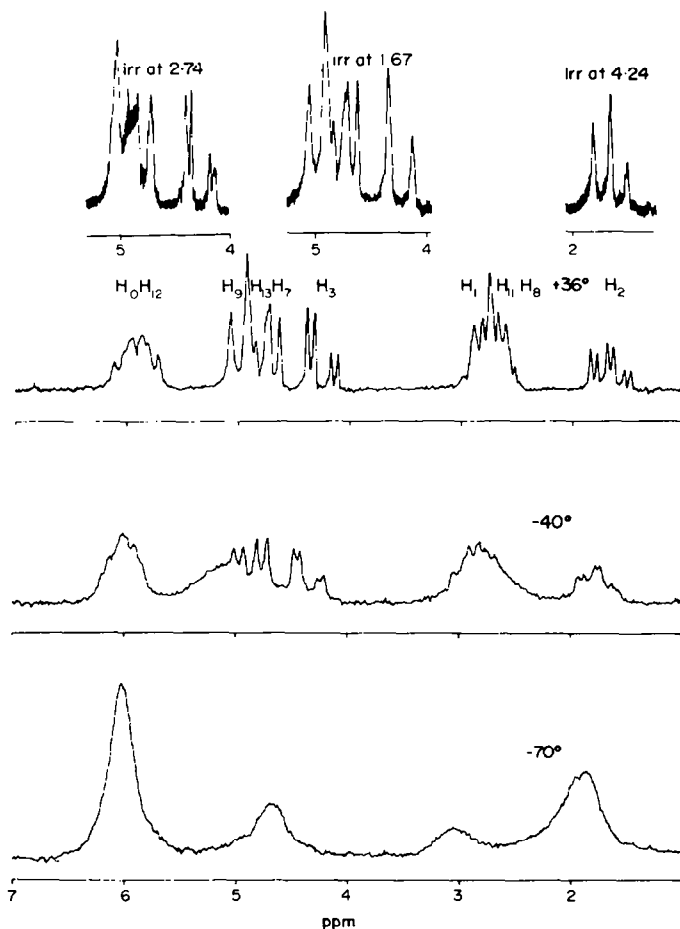
Fig 1.   NMR spectra of 3f⇌4f in CDCl₃ at +36°, −40°, −70° (top to bottom) and spin decoupling spectra at +36°. The spectra from +36° to −85° (−85° and −70° spectra are practically identical) for (CD₃)₂CO solutions of 3f⇌4f do not present any noticeable difference from the corresponding spectra for CDCl₃ solutions.

centered at δ4·55) and H–7. The positions of protons H–1, H–11 resp. protons H–9, H–13 in the spectrum reveal that the two former protons chiefly reside in a cyclopropyl environment. Therefore, tautomer 3b must be more stabilized than 4b. NMR data inspection for 3c⇌4c (Fig 2 and Table 1) shows that H–1, H–11, H–9 and H–13 resonate at very near fields, thus indicating an almost equal quantity of the two valence tautomers at equilibrium. On the contrary in 3i⇌4i protons H–9 and H–13 resonate very near to the vinylic protons H–10 and H–12, thus revealing a definite preponderance of 3i.

Decoupling experiments allowed to conclude that in all cases, except c–e structure 3 is prevalent. Table 1 summarises the NMR data of the monoadducts and reports the 3:4 tautomers ratio in the equilibrium mixture at 36° in CDCl₃, calculated from the equation.

$$\%(3) = \frac{\delta_{36°} - \delta_c}{\delta_v - \delta_c}$$

where $\delta_{36°}$, δ_c and δ_v are the chemical shifts of protons H–9 and H–13 in the equilibrium mixture at 36° and in blocked structures $4(\delta_c)$ and $3(\delta_v)$ respectively. The chemical shifts of H–9, H–13 have been chosen with preference to those of H–1, H–11, because the change along the series a–i of the chemical shifts of these latter protons are brought about not only by change of the 3:4 ratio but also by the through space shielding (or deshielding) effect of the substituent R.*

*The presence of this effect is confirmed by the following evidence: going from 3c⇌4c to 3i⇌4i the Δδ found for the proton H–2 (0·73 ppm) was 2·5 times larger than that of H–8 (0·29 ppm) instead of being nearly equal as expected considering only the 3:4 ratio change.
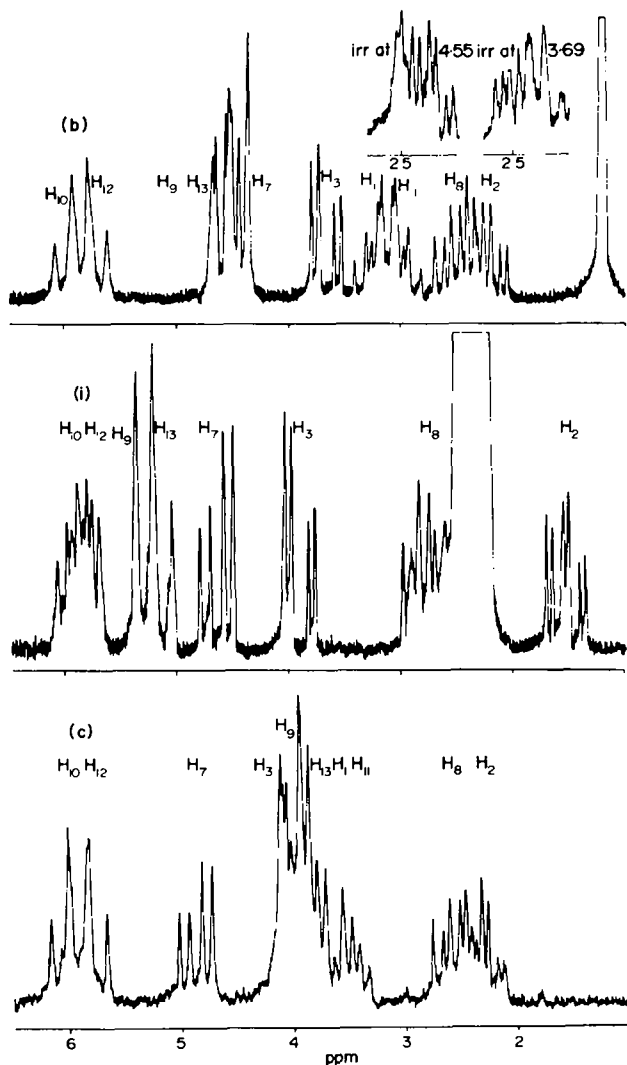
Fig 2. NMR spectra of **3bi,c⇌4b,i,c** in CDCl₃ at +36° (top to bottom) and spin decoupling spectra of **3b⇌4b**.

As vinylic shifts δ_v for H-9 and H-13 we have chosen the medium value of the chemical shifts of H-10 and H-12 at 36° (these protons occupy a vinylic position both in 3 and 4). This value is roughly coincident with the chemical shift of the fairly sharp signals of the vinylic protons at −70°. There are not true cyclopropyl protons at 36° and at −70° these protons show large signals, influenced by the nature of R. Therefore, we have arbitrarily chosen for all monoadducts the value of 1·80 for δ_c, practically coincident with the value obtained for the cyclopropyl protons in **f** and **g** at −70° and for the same protons in the adduct from bullvalene and chlorosulfonyl isocyanate.[9]

In spite of the above mentioned approximations, the percentage values of Table 1 are felt to have a semiquantitative meaning and to allow some considerations on the influence of the isoxazoline ring and of the substituent R on the equilibrium **3⇌4**.

What the conformational position of the aromatic ring is concerned, UV spectral analysis led to the following conclusions:

(i) In **3c–e⇌4c–e** the chromoforic system of 3-arylsubstituted 2-isoxazolines is evidenced (Table 2) and, therefroe, the aromatic ring is coplanar to the C=N double bond;

(ii) Monoadducts **3f,g,i⇌4f,g,i** do not show any absorption above 250 nm, thus indicating that in these cases the aromatic ring is forced toward a position perpendicular to the isoxazoline ring.

As Table 1 shows, in all cases except **c–e**, the tautomeric equilibrium is shifted toward 3, even in

Table 1. NMR parameters[a,b] of isoxazolines 3⇌4 and 3:4 valence tautomers ratio

Comp.	H-2[c]	H-3	H-7	H-8[c]	H-1, H-11	H-9, H-13[d]	H-10, H-12	% Ratio 3:4
a	2·12 td	3·53 dd	4·61 dd	2·43 td	3·25 m	4·37 m	5·79 t; 5·95 t	63·5 : 36·5
b	2·24 td	3·68 dd	4·52 dd	2·53 td	3·14 m	4·55 m	5·79 t; 5·95 t	67·5 : 32·5
c	2·28 td	3·97 dd	4·87 dd	2·53 td	$\ddot{e}$	e	5·81 t; 5·97 t	≃ 50 : 50
d	2·23 td	4·05 dd	4·95 dd	2·57 td	e	e	5·82 t; 6·02 t	≃ 50 : 50
e	2·27 td	3·94 dd	4·83 dd	2·53 td	e	e	5·80 t; 5·98 t	≃ 50 : 50
f	1·67 td	4·23 dd	4·78 dd	f	2·74 m	4·92 m	5·91 m	76 : 24
g	1·65 td	4·02 dd	4·67 dd	2·78 td	f	5·09 m	5·90 m	80 : 20
h	1·80 td	4·09 dd	4·78 dd	2·55 td	3·17 m	4·38 m	5·79 t; 5·95 t	63·5 : 36·5
i	1·55 td	3·93 dd	4·68 dd	2·82 td	f	5·23 m	5·90 m	83·5 : 16·5

[a] Chemical shifts are reported in ppm on δ scale, coupling constants in Hz.

[b] J_{23} varies from 3·3 for c–g, i to 4·5 for a; J_{37} from 11·9 for c, d to 12·5 for f, g; J_{78} from 4·5 for a, b to 5·3 for c–e; $J_{12} = J_{2,11} = 8·6$ for a, b, d, h, g and 8·0 for c, e, f, i; $J_{1,12} = J_{9,10} = J_{10,11} = J_{12,13} = 9·2$ for a–c, e and 8·9 for d, h; $J_{89} = J_{8,13} = 8·6$ for a, b, d, e, g, h and 8·2 for c, i.

[c] The signals corresponding to H-2 and H-8 protons, expected to be doublet of doublets of doublets (if we do not take in account allylic coupling generally very small in these systems)[9], appeared as triplet of doublets owing to $J_{12} = J_{2,11}$ and $J_{89} = J_{8,13}$.

[d] The unresolved 3-line multiplet corresponds to H-9 and H-13 protons which have very similar chemical shifts.

[e] These protons show a complex signal at δ 3·30–4·20 ppm (see spectrum of 3c⇌4c, Fig. 2).

[f] Overlapped by other signals.

3a⇌4a (R=Me), where molecular models show the absence of any relevant steric effect. In tautomer 3 the π acceptor terminus of the heretocyclic ring (viz the C atom of C=N) is homoconiugate to the cyclopropane ring. This preferential disposition of the reaction products parallels the tautomeric preference of the 2 + 2 cycloadduct of bullvalene to chlorosulfonyl isocyanate,[9] and allowance being made for the different molecule complexity, seems consistent with theoretical calculations[11] and experimental results[12] on bridged homotropilidene systems.*

The increase of 3 along the series f,g,i is clearly due to steric interactions, since it parallels the increase in steric encumbrance of R as molecular models show, and is independent from the electronic properties of the substituents on the isoxazoline 3-aryl group.

In c–e the valence tautomers ratio is very near to 1. This fact confirms the independence from the electronic nature of the substituent on R and can be tentatively attributed to a balancing between the electronic effects, favouring the tautomer 3, and the steric effects which would favour tautomer 4 owing to the conformational preference of the ortho - unsubstituted phenyl group. Difficult to explain are the results obtained for 3h⇌4h.

Finally the reaction of bullvalene with other 1,3-dipoles, i.e. diazoethane, 3,4-dihydroisoquinoline -

N-oxide and diphenylnitrilimine have been studied. In all cases the [π^2s + π^4s] monoadducts have been obtained (Scheme 2).
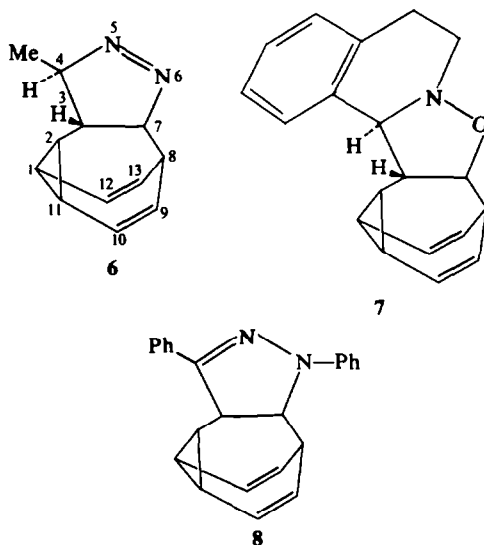
SCHEME 2

Structural assignments relied on NMR spectra, which clearly showed a preference for one valence tautomer, although no definite choice could be made between structures 6–8 and the corresponding valence tautomers. The *trans* relationship between proton H-3 and H-4 in compounds 6 and 7, configurationally homogeneus in NMR, corresponds to an attack of the 1,3-dipole on the

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*Goldstein et al,[6] however recently warned against excessive generalization beyond the semibullvalene system, pointing out that at bullvalene level of homologation (i.e. in our case) both electron-accepting and electron-donating group prefer the cyclopropane side.

bullvalene from the sterically less encumbered side.

The perispecificity observed in the present cycloaddition reaction shows that the $[(\pi^2s + \sigma^2s + \pi^2s) + \pi^4s]$ pathway is energetically more expensive than the normal $[\pi^2s + \pi^4s]$ process, in accordance to what is known on $[(\pi^2s + \sigma^2s) + \pi^2s]$ cycloaddition.[13]

Another factor should disfavour the former reaction pathway: although the distance (2·515 Å)[14] between C_4-C_6 in bullvalene (2) would seem most favourable for the cycloaddition to nitrile oxides (length of the CNO system: 2·396 for 1, R=4—MeO—3, 5Me$_2$C$_6$H$_2$),[15] the oblique disposition of the bullvalene π orbitals evidently prevents them from achieving a favourable overlap with the orbitals of the nitrile oxide, whether linear or bent.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were obtained in EtOH solutions on a Perkin Elmer 137 recording instrument and IR spectra on a Perkin Elmer 257 spectrophotometer. NMR spectra were recorded on a Perkin Elmer R 12A (60 MHz) spectrometer equipped with variable temperature accessory with TMS as internal standard for CDCl$_3$ solns.

The composition of the reaction mixture was determined by TLC on Silicagel GF 254 Merck. In some cases the products were detected on TLC plates with a 3% solution of CrO$_3$ in sulphuric acid (50%) followed by heating at 120° in an air bath.

Elemental analyses were performed by Dr. L. Maggi Dacrema.

Reaction of nitrile oxides (1) *with bullvalene* (2). A mixture of the appropriate nitrile oxide and of 3·5 fold excess of bullvalene in ether was left at room temperature until total disappearance of the dipole (by monitoring through TLC). The nitrile oxide was either generated *in situ* from the hydroximic acid chloride and triethylamine (Method A) or reacted if such is stable (Method B) (see Table 2). The reaction mixture was separated by column chromatography (Silicagel Merck, eluant cyclohexane/AcOEt in different proportions). Monoadducts were homogeneous on TLC with several eluants.

Yields, physical and analytical data of monoadducts 3⇌4 are given in Table 2.

A mixture of compounds with lower R_f was also isolated ($\simeq$ 5% of the total yield) from all reactions.

Two products, m.p. 299–300° and 252°–5°, were separated from this mixture in the case of 2,6 - dichlorobenzonitrile oxide (1f), both of which were identical to adducts isolated from the reaction of 1f with 3f⇌4f (see later).

Trace amounts of the corresponding furazane-N-oxide were isolated in the cycloaddition reactions of unstable nitrile oxides; larger amounts were obtained in the cases of 1a and 1b ($\simeq$ 10%).

Reaction of 1f with 3f⇌4f. A soln of 1f (0·140 g) and 3f⇌4f (0·210 g) in ether was left aside at room temp for 15 days. The ppt was filtered off and crystallized from AcOEt to give a first crop (0·130 g) of product, m.p. 299–300°. The mother liquors were evaporated and chromatographed (cyclohexane/AcOEt 7:3) to give in order of elution some di - (2,6 - dichlorophenyl) - furazane - N - oxide, the compound m.p. 299–300° (0·020 g, total yield 45%), as colour-less needles from AcOEt (Found: C, 57·0; H, 3·4; N, 5·8), the compound m.p. 252°–4° (0·030 g, 9%), as colourless prisms from AcOEt (Found; C, 56·9; H, 3·3; N, 5·9 Calc. for $C_{24}H_{16}Cl_4N_2O_2$: C, 56·9; H, 3·2; N, 5·5%), and a mixture of products which were not characterized.

The lack of NMR data, owing to the insolubility of the two products, did not allow us to determine their structure.

Reaction of bullvalene (2) *with other* 1,3-*dipoles*

(a) *Diazoethane.* A soln of bullvalene (0·500 g) and a large excess of diazoethane in ether was left aside for 6 days at room temp. The solvent was evaporated and the residue chromatographed (cyclohexane/AcOEt 7:3) to give unreacted 2 (0·300 g) and two oily products which were not further purified.

The first eluted product (0·200 g, 30%) had the NMR spectrum at 36° in accordance with a pure single monoadduct which showed fast isomerization between the structure 6 and its valence tautomer. In this case as well as with adducts from 3,4 - dihydroisoquinoline - N - oxide and diphenylnitrilimine (see later), we were not able to determine what isomer was prevalent in the equilibrium mixture, IR (film): ν max 1540 (–N=N–) cm^{-1}, NMR (at

Table 2. Characterization data of isoxazolines 3⇌4

Comp.	M.P.°C	Recrystall. solvent	Method[d]	% Yield	Found % C	Found % H	Found % N	Formula	Calc. % C	Calc. % H	Calc. % N	λ max (EtOH) nm (log ε)
a	Oil	– –	A	55	76·7	6·8	7·6	$C_{12}H_{13}NO$	77·0	7·0	7·5	
b	83–5	Petrol ether[a]	A	53	78·9	8·3	6·2	$C_{15}H_{19}NO$	78·6	8·4	6·1	
c	122–5	EtOH[a]	A	83	81·6	6·1	5·6	$C_{17}H_{15}NO$	81·9	6·1	5·6	265 (3·88)
d	193–4	EtOH[b]	A	95	69·4	4·9	9·7	$C_{17}H_{14}N_2O_3$	69·4	4·8	9·5	316 (4·00)
e	122–4	EtOH[c]	A	89	77·0	6·2	4·9	$C_{18}H_{17}NO_2$	77·4	6·1	5·0	272·5 (4·12)
f	99–105	Petrol ether[a]	B	78	63·9	4·3	4·5	$C_{17}H_{13}Cl_2NO$	64·3	4·1	4·4	e
g	109–100	Petrol ether[a]	B	82	82·3	7·2	5·0	$C_{20}H_{21}NO$	82·5	7·3	4·8	e
h	164–5	Cyclohexane[a]/ benzene	B	84	70·9	6·2	4·2	$C_{20}H_{21}NO_4$	70·8	6·2	4·1	260 (3·89)[f]
i	194–5	EtOH[b]	B	90	66·5	5·4	4·3	$C_{20}H_{19}Cl_2NO$	66·6	5·3	3·9	e

[a] Prisms. [b] Needles. [c] Platelets. [d] A: nitrile oxide generated in situ from hydroximic acid chloride; B: stable nitrile oxide. [e] These compounds do not show any absorption above 240 nm. [f] Shoulder.

+ 36°): δ 1·40 (3H, d, Me), 1·65–2·20 (2H, m, H–2 and H–3), 2·60–3·30 (3H, m, H–1, H–8 and H–11), 4·10–5·00 (4H, m, H–4, H–7, H–9 and H–13), 5·74 (2H, seven line multiplet, H–10 and H–12) ppm.

The second eluted product (0·023 g, 3·3%) had IR and NMR spectra similar, although complicated by same impurities, to the first eluted product which seemed consistent with an epimer of **6** at the pyrazoline 4 position.

The two products are unstable and decompose slowly on standing at room temperature.

(b) *3,4 - Dihydroisoquinoline - N - oxide.* A soln of 3,4 - dihydroisoquinoline - N - oxide (0·440 g) and excess **2** in anhyd benzene was heated under reflux for 48 h. The solvent was removed and the residue chromatographed to give some unreacted **2** and **7** (0·730 g, 88%), as colourless prisms from EtOH m.p. 160–2°. (Found: C, 82·0; H, 7·0; N, 5·2. Calc. for $C_{19}H_{19}NO$: C, 82·3; H, 6·9; N, 5·1%), NMR (at + 36°): δ 4·32 (1H, dd, H–7; J = 3·8 and 10·4 Hz), 4·37 (1H, d, H–4, J_{34} = 10·4 Hz), 4·98 (2H, m, H–9 and H–13), 5·92 (2H, m, H–10 and H–12), 7·15 (10H, aromatics) ppm. All other protons showed a complex signal at δ 3·30–1·70 ppm.

A ratio value of about 77:23 for the valence tautomers can be inferred from the chemical shifts of H–9 and H–13.

(c) *Diphenylnitrilimine.* A soln of α -chlorobenzylidenephenylhydrazine (0·100 g), excess **2** (0·200 g) and Et_3N (0·5 ml) in anhyd benzene (10 ml) was heated under reflux for 6 h. The solvent was evaporated off and excess bullvalene removed by sublimation. The residue was practically pure **8**.

Compound **8**, not stable and decomposing on silicagel, crystallized as yellow needles from EtOH, m.p. 135–145°. (Found: C, 84·8; H, 6·4; N, 8·6. Calc. for $C_{23}H_{20}N_2$: C, 85·2; H, 6·2; N, 8·6%), UV: λ max 227 nm (log ε 4·14), 254 nm (log ε 4·05), 354 nm (log ε 4·17), NMR (at + 36°): δ 2·38 (1H, td, H–2), 2·86 (1H, td, H–8), 3·20 (2H, m, H–1 and H–11), 4·18 (1H, dd, H–3; J_{23} = 4·0 Hz), 4·53 (1H, dd, H–7, J_{37} = 13·0 Hz and J_{78} = 3·3 Hz), 6·02 and 5·76 (4H,

two t, H–10 and H–12; $J_{9,10} = J_{10,11} = J_{1,12} = J_{12,13} = 9·3$), 6·7–7·8 (10H, m, aromatics) ppm. The signals due to H–9 and H–13 are overlapped by the signals of H–3 and H–7.

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