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STUDIES ON REACTIONS OF ISOPRENOIDS—XVI[1]

THE 1,4-CYCLOADDITION REACTIONS OF NEOALLOOCIMENE: COMPETITIVE ISOMERIZATION OF NEOALLOOCIMENE TO ALLOOCIMENE WITH THE CYCLOADDITION

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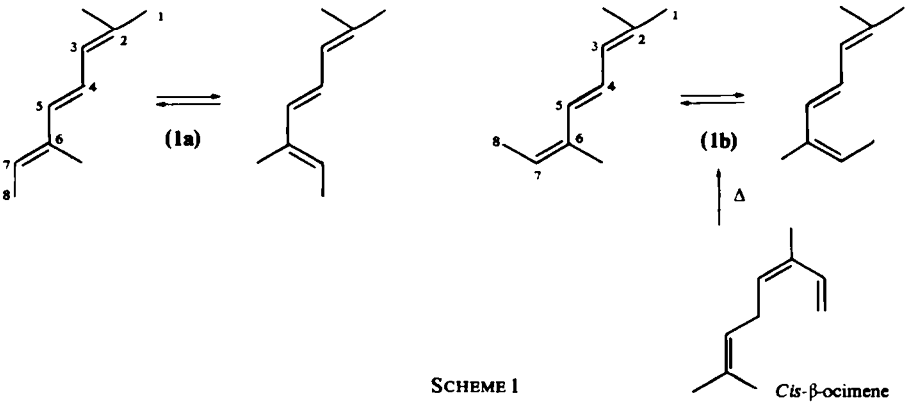
Abstract—The 1,4-cycloaddition of neoalloocimene (**1b**) with several dienophiles is investigated in comparison with that of alloocimene (**1a**). With cyanoacetylene, **1b** gives exclusively a 1:2 adduct **3** *via* an ene-addition. With dimethyl acetylenedicarboxylate, tetracyanoethylene, *p*-benzoquinone, and 4-phenyl-1,2,4-triazoline-3,5-dione, **1b** gives the corresponding 1,4-adducts (**4b**–**7b**) together with their stereoisomers (**4a**–**7a**). The relative yields of **4a**, **5a**, **6a** and **7a** are solvent dependent. The formation of the stereoisomers is shown to originate from the **1b**→**1a** isomerization competing with the 1,4-cycloaddition.

IN A PREVIOUS publication,[2] we described the 1,4-cycloaddition reactions of an isomeric mixture of alloocimene (**1a**) and neoalloocimene (**1b**) with several acetylenic, olefinic and heterodienophiles. On the other hand, we have demonstrated recently that the thermal 1,5-hydrogen migration of *cis*-β-ocimene affords exclusively neoalloocimene (**1b**, 2,6-dimethyl-4-*trans*-6-*cis*-2,4,6-octatriene).[3] This paper deals with the 1,4-cycloaddition reactions of **1b** with various dienophiles including cyanoacetylene, dimethyl acetylenedicarboxylate, tetracyanoethylene, *p*-benzoquinone, and 4-phenyl-1,2,4-triazoline-3,5-dione.

RESULTS AND DISCUSSION

The starting material and the reaction conditions.

Pure neoalloocimene (**1b**) was prepared by the thermal isomerization of *cis*-β-ocimene, followed by a fractional distillation (Scheme 1).[1]



SCHEME 1

The reaction conditions employed were the same as those previously reported;[2] the reaction with *p*-benzoquinone produced a considerable amount of quinhydrone as side-product. The lowering of the reaction temperature to 55–60°, however, did not improve the yield. No polymerization inhibitor was used in all reactions since the polymerization of **1b** could not be observed under the conditions. The yields and the isomer ratios of the adducts are summerized in Table 1 in comparison with those obtained from a 57 : 43 mixture of **1a** and **1b** under the same reaction conditions.[2]

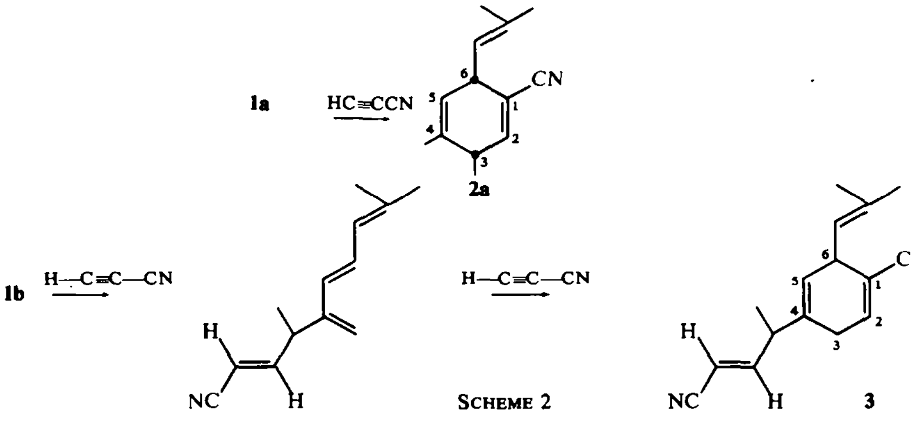
TABLE 1. THE 1,4-CYCLOADDITION REACTIONS OF **1a** AND **1b**

Dienophile	**1a** or **1b**	Temp	Time[a] (days)	Products	Total yield (%)	Relative yield of **a**-to **b**-series (%)	
						GLC	NMR
$HC{\equiv}CCN$	**1a** + **1b**[b]	55–60	4	**2a** + (**3**)	56[c]	100:0	
	1b	55–60	4	**2a** + (**3**)	trace[d]	100:0	
$MeO_2CC{\equiv}CCO_2Me$	**1a** + **1b**	55–60	4	**4a** + **4b**	66	89:11	
	1b	55–60	4	**4a** + **4b**	18	71:29	67:33
$(NC)_2C{=}C(CN)_2$	**1a** + **1b**	20–25	1	**5a** + **5b**	87	60:40	61:39
	1b	20–25	1	**5a** + **5b**	85	7:93	
p-Benzoquinone	**1a** + **1b**	refl	0·3	**6a** + **6b**	14	67:33	72:28
	1b	55–60	1	**6a** + **6b**	10		33:67
4-Phenyl-1,2,4-triazoline-3,5-	**1a** + **1b**	20–25	1	**7a** + **7b**	79	75:25	76:24
dione[e]	**1b**	20–25	1	**7a** + **7b**	88	28:72	

[a] All reactions were carred out in C_6H_6 except for 4-phenyl-1,2,4-triazoline-3,5-dione. [b] **1a** : **1b** = 57 : 43; see ref. 2. [c] Yield of **3** was 25% based on cyanoacetylene. [d] Yield of **3** was 83% based on cyanoacetylene. [e] Reaction was carried out in dioxane.

Structural elucidation of the adducts.

Treatment of **1b** with an equimolar amount of cyanoacetylene afforded a 1 : 2 adduct **3** (83%), which was identified as 1-cyano-4-(1-methyl-3-cyano-2-propenyl)-6-isobutenyl-1,4-cyclohexadiene by the IR and NMR spectral comparison with an authentic specimen.[2] Besides, a trace amount of a 1 : 1 adduct **2a** was obtained, which was



SCHEME 2

identified as 1-cyano-3,4-dimethyl-6-isobutenyl-1,4-cyclohexadiene by GLC comparison with an authentic sample.[2] **2a** might be produced from the 1,4-cycloaddition reaction of **1a** to cyanoacetylene, and **3**, from that of an ene-adduct[4, 5] to cyanoacetylene (Scheme 2).

The fact that **2a** is produced from **1b**, even in trace amount, suggests the occurrence of the **1b** → **1a** isomerization under the reaction conditions (see the discussion below).

The reaction of **1b** with dimethyl acetylenedicarboxylate afforded only a lower yield of the corresponding adduct which was analyzed as a 71 : 29 and a 67 : 33 mixture of **4a** and **4b** by GLC and NMR, respectively. Signals at τ 8·74 for **4a**[2] and that at τ 8·93 for **4b**, both due to C_3—CH_3, were adopted as the key signal for NMR analysis.

1b → **4a** + **4b**

It is of interest that the isomer ratio of the product is more or less similar between the reactions of **1b** and those of the mixture of **1a** and **1b** (Table 1).

The reaction of **1b** with tetracyanoethylene proceeded very rapidly to give the corresponding 1 : 1 adduct in 85% yield. GLC analysis of the adduct revealed two peaks in a 7 : 93 ratio. The minor product was identified as **5a**, the adduct originated from **1a**, and the major one isolated as colourless crystals, m.p. 80·5–81·5°, had a NMR signal at τ 8·46 (d) due to C_3—CH_3, different from that of **5a** at τ 8·37. The structure was assigned as **5b**.

1b → **5a** + **5b**

The reaction with *p*-benzoquinone was carried out at 55–60° in C_6H_6, milder conditions than those in refluxing benzene. The products were purified on a silica gel column to give a 1 : 4 adduct in 10% yield together with a considerable amount of unreacted **1b** (37%). However, no trace of **1a** was detected on GLC. The adduct was characterized as a 33 : 67 mixture of **6a** and **6b** on the basis of the NMR spectrum: signals at τ 8·82 (d) and 8·90 (d) assignable to C_5—CH_3 of **6a** and of **6b** respectively, were used for the analysis.

1b → **6a** + **6b**

The reaction of **1b** with 4-phenyl-1,2,4-triazoline-3,5-dione afforded a 28 : 72 mixture of the 1,4-adducts, **7a** and **7b** (88%). The major product, isolated crystals, m.p. 113·5–114°, had an NMR signal at τ 8·68 (d) due to C_2—CH_3 different from that of **7a** at τ 8·52 (d).[2]

1b → **7a** + **7b**

The competition of the **1b** → **1a** *isomerization with the* 1,4-*cycloaddition reactions*.

As described above, no trace of **1a** was detected in recovered **1b** from the reaction of **1b** with *p*-benzoquinone by GLC, suggesting no formation of **1a** during the reaction of **1b** with the dienophile. In order to confirm this, the mixture from 3 molar equivalent of **1b** and 1 molar equivalent of cyanoacetylene, dimethyl acetylenedicarboxylate, tetracyanoethylene and *p*-benzoquinone as the dienophiles under the conditions shown in Table 1 was analyzed on GLC: no trace of **1a** could be detected at any appropriate reaction time.

The isomer ratios of the products in Table 1 are those obtained from the reactions of an equimolar amount of **1b** and/or of a mixture of **1a** and **1b** with an equimolar amount of the dienophiles. However, the ratios were found to be variable with the molar ratios of **1b** to the dienophiles. In Table 2 the molar ratio effects on the product ratio are summarized by using dimethyl acetylenedicarboxylate and tetracyanoethylene as dienophiles. It is clear that the isomer ratios, **4a** : **4b** and **5a** : **5b** increase as the molar ratio of **1b** becomes higher.

TABLE 2. THE EFFECTS OF MOLAR RATIO OF **1b** TO DIENOPHILES

Dienophile	Molar ratio of **1b** to dienophile	Ratio of Products (GLC)
		(**4a**:**4b**)[a]
Dimethyl acetylenedicarboxylate	1:1	71:29
	3:1	89:11
		(**5a**:**5b**)[b]
Tetracyanoethylene	1:1	21:79
	2:1	22:78
	3:1	26:74
	5:1	37:63
	10:1	64:36

[a] The reaction was examined at 55–60° in C_6H_6 after 4 days.

[b] The reaction was examined at 25° in THF after 1 day.

The reaction time dependency of the isomer ratios of the products were examined in several solvents by using tetracyanoethylene as dienophile. The results are summarized in Table 3. In nonpolar solvents such as C_6H_6, $CHCl_3$ and THF, the time dependency of the isomer ratios was not observed. However, in polar solvents such as acetone and MeCN, the isomer ratios clearly increased as the reactions proceeded. Furthermore, the final ratios of the products were much higher in the polar solvents than in the nonpolar

TABLE 3. THE SOLVENT EFFECTS AND TIME DEPENDENCY ON **5a**:**5b** RATIO[a]

Solvent	Dielectric constant[b] (ε)	**5a**:**5b** ratio (GLC) 10 min.	30 min.	1 hr	3 hr	24 hr	>3 days
C_6H_6	2·284 (20°)	8:92	7:93	7:93	6:94	7:93	7:93
$CHCl_3$	4·806 (20°)	10:90	10:90	10:90	11:89	10:90	10:90
THF	7·39[c] (25°)	14:86	15:86	15:85	14:86	15:85	15:85
Me_2CO	20·70 (20°)	42:58	44:56	44:56	44:56	58:42	65:35
MeCN	37·5 (20°)	57:43	60:40	63:37	66:34	77:23	78:22

[a] The reactions were carried out by using 0·5 m. moles of **1b** and tetracyanoethylene in 10 ml of the solvent at room temp. (*ca.* 20°).

[b] *"Organic Solvents,"* Ed. by J. A. Riddick and E. E. Toops, Jr., second ed., in *"Technique of Organic Chemistry,"* Vol. VII, Ed. by A. Weisberger, (1955).

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ones. The increase was proportional to the value of the dielectric constant for the solvent used as depicted in Figure 1.

To the data described above, the following facts should be added also: (a) The isolated pure **5a** and/or **5b** was stable in these solvents and no isomerization between **5a** and **5b** was observed; (b) The characteristic colours such as green in C_6H_6 and blue in THF or

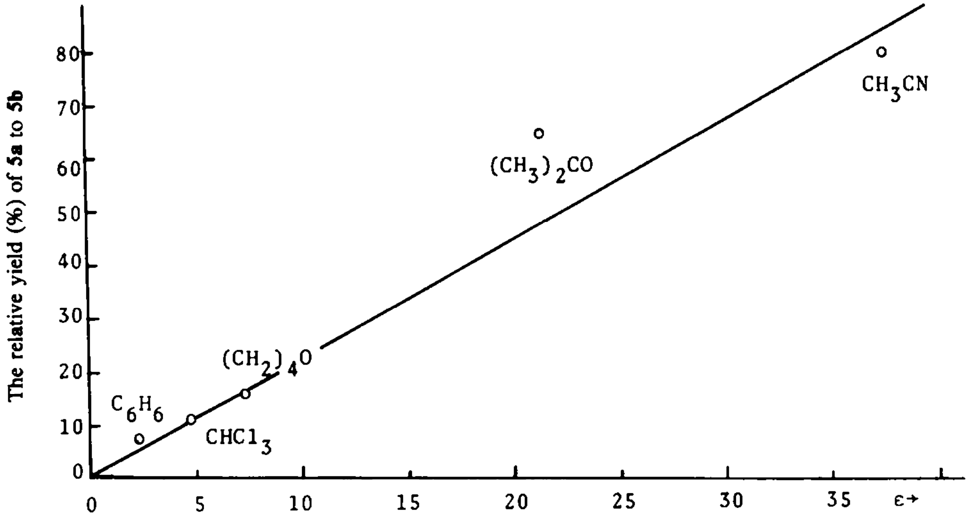


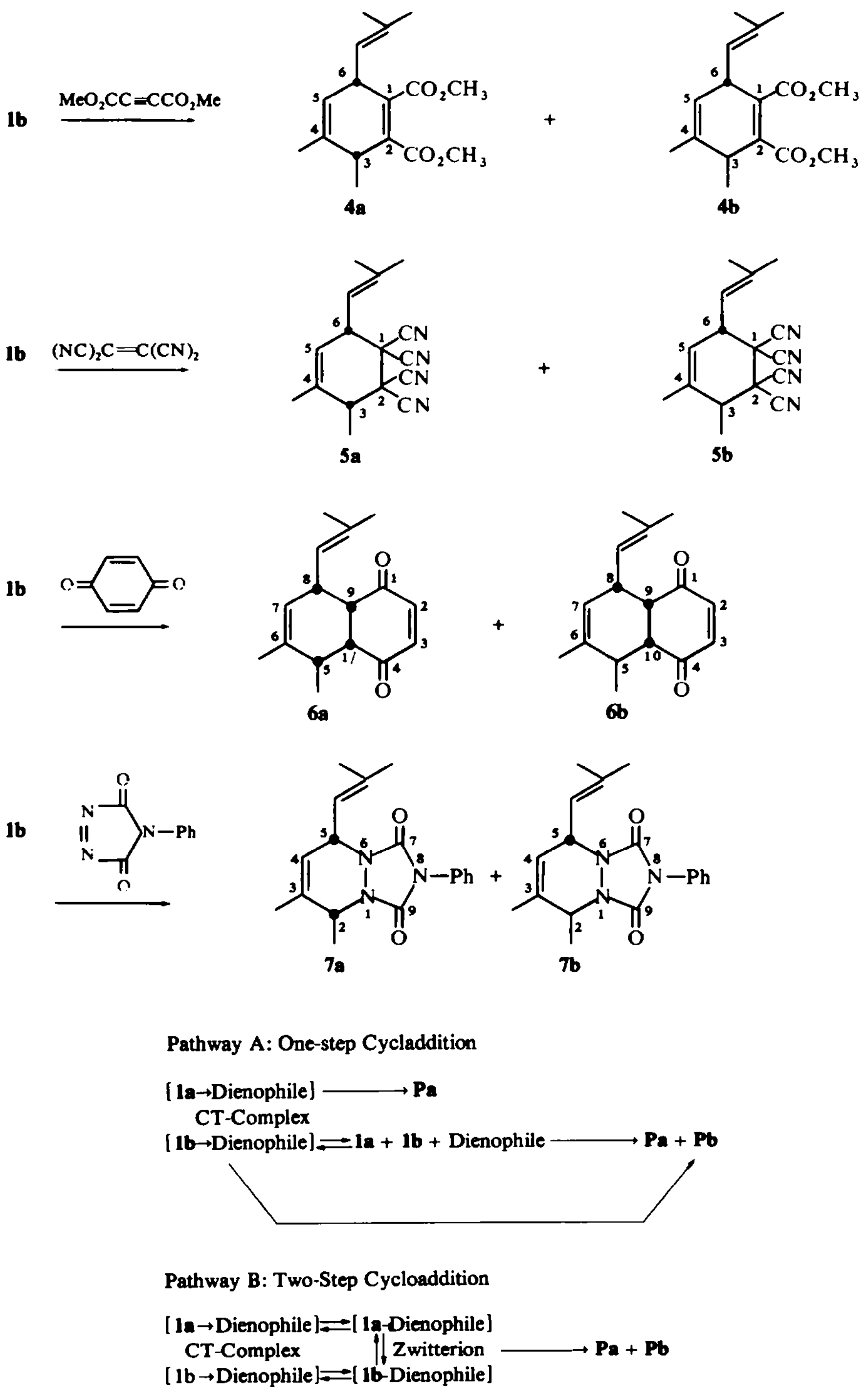
FIG. 1.

$CHCl_3$ were observed when **1b** and tetracyanoethylene were mixed, and these colours disappeared gradually as the reaction proceeded.

The inspection of the data in Table 1 indicates that **1a** affords only the products of the **a**-series, while **1b** leads to both products of the **a**- and **b**-series in different ratios by the dienophiles. Furthermore, it is obvious that the stronger dienophiles such as tetracyanoethylene and 4-phenyl-1,2,4-triazoline-3,5-dione give higher yields of the **b**-series products than the **a**-series from **1b** compared with relatively milder dienophiles such as dimethyl acetylenedicarboxylate and *p*-benzoquinone. These facts seem contradictory to the *cis*-principle well established in the Diels–Alder reactions.[6]

Two possible pathways, by which **1b** can afford both isomeric products of the **a**- and **b**-series could be considered (Scheme 3); the one (pathway A) involves a competitive **1b** → **1a** isomerization with the 1,4-cycloaddition reactions which should proceed concertedly. The other (pathway B) is a two-step cycloaddition, in which a zwitterionic or a diradical intermediate is involved. This intermediate gives rise to afford both isomeric products after the isomerization. The loss of *cis*-principle *via* the path of the type B is often postulated in the 1,2-cycloaddition.[7]

In the present case, the fact that the molar ratio of **1b** to the dienophiles affected the isomer ratios of the products (Table 2) clearly supports pathway A rather than B, because in the latter no change of isomer ratio could be expected in the same solvent. The fact that no trace of **1a** could be detected during the reaction suggests that **1b** → **1a** isomerization is much slower than the cycloaddition of **1a**, and the reactivity of **1a** is


1b
$MeO_2CC{\equiv}CCO_2Me$
CO_2CH_3
4a
4b
1b
$(NC)_2C{=}C(CN)_2$
CN
5a
5b
1b
6a
6b
1b
N—Ph
7a
7b
Pathway A: One-step Cycladdition
[1a→Dienophile] → Pa
CT-Complex
[1b→Dienophile] ⇌ 1a + 1b + Dienophile → Pa + Pb
Pathway B: Two-Step Cycloaddition
[1a→Dienophile] ⇌ [1a-Dienophile]
CT-Complex
Zwitterion → Pa + Pb
[1b→Dienophile] ⇌ [1b-Dienophile]

SCHEME 3

much higher than **1b**. In fact, **1a** is reported to be several orders moere reactive than **1b** with maleic anhydride;[8] confirmed by us. Furthermore, the **1b** → **1a** isomerization was evidently accelerated compared with the 1,4-cycloadditions in polar solvents as seen from the solvent effects (Table 3); the relatively minor solvent effects are well established for the concerted 1,4-cycloadditions.[6] The observed time independency of the product ratio in nonpolar solvents is compatible with no formation of **1a** during the reaction also in C_6H_6, in view of the slower **1b** → **1a** isomerization compared to the cycloaddition in these solvents.

All of these facts well support preference for pathway A, that is, the one-step cycloaddition competitive with the **1b** → **1a** isomerization.

Finally, the isomerization of **1b** to **1a** might be discussed briefly. Although Gustorf and Leitich[8] have reported the occurrence of the **1b** → **1a** isomerization on heating with π-acids, the conditions required seem to be more drastic than those in the present investigation. For example, no isomerization was caused even on heating at 160° with *p*-benzoquinone according to their report in contrast to the above described facile isomerization at 55–60°. The **1b** → **1a** isomerization is evidently ascribable to the formation of the charge-transfer complex between **1b** and the dienophiles on the basis of the following facts: no isomerization without the dienophiles, the appearance of the characteristic colours, and a large solvent effect on the isomer ratio of the products.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. NMR spectra were recorded on a JEOL-C-60HL spectrometer at 60 MHz with TMS as internal standard, and mass spectra on a JEOL JMS-01SG mass spectrometer at 75 eV. IR spectra were obtained with a JASCO IR-S spectrophotometer. GLC analyses were performed on a K-23 Hitachi gas chromatograph, and NEVA gas chromatograph model 1400 (Silicone SE-30). Microanalyses were carried out with a Perkin–Elmer 240 Elemental Analyzer.

1-*Cyano*-3,4-*dimethyl*-6-*isobutenyl*-1,4-*cyclohexadiene* (**2a**) *and* 1-*cyano*-4-(1-*methyl*-3-*cyano*-2-*propenyl*)-6-*isobutenyl*-1,4-*hexadiene* (**3**). A misture of 1·36 g (10 mm) of neoalloocimene **1b** (b.p. 82·85°/30 mm, n_D^{20} 1·5406) and 0·60 g (12 m. mole) of cyanoacetylene[9] in C_6H_6 (20 ml) was heated in a sealed tube at 55–60° for 4 days. After removal of solvent, the oily residue was purified by chromatography on silica gel (Mallinckrodt, 100 Mesh) eluting with C_6H_6 to give 1·16 g (83%) of **3**, n_D^{20} 1·5402 (lit.,[2] 1·5409) together with trace of **2a** (GLC). **3** was identified by IR and NMR spectral comparison with an authentic sample.[2]

1,2-*Dimethoxycarbonyl*-3,4-*dimethyl*-6-*isobutenyl*-1,4-*cyclohexadiene* (**4a** and **4b**). The reaction of 1·36 g (10 mm) of **1b** with 1·42 g (10 mm) of dimethyl acetylenedicarboxylate in C_6H_6 (20 ml) gave 0·49 g (18%) of a 71 : 29 mixture of **4a** and **4b**, colourless oil, n_D^{20} 1·5023; IR (film) 2975, 1723, 1642, 1436, 1378, 1260 and 830 cm^{-1}; NMR (CCl_4) τ 4·85 (m, 1, C_5-H), 5·38 (broad d, J = 11·0 Hz, 1, C=CH), 6·25 (broad m, 1, C_6-H), 6·32 and 6·37 (s, each 3, $COOCH_3 \times 2$), 7·18 (broad m, 1, C_3-H), 8·32 (m, 9, C_4-CH_3 and $C(CH_3)_2$), 8·74 (d, J = 7·0 Hz, 2·0, C_3—CH_3 of **4a**), and 8·93 (d, J = 7·0 Hz, 1·0, C_3—CH_3 of **4b**). (Found: C, 69·29; H, 7·72. $C_{16}H_{22}O_4$ requires: C, 69·04; H, 7·97%).

1,1,2,2-*Tetracyano*-3,4-*dimethyl*-6-*isobutenyl*-4-*cyclohexane* (**5b**). The crude product from 0·68 g (5·0 mm) of **1b** and 0·64 g (5·0 mm) of tetracyanoethylene was purified by chromatography on silica gel eluting with $CHCl_3$ to give 1·12 g (85%) of a 7 : 93 mixture of **5a** and **5b** as semi-solid. Recrystallization from n-hexane afforded **5b** as colourless needles: m.p. 80·5–81·5°; IR (KBr) 2974, 2920, 2250, 1657, 1445, 1391, and 849 cm^{-1}; NMR ($CDCl_3$) τ 4·76 (broad s, 1, C_5—H), 4·88 (broad d, J = 11·0 Hz, 1, C=CH), 6·06 broad d, J = 11·0 Hz, 1, C_6—H), 6·86 (broad m, 1, C_3—H), 8·16 (m, 9, C_4—CH_3 and $C(CH_3)_2$), and 8·46 (d, J = 7·5 Hz, 3, C_3—CH_3); Mass spectrum, *m/e* (rel. intensity) 264 (M^+, 7·9), 248 (6·6), 221 (7·4), 197 (7·9), 195 (8·4), 137 (7·1), 136 (50·8), 122 (14·0), 121 (100·0), 105 (10·0), 95 (6·3), 93 (7·9), 91 (10·8), 79 (10·8), 78 (10·8), 77 (15·0), 67 (10·5), 65 (10·0), 55 (10·0), 53 (14·5), 51 (10·5), 50 (7·1), 42 (7·0), 41 (15·8), and 40 (94·7). (Found: C, 72·66; H, 6·18; N, 20·87. $C_{16}H_{16}N_4$ requires C, 72·70; H, 6·10; N, 21·20%).

5,6-*Dimethyl*-8-*isobutenyl*-5,8,9,10,-*tetrahydro*-1,4-*naphtoquinone* (**6a** and **6b**). The crude product from

1·36 g (10 mm) of **1b** and 1·08 g (10 mm) of *p*-benzoquinone was purified on silica gel by eluting with $CHCl_3$ to give 0·24 g (10%) of a 33 : 67 mixture of **6a** and **6b** as yellowish oil: IR (film) 2925, 1679, 1603, 1448 and 1375 cm^{-1}; NMR ($CDCl_3$) τ 3·42 and 3·46 (each s, 2, C_2-H and C_3-H), 4·85 (broad s, 1, C_7-H), 5·36 (broad d, J = *ca.* 10 Hz, 1, C=CH), 6·69 (m, 2, C_9-H and C_{10}-H), 7·00-7·39 (broad m, 2, C_5-H and C_8-H), 8·30 (broad s, 3, C_6-CH_3), 8·48 (m, 6, $C(CH_3)_2$), 8·82 (d, J = 7·5 Hz, 1·0, C_5-CH_3 of **6a**), and 8·90 (d, J = 7·5 Hz, 2·0, C_5-CH_3 of **6b**). (Found: C, 78·68; H, 8·22. $C_{16}H_{20}O_2$ requires C, 78·65; H, 8·25%).

2,3-*Dimethyl*-5-*isobutenyl*-8-*phenyl*-1,6,8-*triazabicyclo*-[4.3.0]*non*-3-*ene*-7,9–*dione* (**7b**). The crude product from 0·68 g (5·0 mm) of **1b** and 0·88 g (5·0 mm) of 4-phenyl-1,2,4-triazoline-3,5-dione[10] in dioxane (20 ml) was purified on a silica gel eluting with $CHCl_3$ to give 1·38 g (88%) of a 28 : 72 mixture of **7a** and **7b** as semi-solid. Recrystallization from n-hexane gave pure **7b** as colourless crystals, m.p. 113·5–114°; IR (KBr) 3030, 2924, 1767, 1706, 1601, 1500, 1412, 1385, 722 and 687 cm^{-1}; NMR ($CDCl_3$) τ 2·57 (broad m, 5, phenyl protons), 4·64 (broad s, 1, C_5-H), 5·04 (broad s, 2, C=CH and C_4-H), 5·58 (broad q, J = 7·0 Hz, C_2-H), 8·20 (s, 6, $C(CH_3)_2$), 8·31 (s, 3, C_3-H), and 8·68 (d, J = 7·0 Hz, C_2-CH_3); Mass spectrum *m/e* (rel. intensity) 311 (M^{+} 4·8), 217 (7·0), 181 (46·6), 149 (17·2), 140 (13·8), 121 (27·6), 120 (10·3), 107 (11·0), 106 (12·1), 105 (12·0), 104 (12·1), 103 (10·7), 94 (10·3), 93 (10·3), 92 (12·8), 91 (26·6), 90 (41·7), 85 (14·8), 83 (21·4), 80 (12·8), 79 (27·6), 78 (16·9), 76 (12·1), 68 (10·3), 67 (17·2), 66 (14·8), 64 (10·0), 56 (47·2), 55 (41·4), 54 (18·3), 52 (14·1), 50 (10·0), 48 (27·2), 43 (100·0), 42 (36·9), 41 (27·6), 40 (72·8), 39 (21·4), and 38 (33·4). (Found: C, 69·51; H, 6·81; N, 13·41. $C_{18}H_{21}N_3O_2$ requires C, 69·43; H, 6·80; N, 13·50%).

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