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CYCLOADDITION OF NITRILE IMINES TO CYCLOOCTATETRAENE[1]

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Abstract—Nitrile imines react with cyclooctatetraene and its diene adduct with dimethyl acetylenedicarboxylate to yield cyclobutane-condensed pyrazoline systems. The different reactivity of cyclobutene and cyclohexadiene double bonds in the same molecule has been evaluated and compared with the reactivity toward other 1,3-dipoles. The thermolysis of the adducts has been described.

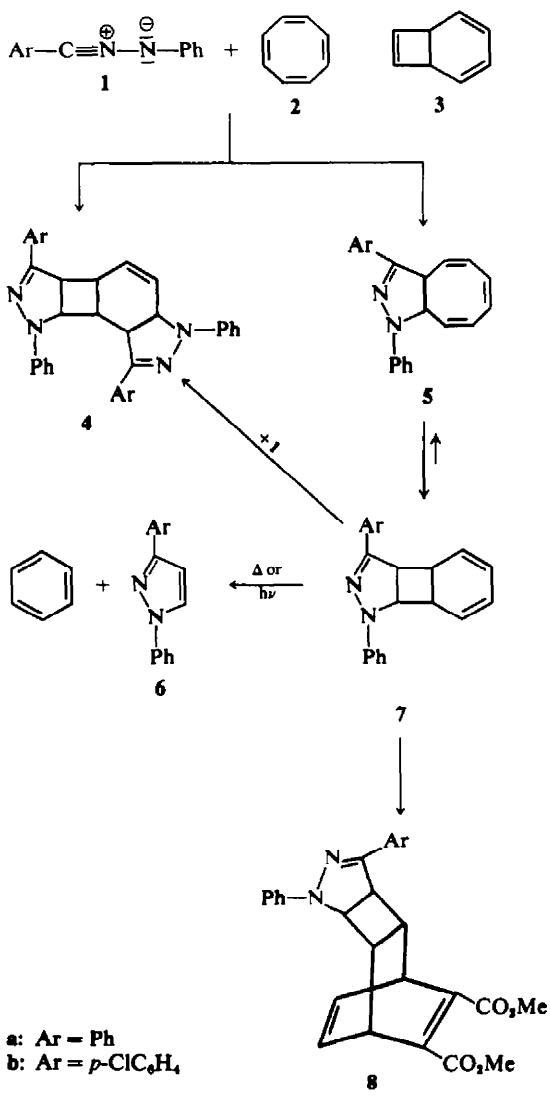
The dipolarophilic activity of cyclooctatetraene (COTE) with nitrones,[1] picrylazide,[2] tetracyanoethylene oxide,[3] fulminic acid[4] and nitrile oxides,[5-7] has already been investigated. We now report our results on the synthetic possibilities of the cycloaddition of nitrile imines to cyclooctatetraene, leading to new cyclobutane-condensed heterocyclic systems.

Reaction of a nitrile imine (**1a, b**) with a nearly equimolar amount of cyclooctatetraene (**2** ⇌ **3**) gave fairly good yields of bis-adducts (**4a, b**) whose nature was deduced by their decomposition in hot acetic acid into 1-phenyl-3-arylindazole (**9**) and 1-phenyl-3-arylpyrazole (**6**) obtained in nearly equimolar amounts.† (Schemes 1 and 2).

Compound **4a** is much more easily decomposed in the presence of chloranil on heating in acetic acid or toluene. Furthermore the disappearance of **4a** is slower when the reaction is carried out under nitrogen than in the presence of oxygen.

These experiments suggest a prior oxidation of the compounds **4** to the dehydro derivatives (**10**; Scheme 2, path A slow step) which in turn decompose (fast step) to give **6** and **9** according to a reaction mechanism recently defined as 1,2-aromatisation.[8] The alternative path B, which involves the intermediate dihydroindazole (**11**) (Scheme 2) seems less probable.

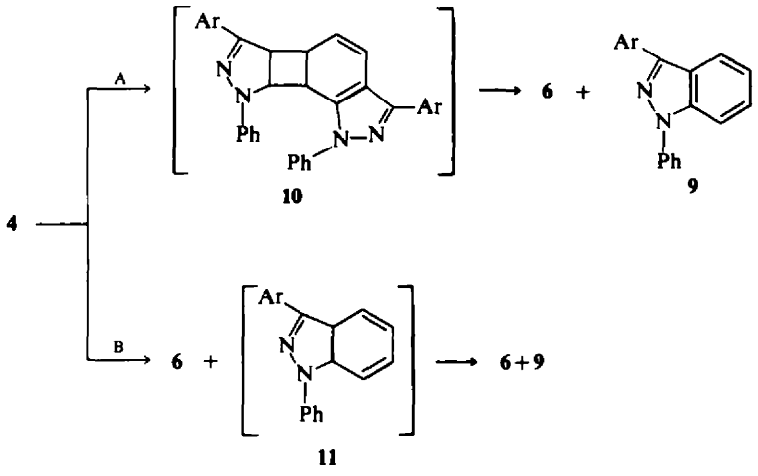
Using COTE in a very large excess, the cycloaddition stopped at the monoadducts **7** which decomposed easily on heating to 1-phenyl-3-arylpyrazole (**6**) and benzene. This behavior parallels that of the monoadducts of the nitrile oxides to COTE,[5,6] but the compounds **7** are less stable being completely decomposed to pyrazole and benzene on silica gel and in solution, if not kept in the dark.



a: Ar = Ph
b: Ar = *p*-ClC$_6$H$_4$

SCHEME 1

†Owing to the lack of NMR data, due to the insolubility of the products, we did not determine which double bond of the cyclohexadiene moiety had reacted, and structure **4** is therefore tentative. In fact, from **1b** a mixture of two regio- or stereo-isomers **4b** was obtained (Experimental).



a and b as in Scheme 1

SCHEME 2

This fact clearly favours the tricyclic structure **7** for the monoadduct. The NMR spectrum is also consistent with the tricyclic structure and shows that in $CHCl_3$ there is no appreciable amount of the bicyclic tautomer **5**.

However we believe that the tautomer **5** must be the primary reaction product which gives rise to the valence isomer **7** by analogy with the reaction of the benzonitrile oxide with COTE.[6,9]

The compound **7** was also characterized through its diene reaction with dimethyl acetylenedicarboxylate. The adducts **8a, b** were thus obtained in good yield and their structures were established through spectral analysis and through the synthesis from the cyclooctatetraene-dimethyl acetylenedicarboxylate adduct **12**, as shown below.

An attempt to pyrolyse the adduct **8a** in order to prepare the still unknown 2,3-diazabicyclo [3.2.0] hepta-3,6-diene system, analogous to the recently explored 2,3-oxazabicyclo [3.2.0] hepta-3,6-diene ring,[7] led to dimethyl phthalate as the sole isolable product.

The dipolarophilic activity of the cyclooctatetraene-dimethyl acetylenedicarboxylate adduct **12**, whose configuration is well established,[10] was next examined (Scheme 3). All three double bonds were found to be reactive toward the nitrile imine (**1a**), one main adduct and two minor adducts being isolated from the reaction by column chromatography. The ratio **13**:**8a**:**14** equals 2·8:1·0:1·0.

The last of the two minor adducts to be eluted was identical with the compound obtained directly from **7a** and dimethyl acetylenedicarboxylate and this proves structure **8a** for this compound. The other minor adduct decomposed thermally to cyclooctatetraene and dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (**17**). The proposed structure **14** is probably correct on the assumption that the 1,3-dipole would attack the compound **12** from the less encumbered side of the molecule.

The fragmentation **14** → COTE + **17** is either a retro Diels-Alder or a bis-homo-retro-Diels-Alder, the latter mechanism taking into account the sterically favourable position of the cyclobutene ring.

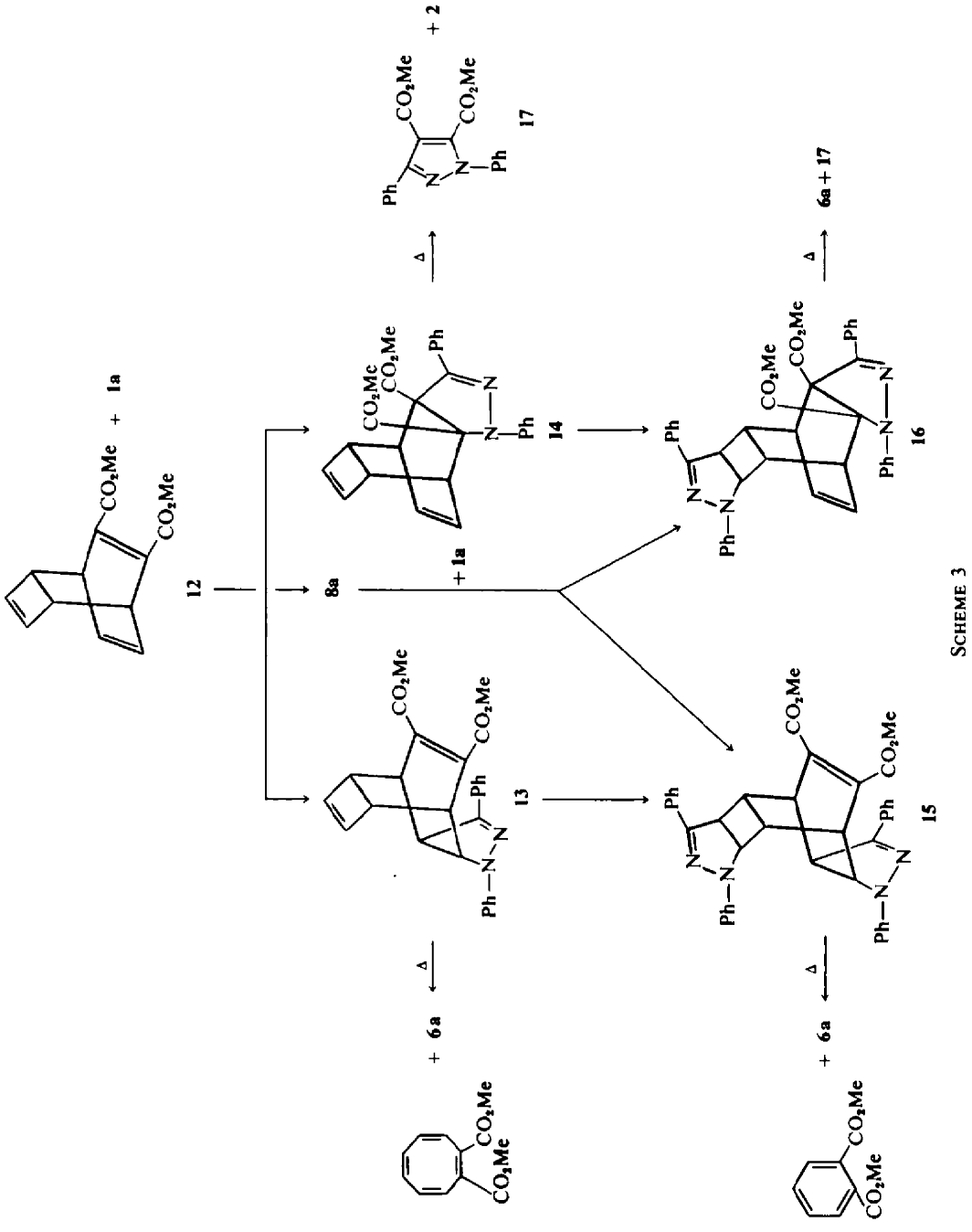
The main adduct, which is thermally more stable than **14**, must be assigned structure **13**. The structure was established through its decomposition to **6a** and 1,2-dicarbomethoxy-cyclooctatetraene.

These structures were confirmed by the results of the further reaction of the three isomeric condensed pyrazolines with a second molecule of nitrile imine. Only two of the three possible isomeric bis-adducts† were obtained: compound **15** was the sole product from **13**, and **16** was the sole product isolated from **14**. The adduct **8a** gave a mixture of both bis-adducts **15** and **16** in the ratio 0·90:1·0, thus fixing their structures, as shown in Scheme 3. Structure **15** and **16** were further substantiated by their thermal decomposition: the former gave **6a** and dimethyl phthalate and the latter gave **6a** and **17**. (Scheme 3).

Therefore, the different double bonds of **12** show the following order of reactivity toward cycloaddition of nitrile imines: unsubstituted cyclohexadiene bond ≫ cyclobutene bond ≈ conjugated cyclohexadiene bond.

In contrast with the behaviour of nitrile imines, neither nitrile oxides[7] nor nitrones[1] react with the dimethoxycarbonyl-conjugated double bond of **12**.

†The addition direction of the second molecule of the nitrile imine is here not considered although the methyl region of the NMR spectrum of the crude reaction product shows the presence of the two regioisomers clearly. In the Scheme 3 only the more symmetrical *cis*-structures are reported.



SCHEME 3

The higher sensitivity of nitrile imines, in comparison with nitrile oxides or nitrones, toward conjugation in the dipolarophile has already been noticed from kinetic data,[11] and our present results underline once more the difference in reactivity between structurally related 1,3-dipoles.

Furthermore there is a remarkable change in dipolarophilic character of the two double bonds belonging to the cyclohexadiene moiety in passing from **8** to **12**.

The cycloaddition of the nitrile imine **1a** to **12** gave **13** and **14** in the ratio of about 2·8 which is quite different from the ratio 0·9 for the compounds **15** and **16** obtained by reaction of the same 1,3-dipole with **8a**. Research on this particular problem is being pursued in this laboratory.

EXPERIMENTAL

UV spectra were obtained in EtOH or CH_2Cl_2 soln in a Perkin Elmer 137 recording instrument and IR spectra as nujol mulls in a Perkin Elmer 257 spectrophotometer. NMR spectra were determined using a Perkin Elmer R 12 A spectrometer with TMS as internal standard in $CDCl_3$ solns at 36°.

Elemental analyses were performed by Dr. L. Maggi Dacrema. The composition of products was determined by TLC (Kieselgel GF 254 Merck) and other chromatographic systems.

Most mixtures were separated on columns of silica gel (Kieselgel H Merck); the effluent was collected fractionally and examined by TLC.

Compounds were detected on TLC plates with a UV lamp or by spraying the developed plates with a 3% CrO_3 soln in H_2SO_4 (50%) followed by heating at 120° in an oven.

M.Ps were taken in capillaries in an oil bath and are uncorrected. GLC were run using a Perkin Elmer 800 gas chromatograph by Dr. M. De Bernardi.

5-Aryl-3,4-diaza-3-phenyltricyclo [5.4.0.0^{2,6}] *undeca-4,8,10-trienes* (**7a**) and (**7b**). A soln of α-chlorobenzilidenphenylhydrazine[12] (0·2 g, 0·87 mmoles) and of Et_3N (0·6 ml, 4·3 mmoles) in COTE (5 ml, 43 mmoles) was kept in the dark at room temp for 48 hr.

The precipitated Et_3N·HCl was filtered off and the excess COTE and Et_3N evaporated off under normal pressure in the dark to give a residue which was dissolved in EtOAc and precipitated on addition of MeOH at −10° to give **7a** (0·16 g, 62%), yellow *needles* m.p. 128–131° (Found: C, 84·4; H, 6·1; N, 9·8. $C_{21}H_{18}N_2$ requires: C, 84·5; H, 6·1; N, 9·4%). λ_{max}^{EtOH} (nm) (log ε): 257 (4·21), 312 (4·01), 379 (4·20); NMR ($CDCl_3$ δ 3·30 (2H, m, H-1 and H-7), 4·23 (1H, m, H-6), 4·77 (1H, m, H-2; J_{26} = 9·3 Hz), 5·83 (4H, m, vinyl protons).

Compound **7b** was obtained in 68% yield as above from *p*-chlorobenzoylchloride phenylhydrazone,[13] Et_3N and COTE as yellow *needles*, m.p. 123–125°. (Found: C, 75·8; H, 5·1; N, 8·7. $C_{21}H_{17}ClN_2$ requires: C, 75·7; H, 5·1; N, 8·4%); λ_{max}^{EtOH} (nm) (log ε): 250 (4·28), 260 (4·27), 307 (3·98), 387 (4·21); NMR ($CDCl_3$) δ: 3·29 (2H, m, H-1 and H-7), 4·12 (1H, m, H-6), 4·77 (1H, m, H-2; J_{26} = 9·3 Hz), 5·83 (4H, m, vinyl protons).

Treatment of the crude reaction mixtures with excess dimethyl acetylenedicarboxylate gave **8a** and **8b** in 65 and 64% yield respectively. For the analytical data see later.

Diadduct **4a**. (i) A soln of α-chlorobenzilidenphenylhydrazine (1·0 g, 4·3 mmoles) and COTE (0·43 g, 4·0 mmoles) in benzene (35 ml) was treated with Et_3N (7 ml) and left at room temp for 7 days. The precipitated Et_3N·HCl was filtered off and the benzene evaporated under reduced pressure. The oily residue was treated with n-hexane to give **4a** (0·7 g, 65%) as yellow *needles* from toluene m.p. 220–222°. (Found: C, 83·1; H, 5·8; N, 11·7. $C_{34}H_{28}N_4$ requires: C, 82·9; H, 5·7; N, 11·4%).

(ii) Monoadduct **7a** (0·075 g), α-chlorobenzilidenphenylhydrazine (0·06 g) and Et_3N (0·5 ml) were dissolved in benzene (3 ml) and left for 7 days. The solid which separated was washed with water to give **4a** (0·090 g, 72%).

Diadduct **4b**. The *p*-chlorobenzoylchloride phenylhydrazone, COTE and Et_3N were treated in benzene as above. Evaporation of the solution and treatment with MeOH gave a solid mixture of two isomeric products **4b** (50%) which were separated by column chromatography (eluent cyclohexane/ethyl acetate = 85:15). The first eluted product (14% of the mixture) had m.p. 224–228°, the second (86%) had m.p. 220–221°. Compound m.p. 224–228° was purified as yellow *prisms* from AcOH. (Found: C, 72·4; H, 4·8; Cl, 12·6%), compound m.p. 220–221° occurred as yellow *prisms* from $EtNO_2$ (Found: C, 72·5; H, 4·5; Cl, 13·1; N, 10·0. $C_{34}H_{26}Cl_2N_4$ requires: C, 72·7; H, 4·7; Cl, 12·7; N, 10·0%).

Thermolysis of **7a** *and* **7b**. Compounds **7a** and **7b** decomposed on heating at 150° for 5 min. The corresponding pyrazoles **6a**[12] and **6b** were obtained in virtually quantitative yields. Compound **6b**, hitherto undescribed, was identical with an authentic sample prepared following a general procedure:[13] yellowish needles from MeOH, m.p. 119–120°. (Found, C, 70·5; H, 4·4; N, 11·2. $C_{15}H_{11}ClN_2$ requires: C, 70·8; H, 4·3; N, 11·0%). Compounds **7a** and **7b** are quite stable in the solid state at room temp but decompose in soln if not kept in the dark. The light induced decomposition could be followed by the UV technique. They are also completely decomposed when passed through silica gel.

Decomposition of **4a**. The diadduct **4a** was heated under reflux in AcOH for 6 hr. The solvent was removed and the residue was chromatographed (cyclohexane–EtOAc = 9:1). The first eluted was the indazole **9a**[15] (0·27 g, 51%), the second the pyrazole **6a** (0·28 g, 64%) both of which were identical to authentic samples.

Decomposition of **4a** *under different conditions*. (i) The decomposition of **4a** has been carried out under three different sets of conditions and followed by TLC to completion. Three flasks were set up, each containing the same amount of **4a** (0·1 g) dissolved in the same volume of AcOH (10 ml). To the first flask chloranil was added (0·200 g). This flask and one without chloranil were heated under reflux in the presence of air while the third flask heated under reflux in the presence of nitrogen. In the first flask decomposition was completed in 10 min, in the second flask in 8 hr, while in the third flask 0·030 g of **4a** could be recovered after 8 hr.

GLC analysis showed that the indazole and the pyrazole were present in equimolar amounts in the first two experiments.

(ii) Two other runs were carried out as above (but without excluding oxygen) using toluene as solvent. Heating under reflux in toluene for 48 hr did not give clear-cut results and **4a** was recovered unchanged in 53% yield.

The run carried out with chloranil produced an intensive green colour which disappeared after 3 hr. The reaction was followed by GLC which showed that the de-

composition was complete giving indazole and pyrazole in equimolar amounts.

Decomposition of **4b**. Both the isomeric diadducts **4b** on heating under reflux in AcOH for 5 hr gave the indazole **9b** and the pyrazole **6b** which were separated by column chromatography (cyclohexane–EtOAc = 80:20). Diadduct **4b** m.p. 224–228° gave the indazole (the first eluted product) in 58% yield and the pyrazole in 60% yield while in the case of the isomer m.p. 220–221° the yields were 60 and 88% respectively. Compound **9b** yellow *needles* from n-heptane, had m.p. 140–141°. (Found; C, 74·7; H, 4·5; N, 9·0. $C_{19}H_{13}ClN_2$ requires: C, 75·0; H, 4·3; N, 9·2%).

Reaction of **1a** *with* **12**. A soln of α-chlorobenzilidenphenylhydrazine (0·6 g), **12** (1·30 g) and Et_3N (1·5 ml) in benzene (15 ml) was heated under reflux for 2 hr. The precipitated solid was filtered off, washed with water and crystallized from EtOH to give a first crop of **13** (0·296 g). The combined mother liquors were evaporated, and chromatographed (cyclohexane–benzene–EtOAc = 9:9:1) to give in the following order some unreacted **12**, **14** (0·21 g, 18%), **16** (47 mg) and a mixture of **13** and **8a** (0·5 g) which was shown to be in a ratio of 1·38 by NMR analysis. Compound **13** (0·59 g, 51%) as yellow *prisms* from benzene, had m.p. 220–222°, (Found: C, 73·7; H, 5·6; N, 6·6). **8a** (0·21 g, 18%) as yellow *prisms* from benzene, had m.p. 195–196°, (Found: C, 73·4; H, 5·5; N, 6·4); **14** as colourless *needles* from MeOAc m.p. 224–225° dec, (Found; C, 73·6; H, 5·5; N, 6·3. $C_{27}H_{24}N_2O_4$ requires: C, 73·6; H, 5·5; N, 6·4%).

The mixtures of **13** and **8a** when further chromatographed (cyclohexane:EtOAc = 85:15) gave as second eluted product some pure **8a** which was identical with the compound obtained from the reaction of **7a** with dimethyl acetylene dicarboxylate. The NMR data of **8a**, **13** and **14** are given in Table 1.

Thermolysis of **14** *and* **16**. The pyrazoline **14** (0·2 g) was heated at its m.p. in a ampoule to give cyclooctatetraene that collected on the walls of the tube. The solid residue, the pyrazole **17** (0·15 g, 98%) was identical (m.p., mixed m.p., IR spectrum) with an authentic sample.[12] The same decomposition was carried out in two different solvents; compound **14** (0·030 g) was completely decomposed into pyrazole **10** and cyclooctatetraene on heating under reflux in xylene (5 ml) for 30 hr and, separately, in decalin (5 ml) for ½ hr.

By analogy compound **16** decomposed at its m.p. to give **6** and **17**, in 90% yields. These were separated by preparative TLC (eluent: cyclohexane–ethyl acetate = 4:1). Compound **6** had the higher R_f.

The decomposition of **16** (0·048 g) went to completation in xylene (5 ml) in 50 hr and in decalin (5 ml) in 1/2 hr.

Thermolysis of **13** *and* **15**. Compounds **13** and **15** were shown to be quite stable to their m.ps. The decomposition of **13** to **6a** and dimethylcyclooctatetraene-1,2-dicarboxylate could be achieved by heating the substance at 300° (oil bath temp) in a sublimator under 600 Torr. The sublimed material was analysed by VPC, NMR and then separated by preparative TLC. Compound **6a** had the higher R_f.

Compound **13** (0·35 g) gave **6a** (0·098 g, 56%) and 1,2-dicarbomethoxycyclooctatetraene (0·032 g, 18%). NMR ($CDCl_3$) δ 3·70 (6H, s), 5·98 (4H, m) 7·20 (2H, d). The values are in agreement with literature data (Ref 14). Compound **15**, treated as above gave **6a** and dimethylphthalate.

Reaction of **1a** *with* **8a**, **13** *and* **14**. (i) α-chlorobenzilidenphenylhydrazine (0·18 g), **8a** (0·263 g) and Et_3N (0·5 ml) were heated under reflux in benzene (15 ml) for 64 hr. Usual treatment gave a residue which, when chromatographed (benzene–EtOAc = 95:5) gave **16** (0·18 g, 47%) and **15** (0·16 g, 42%) in the order. Some unreacted **8a** was recovered (0·023 g).

(ii) α-chlorobenzilidenphenylhydrazine (0·10 g), **13** (0·20 g) and Et_3N (0·5 ml) were heated under reflux in benzene (15 ml) for 50 hr. Treatment as above gave the sole adduct **15** (0·25 g, 90%) as yellow *prisms* from benzene m.p. 272–275°. (Found: C, 75·5; H, 5·4; N, 8·8%).

(iii) α-chlorobenzilidenphenylhydrazine reacted as above with **14** to give **16** (77%) as yellowish *prisms* from MeOAc m.p. 220–221°. (Found: C, 73·3; H, 5·6; N, 8·0. $C_{40}H_{34}N_4O_4 \cdot CH_3COOCH_3 = C_{43}H_{40}N_4O_6$ requires: C, 72·9; H, 5·7; N, 7·9%).

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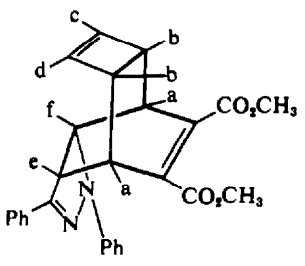
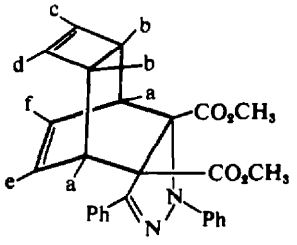
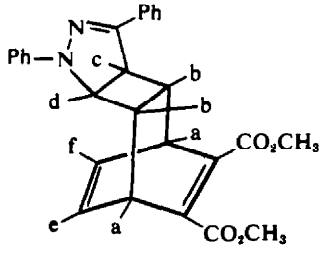
Table 1. NMR data of the monoadducts from **12** and nitrileimine (**1a**)



13



14



8a

	13	**14**	**8a**
Ha	3·70–4·20 m	3·40–3·70 m	4·38 m
Hb	3·82 m		2·49 m
Hc	6·65 d	5·82 s	3·41
Hd			4·02
He	4·10 m	5·62 m	6·72 t
Hf	4·60 m		
$-CH_3$	3·42 s, 3·53 s	3·60 s; 3·70 s	3·76 s

aid, and to BASF, Ludwigshafen, for a generous gift of COTE.

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