Interaction of 1,2,3,4-Tetrahydro-4a-methyl-4a*H*-carbazole with Dimethyl Acetylenedicarboxylate: a Re-examination. Crystal Structures of Dimethyl 2a,3,4,5,5a,10-Hexahydro-10-[(*E*)-1,2-bismethoxycarbonylvinyl]-5a-methylcyclobuta[*j*]carbazole-1,2-dicarboxylate and Dimethyl 1,2,3,3a,4,5,12b,12c-Octahydro-12c-methoxy-4-methoxycarbonylmethylene-12b-methyl-5-oxazepino[3,2,1-*jk*]carbazole-6,7-dicarboxylate

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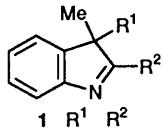
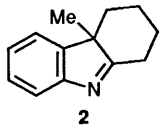
Reaction of 1,2,3,4-tetrahydro-4a-methyl-4a*H*-carbazole with dimethyl acetylenedicarboxylate produces several products, two of which have been characterised by X-ray crystallographic analysis and shown to have the structures dimethyl 2a,3,4,5,5a,10-hexahydro-10-[(*E*)-1,2-bismethoxycarbonylvinyl]-5a-methylcyclobuta[*j*]carbazole-1,2-dicarboxylate, **6** and dimethyl 1,2,3,3a,4,5,-12b,12c-octahydro-12c-methoxy-4-methoxycarbonylmethylene-12b-methyl-5-oxazepino[3,2,1-*jk*]-carbazole-6,7-dicarboxylate, **7**.

Reactions of acetylene dicarboxylates with heterocyclic compounds,[1] especially those which include an imine unit, have been studied extensively. Amongst examples examined since Acheson's two comprehensive reviews[1] are pyrazines,[2] pyrimidines,[3] imidazoles,[4] aromatic Schiff's bases,[5] and simple 4,5-dihydro-3*H*-pyrroles,[6] *i.e.* five-membered cyclic imines. Products obtained from the combination imine/acetylene dicarboxylate are believed to be produced *via* an initial electrophilic attack on the imine nitrogen by the electron-deficient alkyne, followed by sequences which are dependent on the structure of the particular imine-containing molecule.

Two studies[7,8] of the interactions of the imine unit in a 3*H*-indole (indolenine) with acetylene dicarboxylates have appeared. In the first of these, Letcher and Sin reported that 2,3,3-trimethyl-3*H*-indole, **1a**, and 1,2,3,4-tetrahydro-4a-methyl-4a*H*-carbazole, **2**, react with dimethyl acetylenedicarboxylate in 'wet methanol (or acetonitrile, or acetic acid)' giving products to which they assigned the analogous structures **3** and **4**, respectively.[7]



1 R¹ R²
a Me Me
b Me H
c Et H



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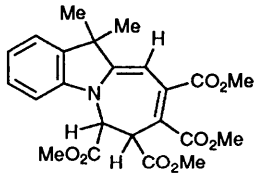

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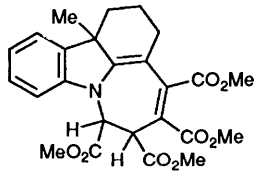
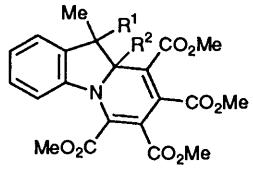


4

The following year, Le Count and Marson described[8] the reactions of bicyclic indolenines **1a–c** with dimethyl acetylenedicarboxylate in dry acetonitrile, concluding that compounds **5a–c** were formed. From the data given, it is not possible to ascertain whether or not the **1a**-derived product(s), obtained by the two groups was the same compound.



5 R¹ R²
a Me Me
b Me H
c Et H

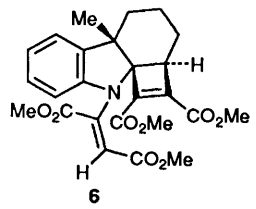
Because of our interest in the construction of indole alkaloids, we were recently led to re-examine the reaction of carbazolenine, **2**, with dimethyl acetylenedicarboxylate and describe our results here.

Results

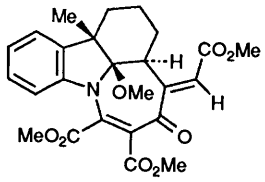
Carbazolenine, **2**, in dry acetonitrile was treated at 0 °C with dimethyl acetylenedicarboxylate over a few hours to give a mixture of at least seven products (TLC), five of which were derived from the carbazolenine (aromatic ^{1}H NMR signals). After column chromatography, crystallisation of the early fractions from methanol afforded one of these, adduct-**A**, pure, as red prisms. Mass spectrometry showed adduct-**A** to contain 2 mol equiv. of the acetylene and one of the carbazolenine. The structure and relative stereochemistry of adduct-**A**, determined by X-ray crystallographic analysis (see Experimental section for details), was revealed as the tetracyclic cyclobutene, **6**.

Extensive column, preparative layer, then high pressure liquid chromatographic purification of the combined later fractions led to the isolation in homogeneous form, of three further components, adducts-**B**, -**C** and -**D**. The mass spectrum of each of these showed them also to be 2:1 adducts of alkyne with starting carbazolenine.

In the hope that a less complex product mixture might be obtained in alternative solvents, reactions in dry ether and dry toluene were examined, but extremely complex product mixtures were obtained and these were not investigated further.



6
Adduct-A



7
Adduct-G

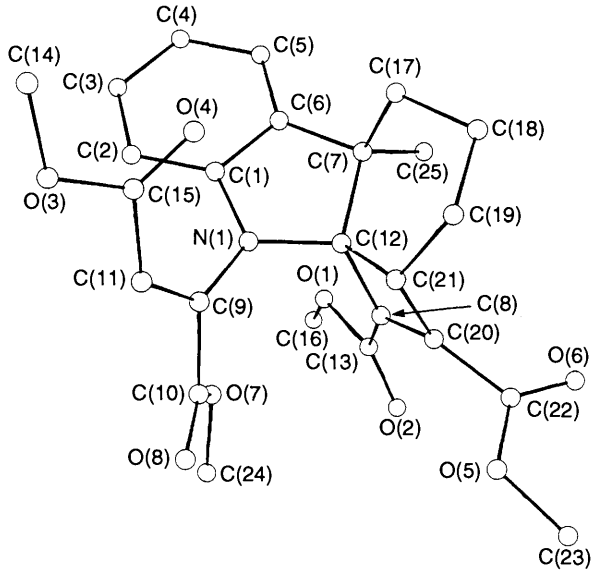


Fig. 1

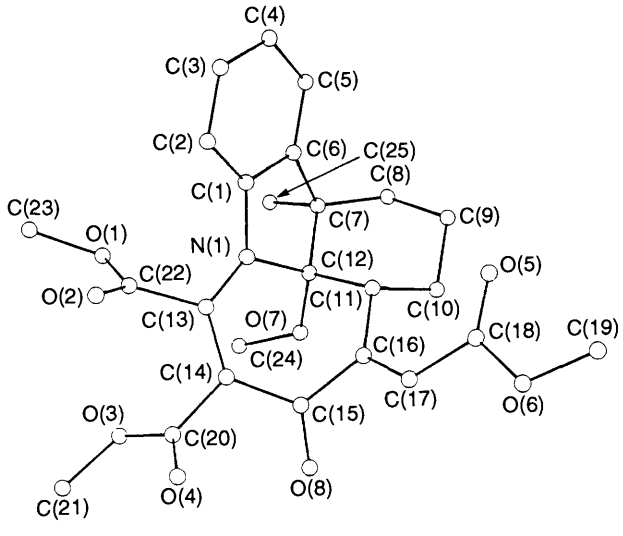


Fig. 2

From a reaction in dry hexane, despite there being a large proportion of material which ran on the base line in the solvent systems which were typically being used, four, further 2:1 adducts-**E**, -**F**, -**G** and -**H**, in order of elution, could be isolated in homogeneous form by semi-preparative HPLC of the crude reaction mixture. Adducts-**E**, -**G** and -**H** crystallised from methanol. Adduct-**G**, as yellow crystals, was found to diffract satisfactorily and was examined by X-ray analysis (see Experimental section for details) and shown to have the structure and relative stereochemistry, **7**. Adducts-**B**, -**C**, -**D** and -**F** remained amorphous.

It is possible to rationalise the formation of structures **6** and **7** based, in each case, on initial electrophilic attack at the nitrogen. Deprotonation of the resulting immonium cation would generate an enamine, **8**, to allow attack by a second acetylene at carbon (→ **9**). After appropriate proton transfers, collapse to a cyclobutene would generate structure **6**; intramolecular C-acylation (→ **10**) would lead to structure **7**.

Experimental

Reaction of 1,2,3,4-*Tetrahydro-4a-methyl-4a*H-*carbazole,* **2** *with Dimethyl Acetylenedicarboxylate in Acetonitrile; Adducts-**A**, -**B**, -**C**, -**D**.*—The carbazolenine, **2** (0.375 g, 2 mmol) was dissolved in dry acetonitrile (5 cm^3). The solution was cooled in ice while dimethyl acetylenedicarboxylate (0.5 cm^3, 4.1 mmol) was added dropwise. After 4 h at 0 °C solvent was removed under reduced pressure and the dark red-brown residue (*ca.* 1 g) purified.

Column chromatography (silica) gave a fast-running fraction, the ^{1}H NMR spectrum of which showed no aromatic signals, which was not investigated further. Pure adduct-**A** (293 mg, 31%) was eluted with 5% ethyl acetate–95% light petroleum (40–60), and crystallised from methanol giving red prisms, m.p. 98.5–100 °C. Further elution of the column did not achieve satisfactory separation and the remaining fractions were recombined (*ca.* 50 mg) and the components separated using preparative layer chromatography [silica, 50% ethyl acetate–50% light petroleum (40–60)]. Front running components were discarded because ^{1}H NMR analysis showed no aromatic signals; the remaining components were again unsatisfactorily separated, and after elution, were recombined (38 mg). Finally, using semi-preparative HPLC (silica; 40% ethyl acetate–60% hexane) it was possible to resolve the mixture and produce homogenous samples of adduct-**B** (12 mg, 1.3%), adduct-**C** (12 mg, 1.3%), and adduct-**D** (9 mg, 0.9%), each as pale brown gums.

Reaction of 1,2,3,4-*Tetrahydro-4a-methyl-4a*H-*carbazole,* **2** *with Dimethyl Acetylenedicarboxylate in hexane; Adducts-**E**, -**F**, -**G** and -**H**.*—To a solution of carbazolenine, **2** (0.5 g, 2.7 mmol) in dry hexane (10 cm^3) at 5 °C was added dimethyl acetylenedicarboxylate (0.73 cm^3, 5.9 mmol). After 20 h at 5 °C the solvent was evaporated under vacuum leaving a brown gum (*ca.* 1.3 g) which was purified using semi-preparative HPLC (silica, 30% ethyl acetate–70% hexane). In order of elution (polarity) there was obtained a homogeneous brown oil (70 mg, 5.5%), crystallisation of which (methanol) gave adduct-**E** as clumped yellow needles, m.p. 128–131 °C. A multi-component mixture (55 mg) was next eluted, ^{1}H NMR analysis of which showing the major component to be adduct-**A**. Further elution produced adduct-**F** (86 mg, 6.8%) as a yellow oil. The final two components, eluted pure from the column, could both then be crystallised from methanol, and were designated adduct-**G** (20 mg, 1.6%), m.p. 193–196 °C and, as the slowest-running component, adduct-**H** (46 mg, 3.6%), m.p. 161–162 °C.

Table 1 summarises spectroscopic and analytical data for the pure adducts.

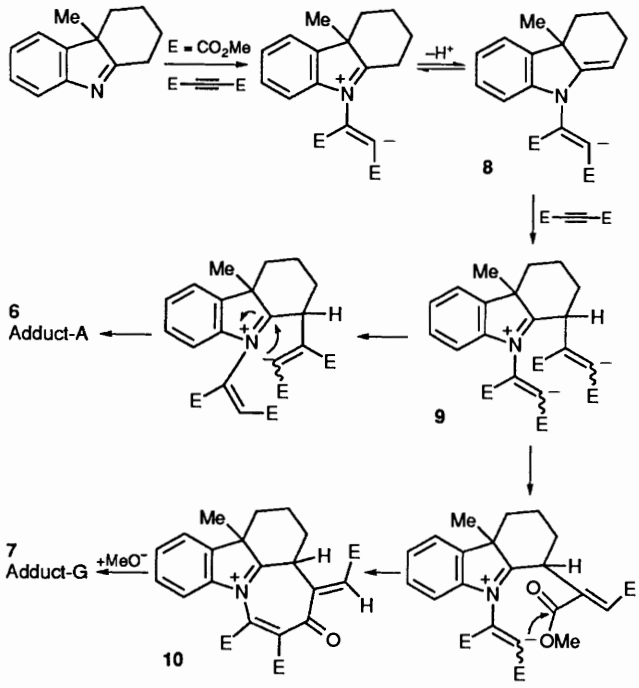
X-Ray Structure Determinations of Compounds **6** *and* **7**.—Crystals were prepared as detailed in the text. Two specimens with dimensions 0.70 × 0.25 × 0.10 and 0.60 × 0.20 × 0.20 mm for compounds **6** and **7** respectively, were mounted on glass fibres with an epoxy resin for use in the analyses.

Crystal data for cyclobutacarbazole **6**. $C_{25}H_{27}NO_8$, M = 469.5, orthorhombic, space group *Pbca* (No. 61), a = 18.026(1), b = 28.607(2), c = 9.190(1) Å, V = 4739.1(7) Å^3 (by least squares refinement on setting angles of 14 automatically centred reflections with 2θ values between 63 and 77°), Z = 8, D_x = 1.32 g cm^{-3}, μ(Cu-Kα) = 0.78 mm^{-1}.

Crystal data for azepinocarbazole **7**. $C_{25}H_{27}NO_8$, M = 469.5, triclinic, space group $P\bar{1}$ (No. 2), a = 11.186(2), b = 14.782(4), c = 7.124(4) Å, α = 99.04(3)°, β = 92.50(4)°,

Table 1 Experimental data for adducts-**A**–**H**

Name	Structure	M found (C,H,N%)	Formula (*M*) (C,H,N% calc.)	δ_H(C–Me)	δ_H(OMe)	δ_H ($\delta 4 \rightarrow 6$) (*J*/Hz)	λ_{max}(EtOH)/nm (log ε/dm^3 mol^{-1} cm^{-1})	ν_{max}(KBr disc)/cm^{-1}
Adduct-**A**	**6**	469.1707	$C_{25}H_{27}NO_8$ (469.1737)	1.45	3.43, 3.67, 3.72, 3.85		243 (4.25), 290 (3.48), 300 (3.40), 395 (3.40)	1596, 1619, 1649, 1725
Adduct-**B**		469.1732	$C_{25}H_{27}NO_8$ (469.1737)	1.32	3.63, 3.67, 3.71, 3.79	5.58 (1 H, bs)	255 (3.82), 304 (3.18), 391 (3.93)	
Adduct-**C**		469.1727	$C_{25}H_{27}NO_8$ (469.1737)	1.18	3.54, 3.60, 3.72, 3.79	5.18 (1 H, d, 5.5), 5.53 (1 H, d, 5.5)	249 (3.79), 298 (3.37), 400 (3.80)	
Adduct-**D**		469.1734	$C_{25}H_{27}NO_8$ (469.1737)	1.37	3.69, 3.70, 3.75, 3.85	5.75 (1 H, bs)	244 (3.40), 297 (2.98), 379 (3.36)	
Adduct-**E**		(64.0, 5.3, 3.0)	$C_{25}H_{27}NO_8$ (63.9, 5.8, 3.0)	1.15	3.39, 3.60, 3.78, 3.99, 4.02 (all *ca.* 1.5 H), 3.76 (*ca.* 4.5 H)		229 (3.84), 291 (3.71), 333 (4.26)	1565sh, 1719sh, 1748
Adduct-**F**		469.1721	$C_{25}H_{27}NO_8$ (469.1737)	1.25	3.58, 3.68, 3.84, 3.89		235 (4.05), 274 (3.80), 393 (3.45)	
Adduct-**G**	**7**	(63.6, 5.7, 3.2)	$C_{25}H_{27}NO_8$ (63.9, 5.8, 3.0)	1.49	3.58, 3.64, 3.80, 3.87	5.93 (1 H, d, 2.3)	240 (4.10), 389 (4.04)	1575, 1648, 1712, 1737
Adduct-**H**		(63.4, 5.8, 2.9)	$C_{25}H_{27}NO_8$ (63.9, 5.8, 3.0)	1.13	3.70, 3.73, 3.79, 4.03		261 (4.24), 289 (4.00), 416 (4.02)	1578, 1698, 1724, 1752



$\gamma = 94.51(2)°$, $V = 1158.0(1)$ Å^3 (by least squares refinement on setting angles of 22 automatically centred reflections with 2θ values between 40 and 51°), $Z = 2$, $D_x = 1.35$ g cm^{-3}, μ(Cu-Kα) = 0.80 mm^{-1}.

Data Collection and Processing.—Rigaku AFC5 diffractometer/RU200 rotating anode system at 22 °C using graphite monochromated Cu-Kα radiation. X-Ray settings 50 kV, 140 mA. For **6**: $\omega/2\theta$ mode with ω scan width = 1.26 + 0.3° tan θ, θ scan time 32.0° min^{-1}, 4009 measurements to 2θ limit of 120.1° giving 2290 with $I > 3\sigma(I)$, absorption correction by Ψ scans[9] minimum transmission 0.88, average transmission 0.96, Lorentz and polarization corrections applied, 1% decay correction on basis of standards monitoring. For **7**: $\omega/2\theta$ mode with ω scan width = 1.31 + 0.3° tan θ, θ scan time 16.0° min^{-1}, 2978 measurements to 2θ limit of 120.1° giving 2460 with $I > 3\sigma(I)$, absorption correction by Ψ scans[9] minimum transmission 0.90, average transmission 0.96, Lorentz and polarization corrections applied, 3% decay correction on basis of standards monitoring.

Structure Analysis and Refinement.—Both structures solved by direct methods (MITHRIL)[10] and refined by full-matrix least-squares method. Non-hydrogen atoms were treated anisotropically. Hydrogen atoms were all located from difference Fourier syntheses and subject to positional and isotropic refinement. All calculations were performed using the TEXSAN-TEXRAY crystallographic software package from Molecular Structure Corporation. The weighting scheme $w = 4F_o^2/\sigma^2(F_o^2)$ proved satisfactory. For **6**: $R = 0.052$, $R_w = 0.065$ [$w = 1/\sigma^2(F_o)$ for 2290 independent reflections with $I > 3\sigma(I)$]. For **7**: $R = 0.052$, $R_w = 0.066$ [$w = 1/\sigma^2(F_o)$ for 2460 independent reflections with $I > 3\sigma(I)$]. Neutral atomic scattering factors taken from the standard tables.[11]

Figs. 1 and 2 show PLUTO[12] plots for compounds **6** and **7**. Tables of atomic coordinates, bond lengths and angles, torsion angles, thermal parameters, structure factors and selected diagrams have been deposited at the Cambridge Crystallographic Data Centre.

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