High-pressure Synthesis, Structures, and Conformational Properties of Some Derivatives of 7-Azabicyclo[2.2.1]heptane. *X*-Ray Determination of *endo*-10-Benzoyl-4-phenyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione and *exo*-10-Acetyl-4-phenyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione

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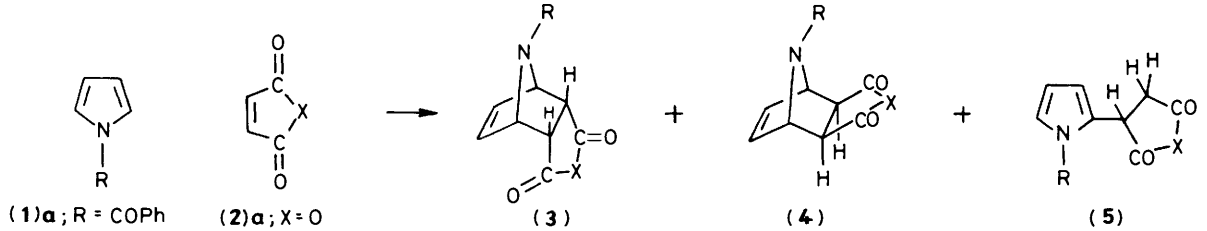
The syntheses, using pressures of up to 1.4 GPa, and the properties of Diels–Alder adducts of some *N*-acylated pyrroles are described. Both *exo* and *endo* adducts may be obtained and purified and are, in general, unstable with respect to the retro reaction. Progress towards a general synthesis of the 7-azabicyclo[2.2.1]heptane system is described. Structures of two of the adducts, those between *N*-phenylmaleimide (**2b**) and *N*-benzoylpyrrole (**1a**) and the dihydro adduct of (**2b**) with *N*-acetylpyrrole (**1b**), have been determined by *X*-ray crystallographic analysis. Examination of these structures by means of ^{1}H n.m.r. temperature-dependent spectra and nuclear Overhauser effect differences confirm that conformational isomerism is due to restricted rotation about the amide C–N bond, the energy barrier, 70 kJ mol^{-1}, being similar to that in acyclic amides.

Pyrrole and its derivatives, unlike furan, tend to be unreactive towards Diels–Alder cycloadditions.[1] Butynedioic acid and its esters will add in 10% yield to *N*-methylpyrrole[2] and in 8% yield to *N*-benzylpyrrole[3] but give rather better yields with *N*-carbonyl- or -sulphonyl-substituted pyrroles[1,4] to afford products such as the bicycles (**6**). Aluminium chloride can catalyse such reactions. Highly reactive dienophiles, such as arynes[5–7] or oxyallyl cations,[8] will, however, readily undergo the Diels–Alder reaction with *N*-alkyl- or -acyl-pyrroles. A further complication which may supervene is the extreme readiness of the pyrrole system to undergo substitution at C–2 forming products of type (**5**). Cycloadducts (**3**) and (**4**) or the hydrogenated derivates (**7**) are of interest as versatile precursors to a variety of compounds of potential pharmacological interest. We have sought more efficient means of potentiating cycloadditions of pyrroles, the most obvious being the application of external pressure. Volumes of activation of Diels–Alder reactions are among the most thoroughly studied and are of the order −30 to −40 cm^{-3} mol^{-1}.[9] This can imply a rate acceleration of about an order of magnitude at 100 MPa pressure, or 1.5 × 10^6 at 1 GPa [assuming a linear relationship between ln *k* and pressure, not (in practice) normally found to occur to this limit]. One may be confident in any event that pressure will greatly accelerate the cycloaddition and may also retard the retro reaction. We report the successful cycloadditions of a series of *N*-acylated pyrroles (**1**) with a variety of dienophiles (**2**) as well as dimethyl butynedioate at temperatures between ambient and 50 °C, utilising pressures in the range 1.0–1.4 GPa. Yields are high and products (**3**) and (**4**) uncontaminated by side-reactions. In most cases the *exo* isomers only were obtained but in others either or both *exo* and *endo* isomers were formed and could be readily separated. There is evidence that, in some cases at least, the *endo* isomers are formed under kinetic control and isomerise to the *exo* form. The structures of two of the products, (**3a**) and *exo*-(**7c**), were established by *X*-ray crystallographic analysis (Figure 1a and



(**1**)**a**; R = COPh
b; R = COMe
c; R = CO_2Et
d; R = CH_2Ph
e; R = CO_2CH_2Ph

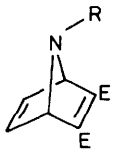
(**2**)**a**; X = O
b; X = NPh
c; X = NMe

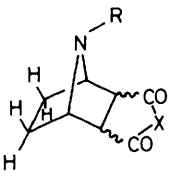
(**3**)

(**4**)

(**5**)

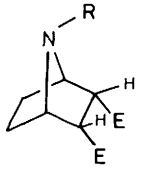
(**3**)–(**5**)**a**; R = COPh, X = NPh
b; R = COPh, X = O
c; R = COMe, X = NPh
d; R = COMe, X = O
e; R = CO_2Et, X = NPh
f; R = CO_2CH_2Ph, X = NPh
g; R = COC_6H_4Cl-*p*, X = NPh
h; R = CO_2Et, X = O
i; R = H, X = NPh
j; R = COPh, X = NMe
k; R = COMe, X = NMe





(6)a; E = CO_2Me, R = COPh
b; E = CO_2Me, R = COMe
c; E = CO_2Me, R = CO_2Et

(7)a; R = COPh, X = NPh
b; R = COPh, X = O
c; R = COMe, X = NPh
d; R = COMe, X = O
e; R = CO_2Et, X = NPh
f; R = CO_2CH_2Ph, X = NPh
g; R = COC_6H_4Cl-*p*, X = NPh
h; R = CO_2Et, X = O
i; R = H, X = NPh
j; R = COPh, X = NMe
k; R = COMe, X = NMe



(8)a; E = CO_2Me, R = COPh
b; E = CO_2Me, R = CO_2Et
c; E = CO_2Et, R = CO_2Me

b), and their conformational mobility was also studied using variable-temperature n.m.r. spectroscopy.

Experimental

High-pressure Equipment.—A double-walled cyclindrical pressure vessel (Psika, Ltd.) was fitted with a piston powered by a 100-tonne hydraulic ram, the whole being contained in a press frame. The experimental volume measured approximately 25 × 150 mm. Samples of up to 15 ml were placed in a poly(tetrafluoroethylene) (PTFE) cylindrical cell closed by a sliding stopper. This was placed within the cylinder which was filled with hydraulic fluid (Plexol 244) and the desired pressure was applied, monitored by a calibrated strain gauge directly connected to the cylinder. The temperature was controlled by an external heating jacket. Pressures up to 1.4 GPa and temperatures up to 100 °C could be employed. Light petroleum refers to that fraction boiling in the range 40—60 °C.

Alkyl- and Acyl-pyrroles (**1**).—N-*Benzoylpyrrole.* A suspension of potassium pyrrole (0.38 mol) in tetrahydrofuran (200 ml) was vigorously stirred under nitrogen at 0 °C, and benzoyl chloride (0.38 mol) was added dropwise during 15 min. The mixture was heated under reflux for 8 h, after which the precipitate of potassium chloride was removed by filtration and water (250 ml) was added to the filtrate. This was then extracted by dichloromethane (3 × 100 ml) and the extract was dried ($MgSO_4$), evaporated, and distilled *in vacuo* to give *N*-benzoylpyrrole (**1a**), b.p. 120 °C at 2 mmHg (0.35 mol, 92%).

In an analogous manner the following pyrroles were prepared, by replacing benzoyl chloride by the appropriate acyl or alkyl chloride: *N*-acetylpyrrole (**1b**) (90%), b.p. 180 °C at 760 mmHg;[10] *N*-ethoxycarbonylpyrrole (**1c**) (90%), b.p. 65 °C at 12 mmHg; *N*-benzylpyrrole (**1d**) (90%), b.p. 54 °C at 5 mmHg; *N*-benzyloxycarbonylpyrrole (**1e**) (85%), b.p. 110 °C at 5 mmHg.

Diels–Alder Adducts (**3**) and (**4**).—A typical preparation was as follows; *N*-benzoylpyrrole (**1a**) (4 g, 22 mmol) and *N*-phenylmaleimide (4 g, 23 mmol) were dissolved in ethyl acetate (10 ml) and the solution was placed in a PTFE cylinder and pressurised as described. The solution was maintained at 34 °C and 1.1 GPa for 18 h. On removal of the cylinder, and evaporation of the solvent, a white solid remained from which a mixture 7.3 g, 91%) of *exo* and *endo* adducts (**4a**) and (**3a**) in the approximate ratio 1:1 was isolated. Separation of the isomers was accomplished by flash chromatography on silica, with ethyl acetate–light petroleum (2:1) as eluant, from which the products emerged in the order (**3a**), then (**4a**); the respective R_F-values from t.l.c. on silica, with the same solvent system as developer, were 0.31 and 0.15. When the reaction was carried out in dichloromethane or benzene as solvent, the sole product isolated was the *endo* isomer (**3a**), Table 1. The following adducts were prepared. endo-10-*Benzoyl*-4-*phenyl*-4,10-*diazatricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene*-3,5-*dione* (**3a**) had m.p. 96.5—97 °C (decomp. on prolonged heating), *d* 1.332 g cm^{-3} (Found: C, 73.3; H, 4.7; N, 8.15. $C_{21}H_{16}N_2O_3$ requires C, 73.26; H, 4.65; N, 8.14%). The ^1H n.m.r. spectrum is shown in Figure 2a.

The corresponding *exo* isomer (**4a**) had m.p. 138 °C (Found: C, 73.1; H, 4.7; N, 8.0%).

Hydrogenation over 5% Pd–charcoal converted the adducts (**3a**) and (**4a**) to the corresponding 4,10-diazatricyclo-[5.2.1.$0^{2,6}$]decanes (**7**). endo-10-*Benzoyl*-4-*phenyl*-4,10-*diazatricyclo* [5.2.1.$0^{2,6}$]*decane*-3,5-*dione* [*endo*-(**7a**)] had m.p. 238 °C (Found: C, 72.6; H, 5.4; N, 8.1. $C_{21}H_{18}N_2O_3$ requires C, 72.83; H, 5.62; N, 8.09%). The exo *isomer* had m.p. 163 °C (Found: C, 72.9; H, 4.9; N, 8.0%).

exo Adducts (**4**) were readily distinguished from their *endo* isomers (**3**) in their ^1H n.m.r. spectra by the sharp singlet resonance due to 2- and 6-H at δ 2.9—3.8. By contrast, the *endo* isomers showed a broad resonance for these protons.

Other products were made in an analogous way. The adducts from maleic anhydride especially were thermally unstable even at room temperature and were usually characterised as the dihydro compounds (n.m.r. characteristics: u = unresolved).

endo-10-*Benzoyl*-4-*methyl*-4,10-*diazatricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene*-3,5-*dione* (**3j**), from *N*-benzoylpyrrole and *N*-methylmaleimide, had m.p. 118—119 °C (Found: C, 68.3; H, 4.9; N, 9.9. $C_{16}H_{14}N_2O_3$ requires C, 68.09; H, 4.96; N, 9.93%).

Dimethyl 7-*Benzoyl*-7-*azabicyclo*[2.2.1]*hepta*-2,5-*diene*-2,3-

Table 1. Summary of Diels–Alder reactions of acylpyrroles

Pyrrole (**2**) R =	Dienophile[a]	Solvent	Conditions *t*/°C	*t*/h	*P*/GPa	Yields (%) (**3**)	(**4**)	(**6**)
COPh	NPM	EtOAc	34	90	1.4	45	46	
		CH_2Cl_2	40	18	1.1			
			25	150	1.2	34	58	
		Benzene	25	60	1.1	0	80	
COPh	DMAD	None	25	24	1.3			40
COPh	MA	$CHCl_3$	24	160	1.1	0	25	
COPh	MA	EtOAc	25	300	1.2	20	0	
COPh	NMM	CH_2Cl_2	30	65	1.2	66	11	
COMe	NPM	CH_2Cl_2	30	20	1.0	0	84	
COMe	DMAD	EtOAc	30	20	1.2			10
COMe	MA	$CHCl_3$	20	150	1.1	35	0	
COMe	NMM	CH_2Cl_2	30	65	1.2	77		
CO_2Et	NPM	CH_2Cl_2	22	70	1.2		46	
CO_2Et	DMAD	EtOAc	24	100	1.2			35
CO_2Et	MA	CH_2Cl_2	24	160	1.2		26	
CO_2CH_2Ph	NPM	CH_2Cl_2	30	48	1.4	90	0	
COC_6H_4Cl-*p*	NPM	CH_2Cl_2	30	24	1.2	90	0	

[a] NPM = *N*-Phenylmaleimide (**2b**); NMM = *N*-methylmaleimide (**2c**); DMAD = dimethyl acetylenedicarboxylate (dimethyl butynedioate); MA = maleic anhydride (**2a**).

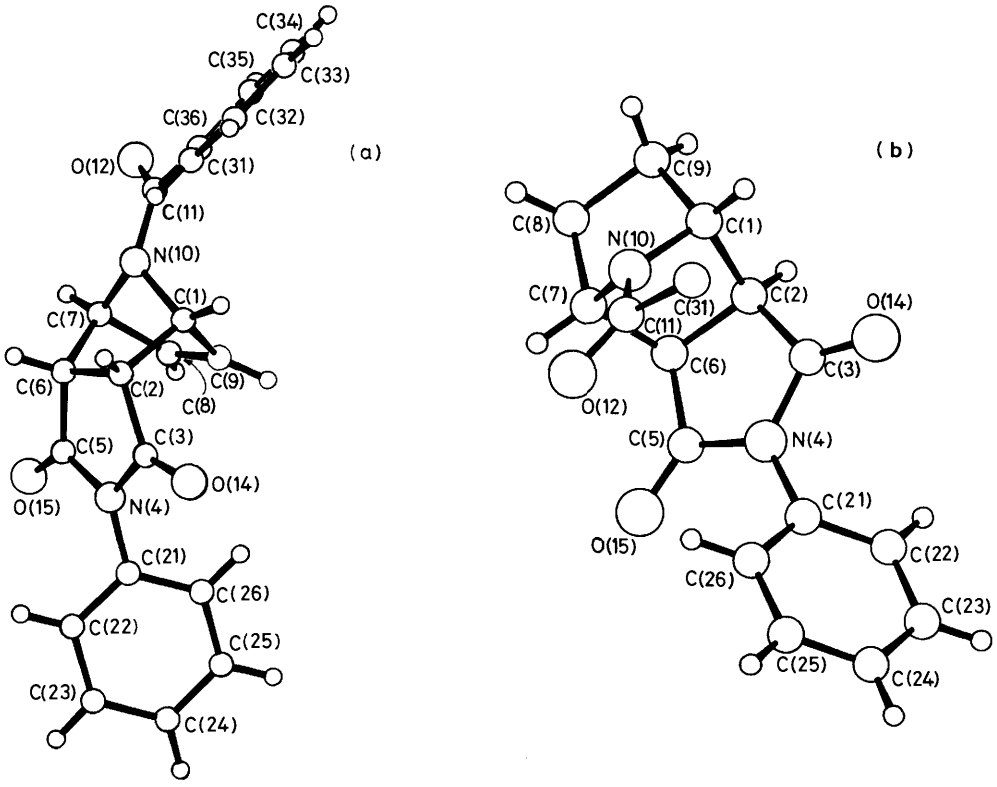


Figure 1. Projection structures from *X*-ray crystallographic data of (a) *endo*-10-benzoyl-4-phenyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**3a**), (b) *exo*-10-acetyl-4-phenyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione *exo*-(**7c**)

dicarboxylate (**6a**), from *N*-benzoylpyrrole and dimethyl butynedioate, had m.p. 75—76 °C (decomp.) (Found; C, 65.15; H, 4.9; N, 4.55. $C_{17}H_{15}NO_5$ requires C, 65.18; H, 4.79; N, 4.47%); δ_H ($CDCl_3$) 7.1—7.4 (2 H, u br d) and 5.6—6.0 (2 H, u br d).

Dimethyl endo-7-*Benzoyl*-7-*azabicyclo*[2.2.1]*heptane*-2,3-*dicarboxylate* (**8a**), by hydrogenation of (**6a**) (Found: 64.6; H, 5.9; N, 4.25. $C_{17}H_{19}NO_5$ requires C, 64.35; H, 5.99; N, 4.42%); δ_H ($CDCl_3$) 4.6 (2 H, vbr s), 3.3 (2 H, vbr s), 3.3 (2 H, vbr s), and 1.7—2.2 (4 H, br m).

exo-10-Benzoyl-4-oxa-10-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**4b**), from *N*-benzoylpyrrole and maleic anhydride, had m.p. 87 °C (decomp.); δ_H ($CDCl_3$) 6.65 (2 H, br s), 5.46 (2 H, br s), and 3.20 (2 H, s). The compound was thermally labile at 25 °C.

exo-10-Benzoyl-4-oxa-10-azatricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione (**7b**), by hydrogenation of (**4b**), had m.p. 195 °C; δ_H ($CDCl_3$) 4.93 (2 H, br t), 3.22 (2 H, s), and 1.5—2.05 (4 H, m); M^+, 271.2736; $C_{15}H_{13}NO_4$ requires *M*, 271.2744.

Exo-10-*Acetyl*-4-*phenyl*-4,10-*diazatricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene*-3,5-*dione* (**4c**), from *N*-acetylpyrrole and *N*-phenylmaleimide, had m.p. 129 °C (Found: C, 68.2; H, 5.0; N, 10.1. $C_{16}H_{14}N_2O_3$ requires C, 68.09; H, 4.96; N, 9.93%) (see Figure 2b).

exo-10-*Acetyl*-4-*phenyl*-4,10-*diazatricyclo*[5.2.1.$0^{2,6}$]*decane*-3,5-*dione* (**7c**), from hydrogenation of (**4c**), had m.p. 222—223 °C (Found: C, 67.7; H, 5.8; N, 9.8. $C_{16}H_{16}N_2O_3$ requires C, 67.60; H, 5.63; N, 9.86%); δ_H ($CDCl_3$) 4.6—5.2 (2 H, vbr d), 3.03 (2 H, br s), and 1.6—2.1 (4 H, m).

endo-10-acetyl-4-methyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**3k**), from *N*-acetylpyrrole and *N*-methylmaleimide, had m.p. 220—221 °C; δ_H ($CDCl_3$) 6.6 (2 H, vbr s), 5.05—5.2 (2 H, vbr d), and 2.9 (2 H, m).

endo-10-Acetyl-4-methyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]-decane-3,5-dione (**7k**), from hydrogenation of (**3k**), had m.p. 155—156 °C; δ_H ($CDCl_3$) 4.5—5.1 (2 H, vbr d), 2.9 (2 H, m), and 1.5—2.1 (4 H, m); M^+, 222.2447; $C_{11}H_{14}N_2O_3$ requires *M*, 222.2453.

Dimethyl 7-acetyl-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dioate (**6b**), from dimethyl butynedioate and *N*-acetylpyrrole, had been previously prepared by Kotsuki *et al.*[11]

endo-10-Acetyl-4-oxa-10-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**3d**), from *N*-acetylpyrrole and maleic anhydride, had m.p. 82 °C (decomp.); δ_H ([$^2H_6$]acetone) 6.6 (2 H, brs), 5.25 (2 H, t), and 3.4 (2 H, br s).

endo-10-*Acetyl*-4-*oxa*-10-*azatricyclo*[5.2.1.$0^{2,6}$]*decane*-3,5-*dione* (**7d**), by hydrogenation of (**3d**), had m.p. 151—152 °C (Found: C, 57.2; H, 5.9; N, 6.3. $C_{10}H_{11}NO_4$ requires C, 57.42; H, 5.26; N, 6.7%).

exo-10-*Ethoxycarbonyl*-4-*phenyl*-4,10-*diazatricyclo*-[5.2.1.$0^{2,6}$]*dec*-8-*ene*-3,5-*dione* (**4e**), from *N*-ethoxycarbonylpyrrole and *N*-phenylmaleimide, had m.p. 134 °C (decomp.) (Found: C, 65.1; H, 5.6; N, 8.9. $C_{17}H_{16}N_2O_4$ requires C, 65.38; H, 5.13; N, 8.91%).

exo-10-*Ethoxycarbonyl*-4-*phenyl*-4,10-*diazatricyclo*-[5.2.1.$0^{2,6}$]*decane*-3,5-*dione* (**7e**), by hydrogenation of (**4e**), had m.p. 124—125 °C (Found: C, 64.8; H, 5.85; N, 8.8. $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.73; N, 8.92%); δ_H ($CDCl_3$) 4.75 (2 H, m), 2.92 (2 H, s), and 1.4—2.1 (4 H, br m).

Dimethyl 7-ethoxycarbonyl-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**6c**), from *N*-ethyoxycarbonylpyrrole and dimethyl butynedioate, had m.p. 45—47 °C, δ_H ($CDCl_3$) 7.13 (2 H, t) and 5.41 (2 H, t).

Dimethyl *endo*-7-ethoxycarbonyl-7-azabicyclo[2.2.1]-heptane-2,3-dicarboxylate (**8c**) from the hydrogenation of (**6c**), showed δ_H ($CDCl_3$) 4.3 (2 H, br m), 3.1 (2 H, br m), and 1.6—2.0 (4 H, br m).

exo-10-*Ethoxycarbonyl*-4-*oxa*-10-*azatricyclo*[5.2.1.$0^{2,6}$]*dec*-

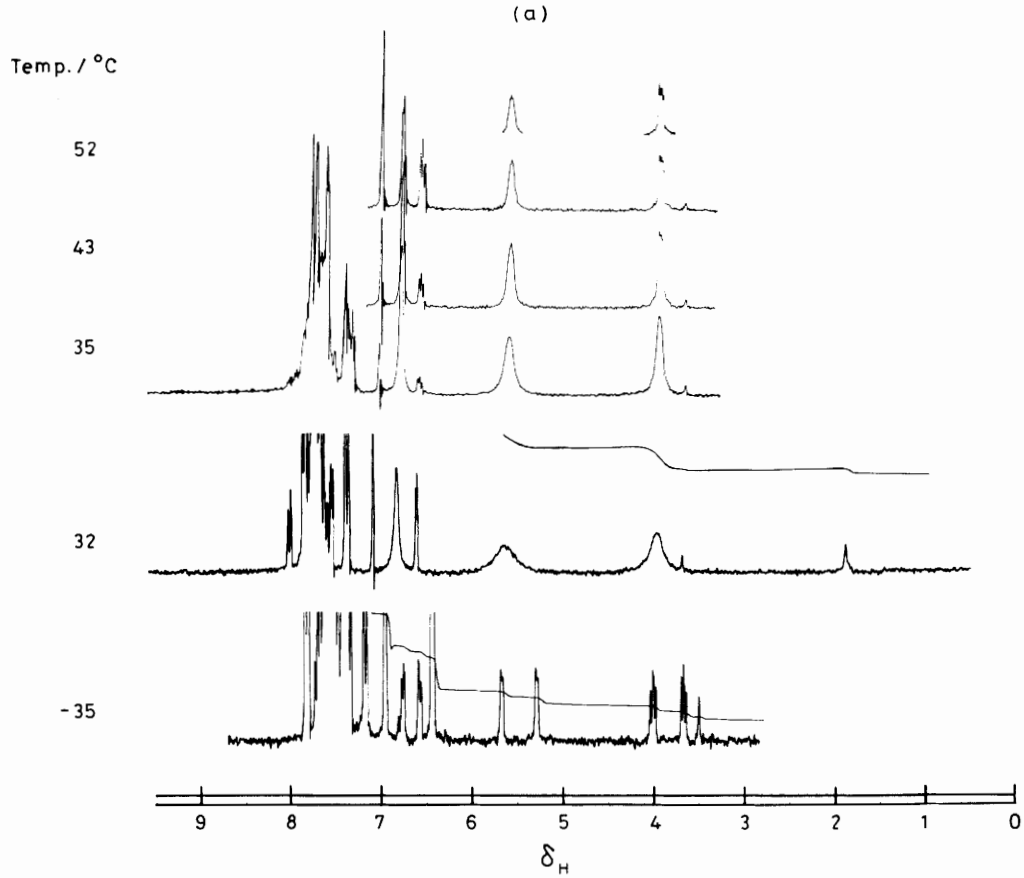


Figure 2. Temperature-dependent ^{1}H n.m.r. spectra at 250 MHz: (a) (**3a**), (b) (**4c**)

8-*ene*-3,5-*dione* (**4h**), from *N*-ethoxycarbonylpyrrole and maleic anhydride, had m.p. 90—91 °C (decomp.) (Found: C, 56.0; H, 4.4; N, 6.0. $C_{11}H_{11}NO_5$ requires C, 55.70; H, 4.64; N, 5.91%); δ_H ([$^2H_4$]methanol) 6.6 (2 H, t), 5.1 (2 H, br s), and 3.35 (2 H, s).

exo-N-*Ethoxycarbonyl*-4-*oxa*-10-*azatricyclo*[5.2.1.0^{2,6}]-*decane*-3,5-*dione* (**7h**), by hydrogenation of (**4h**), had m.p. 109.5—110 °C (Found: C, 54.9; H, 5.0; N, 5.9. $C_{11}H_{13}NO_5$ requires C, 55.23; H, 5.44; N, 5.85%).

exo-N-*Ethoxycarbonyl*-4-*oxa*-10-*azatricyclo*[5.2.1.0^{2,6}]-[5.2.1.0^{2,6}]*dec*-8-*ene*-3,5-*dione* (**4f**), from *N*-benzyloxypyrrole and *N*-phenylmaleimide, had m.p. 156 °C (Found: C, 70.4; H, 4.7; N, 7.55. $C_{22}H_{18}N_2O_4$ requires C, 70.6; H, 4.80; N, 7.48%).

endo-10-*Acetyl*-4-*methyl*-4,10-*diazatricyclo* [6.2.1.0^{2,6}]*dec*-8-*ene*-3,5-*dione* (**3k**) from *N*-acetylpyrrole and *N*-methylmaleimide had m.p.120 °C (Found: C, 60.2; H, 5.57; N, 12.7. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.45; N, 12.7%.

endo-10-*Acetyl*-4-*oxa*-10-*azatricyclo* [5.2.1.0^{2,6}]*dec*-8-*ene*-3,5-*dione*, (**3d**) from *N*-acetylpyrrole and maleic anhydride had m.p. 81—82 °C (decomp.), M^+ (mass spectroscopy), 207.0527; $C_{10}H_9NO_4$ requires *M*, 207.0531. Because of the instability of this compound even at room temperature it was converted by hydrogenation into (**7d**).

endo-10-*Acetyl*-4-*oxa*-10-*azatricyclo* [5.2.1.0^{2,6}]*decane*-3,5-*dione* had m.p. 151—152 °C (Found: C, 57.8; H, 5.36; N, 6.75. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.26; N, 6.70%).

Crystal Structure Determination.—For *X*-ray diffraction measurements, single crystals of compounds (**3a**) and *exo*-(**7c**) were mounted on a Stoe STADI2 diffractometer and data were collected *via* variable-width ω scan. Background counts were performed for 20 s and the scan rate of 0.033° s^{-1} was applied to a width of (1.5 + sin μ/tan θ). Crystal data and details of the data collection are given in Table 2. The two structures were solved by statistical methods using SHELX 76.[12] The heavy atoms were refined anisotropically. The hydrogen atoms were positioned in trigonal or tetrahedral positions at 0.95 Å from the appropriate carbon atom and were refined isotropically.

The structures were then refined using full-matrix least-squares using SHELX76.[12] The weighting schemes used were chosen to give equivalent values of $\omega\Delta^2$ over ranges of F_0 and (sin θ/λ). For both structures this was $\omega = 1/[\sigma^2(F) + 0.003 F^2]$ where $\sigma(F)$ was taken from counting statistics. The scattering factors were taken from International Tables.[13] Calculations were made using the CDC7600 computer at the University of Manchester Computer Centre.

Atomic co-ordinates for the two structures are listed in Tables 3 and 4. Details of interatomic distances and angles are listed in Table 5, and least-squares planes in Table 6. Thermal parameters for non-hydrogen atoms, and atomic co-ordinates for hydrogen atoms, are given for both compounds in Supplementary Publication No. SUP 56245 (7 pp.)*

Discussion

Attempted Diels–Alder reactions between *N*-methyl- or *N*-benzyl-pyrrole with *N*-phenylmaleimide or methyl butynedioate

* For details of the Supplementary Publications Scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1985 Issue 1. Structure factor tables are available from the editorial office on request.

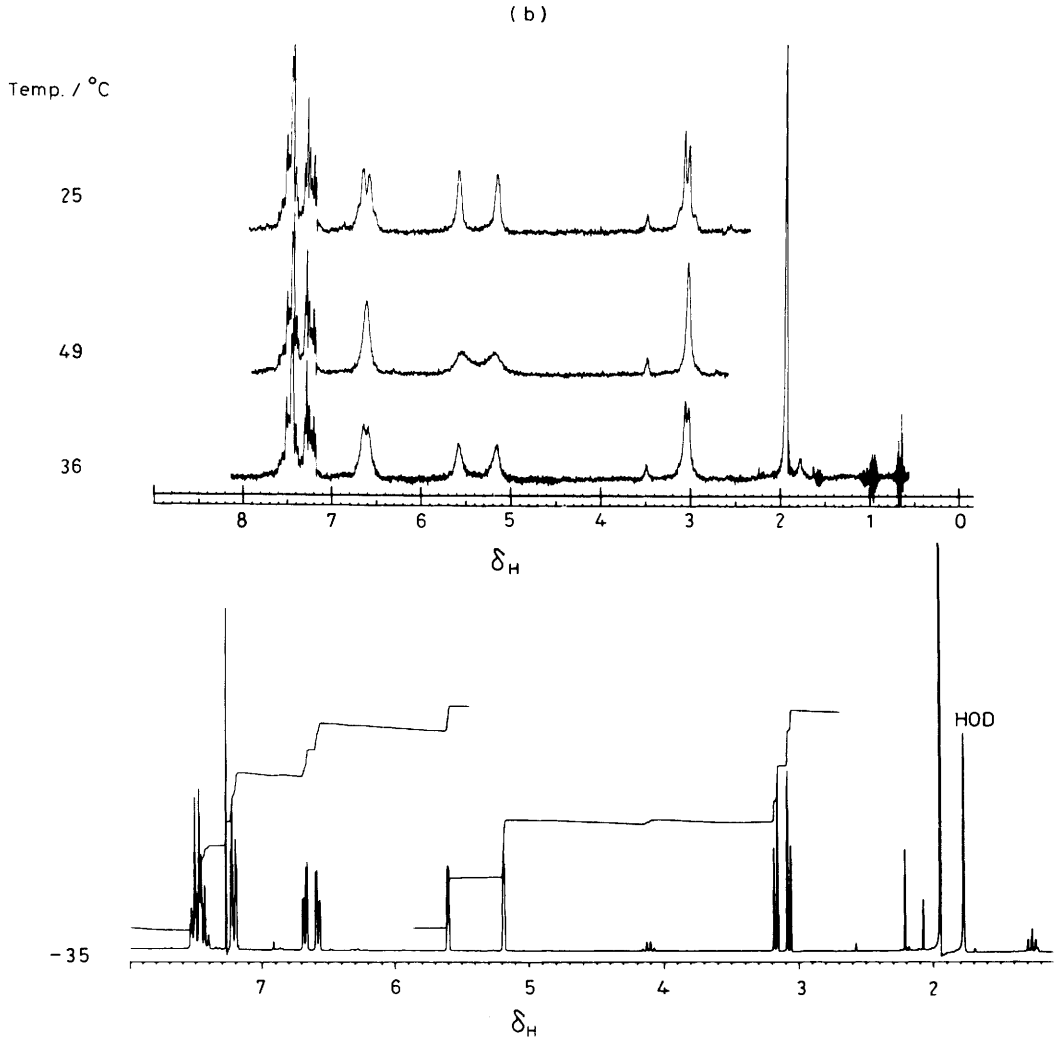


Figure 2. Temperature-dependent ^{1}H n.m.r. spectra at 250 MHz: (a) (**3a**), (b) (**4c**)

under high-pressure conditions failed, the products being those of substitution of the pyrrole (**5**). *N*-Acylpyrroles, on the other hand, underwent cycloaddition under these conditions with facility. The reasons for this difference in behaviour are evidently two-fold; a $-M$ group on nitrogen will reduce the tendency of electrophilic attack at the α-carbon by the dienophile, at the same time reducing the aromaticity of the pyrrole ring. This is presumably the cause of the reluctance of the parent system to undergo cycloaddition. Nonetheless, dienophiles of quite high reactivity are still required. Ethyl acrylate, for example, failed to react with *N*-benzoylpyrrole: acrylonitrile polymerised. At present it is not clear to what extent a failure to react is due to a small forward rate or a large retrograde rate. The acylpyrrole adducts with maleic anhydride (**3d**), (**4b**), and (**4h**) are formed in much lower yield than those of *N*-phenylmaleimide (**3a**, **c**, and **e**) and (**4a**, **c**, and **e**) and are very labile, reverting to the constituents at room temperature in the solid phase over a few days or in solution in a few hours. It seems likely that the low yields represent equilibrium amounts in which case even higher pressures would be desirable. This is clearly a further reason for the failure of all these reactions under thermal conditions at ambient pressure. The stereospecificity of the cycloaddition was variable and solvent-dependent. A change of medium from ethyl acetate to dichloromethane or benzene, for example, was accompanied by a change of *endo*/*exo* ratio in favour of the former in the formation of adducts (**3a**) and (**4a**). It might appear that the *endo* isomer is favoured by the less polar solvent in contrast [14] to the well documented behaviour of the cycloaddition of methyl acrylate to cyclopentadiene for which an increasing *endo*/*exo* ratio follows an increase in polarity. Evidently, in the present case this aspect of the solvent is not determining stereoselectivity. However, the ratios are dependent upon temperature and reaction time also and it is likely that the product ratios result from mixed kinetic and thermodynamic control which will require further study in order to be understood. Reduction of the cycloadducts by catalytic hydrogenation produced products of type (**7**) which were thermally stable. Hence, the pressure-promoted Diels–Alder reactions of acylpyrroles with a range of dienophiles provides a useful route to 7-azabicyclo[2.2.1]heptanes of potential pharmacological interest for which it would be desirable to remove the *N*-substituent before further structural elaborations. Compounds (**7a**—**d**) proved to be unexpectedly resistant both to basic and acidic hydrolysis. Consequently, the benzyloxycarbonyl derivative (**4f**) was prepared in the usual way since there are ample precedents for removal of a benzyloxycarbonyl group from such compounds by hydrogenolysis.[15] This is currently under investigation.

Structures and Conformational Isomerism.—The 100 MHz

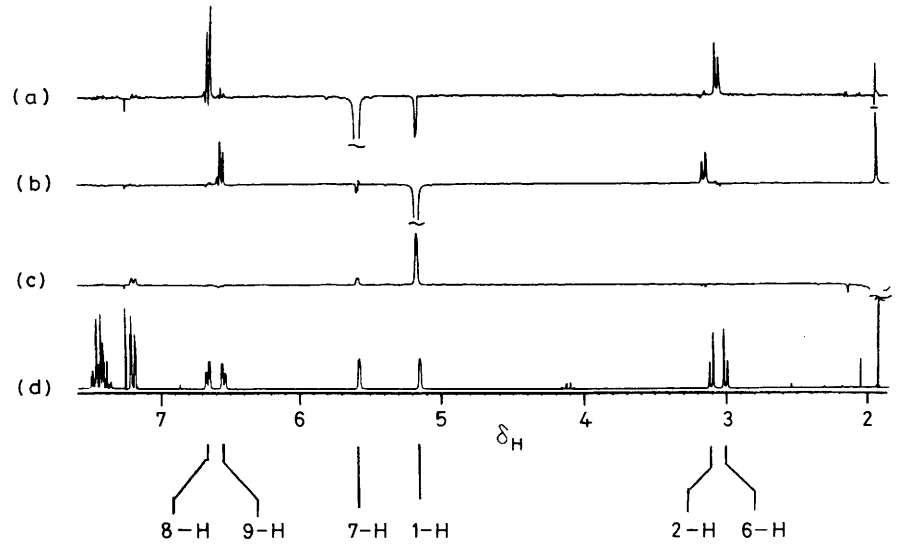


Figure 3. Difference spectra at 250 MHz and −33 °C for adduct (**4c**) showing nuclear Overhauser enhancements. (a) Saturation frequency applied to 7-H, enhancement for 6- and 8-H. No enhancement for 2-and 9-H. (b) Saturation frequency applied to 1-H, enhancement for 2-and 9-H, and $COCH_3$. No enhancement of absorption for 6- and 8-H. (c) Saturation frequency applied to $COCH_3$. Enhancement of 1-H only. (d) Absorption spectrum.

Table 2. Crystal data and refinement details

Compound	(**3a**)	*exo*-(**7c**)
Formula	$C_{21}H_{16}N_2O_3$	$C_{16}H_{15}N_2O_3$
M	344.1	283.1
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/n$	*Pcab* (No. 61)
Systematic absences	$0k0$, $k = 2n + 1$ $h0l$, $h + l = 2n + 1$	$hk0$, $k = 2n + 1$ $0kl$, $l = 2n + 1$ $h0l$, $h = 2n + 1$
a (Å)	17.189(11)	10.95(1)
b (Å)	6.836(7)	16.94(1)
c (Å)	15.182(11)	15.24(1)
β (°)	106.2(1)	(90)
V (Å^3)	1 713.1	2 826.9
F (000)	648	1 200
Z	4	8
D_m	1.33	1.34
D_c	1.33	1.35
μ (cm^{-1})	1.54	1.23
λ	0.7107	0.7107
$2\theta_{max.}$(°)	50	50
No. of data measured	2 298	2 017
No. of data used in refinement	1 101	1 089
Criterion for data inclusion	$I > 3\sigma(I)$	$I > 3\sigma(I)$
Final *R*-value	0.061	0.069

Table 3. Atomic co-ordinates (× 10^4) for (**3a**) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
C(1)	7 934(4)	338(9)	−590(4)
C(2)	7 731(4)	1 997(9)	−1 324(4)
C(3)	8 274(4)	2 046(12)	−1 930(5)
N(4)	8 783(3)	3 685(8)	−1 702(3)
C(5)	8 611(4)	4 755(11)	−1 001(5)
C(6)	7 916(4)	3 830(10)	−740(4)
C(7)	8 168(4)	2 990(9)	249(5)
C(8)	8 981(4)	1 983(10)	375(5)
C(9)	8 832(4)	413(9)	−144(4)
N(10)	7 605(3)	1 287(7)	99(3)
C(11)	7 403(4)	389(10)	798(5)
O(12)	7 567(3)	1 077(7)	1 562(3)
C(31)	6 932(4)	−1 484(9)	567(4)
C(32)	7 016(4)	−2 898(10)	1 239(5)
C(33)	6 601(5)	−4 656(11)	1 063(6)
C(34)	6 082(5)	−4 964(11)	222(6)
C(35)	5 968(5)	−3 590(13)	−452(6)
C(36)	6 398(4)	−1 819(11)	−273(5)
O(14)	8 312(4)	879(8)	−2 513(3)
O(15)	9 002(4)	6 226(8)	−663(4)
C(21)	9 462(4)	4 026(9)	−2 037(4)
C(22)	9 553(4)	5 832(10)	−2 414(5)
C(23)	10 241(6)	6 090(16)	−2 724(5)
C(24)	10 811(6)	4 640(19)	−2 643(6)
C(25)	10 686(5)	2 867(16)	−2 276(6)
C(26)	10 026(4)	2 585(12)	−1 962(5)

^{1}H n.m.r. spectra of several of the adducts, though of evidently pure compounds, showed unexpected features, notably broad resonances corresponding to the bridgehead protons 1- and 7-H (δ_H 5.4) and 2- and 6-H (δ_H 3.75) and also the olefinic protons 8- and 9-H (δ_H 6.6) (Figure 2a). These all become sharp at lower temperatures and, for compound (**3a**) at −35 °C under 250 MHz resolution, can be discerned as doublet doublet, doublet quartet, and doublet quartet, respectively. For *endo* isomers, the coupling constant $J_{1,2}$ is 8 Hz whereas for *exo* isomers, $J_{1,2} \sim 0$: other coupling constants ($J_{7,8}$ 2.3; $J_{8,9}$ 5.8; $J_{2,6}$ 6.7 Hz) are consistent with the proposed structures. The temperature dependence is evidently due to the freezing of conformational interchange and shows that at low temperatures the pairs of protons 1- and 7-H, 2- and 6-H, and 8- and 9-H become non-equivalent, resonating with different chemical shifts and showing mutual coupling. The obvious internal motion which may give rise to such an effect is restricted rotation about the amide C–N bond. That this is correct was confirmed for adduct (**4c**) by the observation of a large nuclear Overhauser effect (n.O.e.) between protons of the acetyl group and that of 1-H but not with the corresponding proton on the other side of the ring, 7-H (Figure 3).

These results point to the lack of a plane of symmetry in the low-temperature conformers of the adducts and consequently indicate that the carbonyl substituents lie in or near the plane of the atoms C–1, N–10, and C–7, rather than orthogonal to it, a

Table 4. Atomic co-ordinates ($\times 10^4$) for (**7c**) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
C(1)	2 966(5)	2 811(3)	6 904(4)
C(2)	3 711(5)	2 604(3)	6 063(3)
C(3)	3 569(5)	1 734(3)	5 816(3)
N(4)	2 885(4)	1 690(2)	5 046(3)
C(5)	2 551(5)	2 437(3)	4 723(3)
C(6)	3 022(5)	3 051(3)	5 349(3)
C(7)	1 980(6)	3 456(3)	5 863(4)
C(8)	2 518(6)	4 130(4)	6 411(5)
C(9)	3 214(6)	3 679(3)	7 132(4)
N(10)	1 727(4)	2 866(3)	6 545(3)
C(11)	840(6)	2 296(3)	6 479(4)
C(31)	940(6)	1 622(4)	7 134(4)
O(12)	18(4)	2 344(3)	5 951(3)
O(14)	3 949(4)	1 166(2)	6 219(3)
O(15)	1 963(4)	2 528(2)	4 054(3)
C(21)	2 595(5)	956(3)	4 614(3)
C(22)	3 527(5)	446(3)	4 361(3)
C(23)	3 243(6)	−250(3)	3 922(4)
C(24)	2 054(6)	−424(3)	3 726(4)
C(25)	1 120(6)	80(3)	3 977(4)
C(26)	1 402(5)	784(3)	4 425(4)

Table 5. Dimensions in compounds (**3a**) and *exo*-(**7c**). Bond distances (Å) and angles (°)

(i) Bond distances	(**3a**)	*exo*-(**7c**)
C(1)–C(2)	1.560(8)	1.559(7)
C(1)–C(9)	1.504(8)	1.536(7)
C(1)–N(10)	1.471(7)	1.465(7)
C(2)–C(3)	1.483(9)	1.528(7)
C(2)–C(6)	1.517(9)	1.527(7)
C(3)–N(4)	1.403(9)	1.394(7)
C(3)–O(14)	1.207(8)	1.216(6)
N(4)–C(5)	1.389(8)	1.406(6)
N(4)–C(21)	1.418(8)	1.444(6)
C(5)–C(6)	1.498(9)	1.502(7)
C(5)–O(15)	1.239(9)	1.217(6)
C(6)–C(7)	1.552(9)	1.545(8)
C(7)–C(8)	1.521(9)	1.532(8)
C(7)–N(10)	1.490(8)	1.469(7)
C(8)–C(9)	1.313(9)	1.539(9)
N(10)–C(11)	1.353(8)	1.374(7)
C(11)–O(12)	1.209(7)	1.210(7)
C(11)–C(31)	1.503(9)	1.520(9)
C(31)–C(32)	1.384(8)	
C(31)–C(36)	1.367(9)	
C(32)–C(33)	1.385(9)	
C(33)–C(34)	1.354(10)	
C(34)–C(35)	1.363(10)	
C(35)–C(36)	1.405(10)	
C(21)–C(22)	1.388(9)	1.391(7)
C(21)–C(26)	1.364(9)	1.369(7)
C(22)–C(23)	1.400(10)	1.390(7)
C(23)–C(24)	1.374(12)	1.368(8)
C(24)–C(25)	1.375(12)	1.386(8)
C(25)–C(26)	1.362(10)	1.408(7)
(ii) Bond angles		
C(2)–C(1)–C(9)	107.1(4)	108.0(5)
C(2)–C(1)–N(10)	97.7(4)	101.1(4)
C(9)–C(1)–N(10)	102.4(4)	100.8(4)
C(1)–C(2)–C(3)	113.9(5)	111.5(4)
C(1)–C(2)–C(6)	102.4(4)	102.4(4)
C(3)–C(2)–C(6)	106.2(5)	104.6(4)
C(2)–C(3)–N(4)	108.7(6)	108.3(4)
C(2)–C(3)–O(15)	127.7(6)	127.1(5)
N(4)–C(3)–O(15)	123.5(6)	124.5(5)
C(3)–N(4)–C(5)	111.0(5)	112.7(4)

Table 5 (*continued*)

(ii) Bond angles	(**3a**)	*exo*-(**7c**)
C(3)–N(4)–C(21)	124.2(5)	123.3(4)
C(5)–N(4)–C(21)	124.1(5)	124.0(4)
N(4)–C(5)–C(6)	109.6(6)	108.2(4)
N(4)–C(5)–O(15)	122.5(6)	123.0(4)
C(6)–C(5)–O(15)	127.8(6)	128.8(5)
C(2)–C(6)–C(5)	104.3(5)	106.2(4)
C(2)–C(6)–C(7)	102.5(4)	102.9(4)
C(5)–C(6)–C(7)	112.6(5)	112.1(4)
C(6)–C(7)–C(8)	106.7(4)	108.9(5)
C(6)–C(7)–N(10)	98.5(5)	101.3(4)
C(8)–C(7)–N(10)	101.6(4)	101.2(4)
C(7)–C(8)–C(9)	106.0(5)	102.1(5)
C(1)–C(9)–C(8)	107.6(5)	103.1(5)
C(1)–N(10)–C(7)	95.2(4)	97.6(4)
C(1)–N(10)–C(11)	126.3(5)	129.6(4)
C(7)–N(10)–C(11)	122.2(5)	124.0(5)
N(10)–C(11)–O(12)	122.2(6)	121.9(5)
N(10)–C(11)–C(31)	116.3(5)	115.4(5)
O(12)–C(11)–C(31)	121.5(6)	122.7(5)
C(11)–C(31)–C(32)	119.0(6)	
C(11)–C(31)–C(36)	122.6(5)	
C(32)–C(31)–C(36)	118.4(6)	
C(31)–C(32)–C(33)	121.5(7)	
C(32)–C(33)–C(34)	119.0(7)	
C(33)–C(34)–C(35)	121.3(7)	
C(34)–C(35)–C(36)	119.4(7)	
C(31)–C(36)–C(35)	120.3(6)	
N(4)–C(21)–C(22)	119.5(6)	120.0(5)
N(4)–C(21)–C(26)	119.2(6)	119.3(4)
C(22)–C(21)–C(26)	121.2(6)	119.4(5)
C(21)–C(22)–C(23)	117.0(7)	119.7(5)
C(22)–C(23)–C(24)	121.8(8)	120.0(5)
C(23)–C(24)–C(25)	119.0(7)	120.6(5)
C(24)–C(25)–C(26)	120.4(9)	119.6(5)
C(21)–C(26)–C(25)	120.7(8)	119.5(5)

conclusion confirmed by the *X*-ray structures of the adduct (**3a**) and a hydrogenated adduct (**7c**). This is the normal stable conformation for an amide[16–18] and the barrier height observed (69.5 ± 1.5 kJ mol^{-1}; *k* (310 K) 30 s^{-1} is of a similar magnitude to those of other amides (both acyclic and cyclic), which is commonly found to fall within the range 65—85 kJ mol^{-1}. A further feature of the spectra is the solvent dependence. Spectra similar to those of Figure 2 are found for compounds (**4**) in deuteriated solvents chloroform, dichloromethane, acetonitrile, methanol, pyridine, and trifluoroacetic acid, whereas in [$^2H_6$]dimethyl sulphoxide and [$^2H_6$]*N*,*N*-dimethylformamide the two resonances of 1–H and 7–H are coincident, others being unaffected. This may be due to a difference in the solvation of the amide group, though for no clear reason.

Discussion of the Structures

The structures of two products, (**3a**) and (**7c**), are shown in Figures 1a and 1b together with the atomic numbering scheme adopted for each and common for the central tricyclic system (**8**). The conformations of the molecules are best described by the least-squares planes in Table 6. The angle between plane 1 [atoms C(1), C(9), C(8), and C(7)] and plane 3 [atoms C(2), C(3), N(4), C(5), and C(6)] is 55.1° in (**3a**) which has the *endo* conformation and 4.4° in (**7c**) which has the *exo* conformation and the dihydro structure.

Apart from this major difference in conformation, several aspects of the molecular shape are common to both compounds (**3a**) and (**7c**). Thus of the two nitrogen atoms in the structure, N–4 is closely trigonal planar; for (**3a**) it is 0.07 Å and for (**7c**) it

Table 6. Least-squares planes for (**3a**) and *exo*-(**7c**). Distances of atoms from the planes are given in Å. Values for (**3a**) are given before those of *exo*-(**7c**). Atoms not contributing to the planes are marked by an asterisk

Plane 1: C(1) 0.00, 0.00; C(7) 0.00, 0.00; C(8) 0.01, 0.00; C(9) −0.01, 0.00; C(2)* −1.32, −1.40; C(6)* −1.34, −1.39; N(10)* 0.72, 0.81

Plane 2: C(1) 0.01, 0.00; C(2) −0.01, 0.00; C(6) 0.01, 0.00; C(7) −0.01, 0.00; N(10)* 0.85, 0.80

Plane 3: C(2) 0.02, −0.01; C(3) −0.01, −0.00; N(4) −0.00, 0.01; C(5) 0.02, 0.01; C(6) −0.02, 0.01; O(14)* −0.02, 0.03; O(15)* 0.08, −0.02; C(1)* 1.54, 1.35; C(7)* 1.43, 1.36; C(21)* 0.20, −0.02

Plane 4: C(21) −0.00, −0.02; C(22) 0.00, −0.00; C(23) −0.01, −0.00; C(24) 0.01, 0.01; C(25) −0.01, 0.00; C(26) 0.01, −0.01; N(4)* 0.02, 0.02

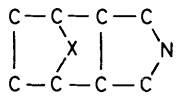
Plane 5: [(**3a**) only] C(31) 0.01; C(32) 0.01; C(33) 0.01; C(34) 0.00; C(35) −0.00; C(36) −0.00; C(11)* 0.00; N(10)* 0.56; O(12)* −0.52

Plane 6: C(11), N(10), and O(12) each 0.00, 0.00; C(13)* 0.05, 0.01

Plane 7: C(1), C(7), and C(11) each 0.00, 0.00; N(10)* 0.37, 0.24

Angles between planes (°)

1 and 2: 56.2, 67.5; 1 and 3: 55.1 and 4.4; 2 and 3: 68.8, 63.2; 3 and 4: 63.3, 55.8; 5 and 6 [(**3a**) only]: 29.2



(**9**)

is 0.03 Å from the plane of the three carbon atoms, C(3), C(5), and C(21), to which it is bonded. By contrast N-10 is approximately pyramidal, being 0.33 Å[(**3a**)], and 0.24 Å [(**7c**)] from the plane of atoms C(1), C(7), and C(11).

It is noteworthy that in both structures the conformation of the phenyl ring attached to the maleimide nitrogen is similar and makes angles of 55.3° [(**3a**)] and 55.8° [(**7c**)] with the adjacent five-membered ring [plane 3—atoms C(2), C(3), N(4), C(5), and C(6)]. Clearly an angle of 0° would be most suitable for delocalisation between the two rings but this would involve impossibly close contacts between the carbonyl oxygens and the phenyl hydrogen atoms. The angles of *ca.* 55° are thus a compromise between steric and electronic effects. In adduct (**3a**), the phenyl ring of the amide group is twisted such that the angle between the N(10)–C(11)–O(12) plane and the phenyl ring is 31.8°. The Cambridge Data Centre files were searched for structures containing the moiety (**9**). Nineteen examples, almost equally split between *endo* and *exo* types, were found with bridging atoms X = O, N, and C. The two structures (**3a**) and (**7c**) and these molecules had many features in common. The list included structures with both single and double bonds at C(8) and C(9). However in no case did this affect the conformation as the C(7)–C(8)–C(9)–C(1) torsion angles were all less than 2.3°. In compounds (**3a**) and (**7c**), the C(1)–N(10)–C(7) angles are 95.2(4) and 97.6(4)° respectively. In the 21 structures now available for comparison, this angle ranges from 91.0 to 99.0° with a mean of 94.7°. There seems no consistent difference in the (1–10–7) angle whether the central atom is N, O, or C.

It is interesting to compare the angles between planes in the various structures which have very different subsituents on the basic 10-atom core. For *exo* structures, the angles between planes 1 and 3 range from 0.1 to 9.0° with a mean of 4.2°. For *endo* structures, the angles range from 48.7 to 58.3° with a mean of 51.6°. The values for compounds (**3a**) and (**7c**) fall well within this range. The constrained structure therefore has just one basic shape and because of steric constraints substituent groups can cause very little structural change. In both structures there are no significant intramolecular contacts less than the sum of Van der Waals radii.

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