Conformations of Derivatives of 3,7-Diazabicyclo[3.3.1]nonan-9-one. Comparison of 3-Ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-diazabicyclo-[3.3.1]nonan-9-one and 3,7-Di(ethoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one: Effect of a Nucleophile ••• Electrophile Interaction on Molecular Geometry

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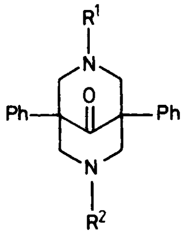
X-Ray analyses of 3-ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**4**) and 3,7-di(ethoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**5**) have established that both molecules adopt twin-chair conformations. In compound (**5**) the urethane N atoms have the expected nearly coplanar arrangement of bonds whereas in compound (**4**) the urethane N atom has a distinctly pyramidal pattern of bonds; the N–CO_2Et bond in (**4**) is bent out of the CH_2–N–CH_2 plane towards the NMe group so that the N ••• C separation between the NMe and CO_2Et groups is 2.665 Å whereas the corresponding distances in compound (**5**) are 3.363 and 3.150 Å. The results demonstrate the existence of an attractive nucleophile–electrophile interaction in (**4**).

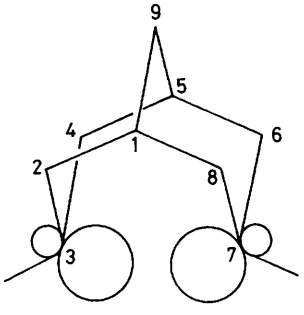
In studies of the conformational effects of non-bonding electrons, an investigation of *N,N'*-disubstituted derivatives of 1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**1**) found that the pyramidal or planar bonding pattern of the N(3) and N(7) atoms is related to the preference for the boat–chair or twin-chair conformation.[1] When the geometry at N is markedly pyramidal, *e.g.* for alkyl or arylsulphonyl *N,N'*-substituents, the twin-chair conformation has appreciable concentration of lone-pair electron density in the *endo* region [see (**2**)] and the alternative boat–chair conformation is favoured. When the geometry at N is planar, *e.g.* for acyl *N,N'*-substituents, the lone-pair electron density is distributed equally between *endo* and *exo* lobes [see (**3**)], reducing electron repulsion in the twin-chair conformation and favouring adoption of this rather than the alternative boat–chair conformation; moreover, substituents that induce sp^2 hybridization at N also result in delocalization of the lone-pair electron density away from N, reducing further the 3 ••• 7 electron repulsion.

In examining this conformational switch in more detail we prepared 3-ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**4**), with an acyl group at N(3) and an alkyl group at N(7), and compared the molecular geometry with that of 3,7-di(ethoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**5**) which has acyl groups at both N(3) and N(7) and adopts the twin-chair conformation in the crystal.[1] The crystal structures were determined by direct phasing procedures[2] and Figures 1 and 2 show the molecular details. Compound (**4**) proved to have a twin-chair conformation with N(3) ••• N(7) 2.753(3) Å, significantly shorter than the N(3) ••• N(7) separation of 2.801(3) Å in compound (**5**). For comparison, compound (**6**), which has alkyl groups at both N(3) and N(7), is constrained to a twin-chair conformation by the bulky spiro hydantoin at C(9) and the increased N(3) ••• N(7) separation of 2.873 Å reflects the *endo* electron repulsion between sp^3 hybridized pyramidal N atoms.[3]

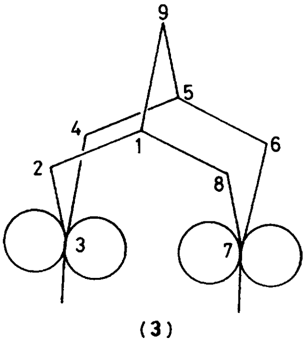
In assessing the factors responsible for the conformation of (**4**) we observed that the C(22) ••• N(7) distance of 2.665 Å in (**4**) is appreciably shorter than the C(25) ••• N(3) and C(22) ••• N(7) distances of 3.363 and 3.150 Å in the *N,N'*-di(ethoxycarbonyl) compound (**5**) and the contraction involves the N(3)–C(22) bond in (**4**) being bent out of the C(2)N(3)C(4) plane by 26.4° in the direction of N(7). Molecular distortions reminiscent of those in (**4**) have been reported in a series of 1,8-disubstituted naphthalenes (**7**) with a nucleophilic centre, *e.g.* NMe_2, at one of the *peri* positions and an electrophilic centre, *e.g.* carbonyl C, at the other.[4] The compounds (**7**) do not suffer the usual repulsive interactions that characterise other 1,8-disubstituted naphthalenes[5] and their N ••• C distances of *ca.* 2.6 Å are distinctly shorter than the distances in symmetrically 1,8-disubstituted naphthalenes. There is a small, but significant, pyramidalisation of the carbonyl group in (**7**) and the unusual geometries have been attributed to an incipient addition of a nucleophile to a carbonyl electrophile.[4] The situation in (**4**) can



(**1**)
(**4**) R^1 = Me ; R^2 = CO_2Et
(**5**) R^1 = R^2 = CO_2Et



(**2**)



(**3**)

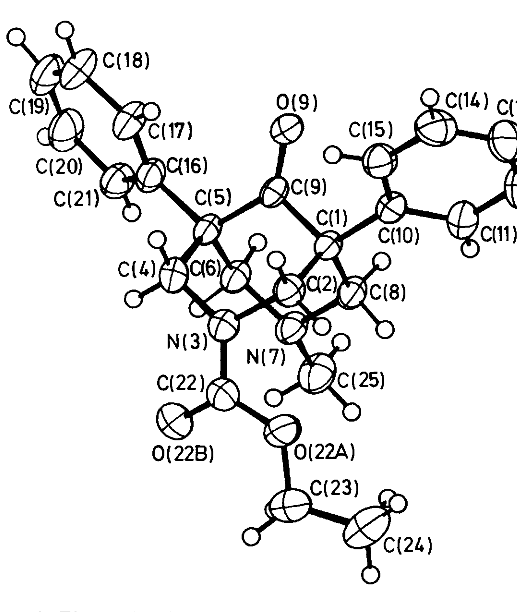


Figure 1. The molecular structure of 3-ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**4**). The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level and the H atoms are represented by spheres of radius 0.1 Å.

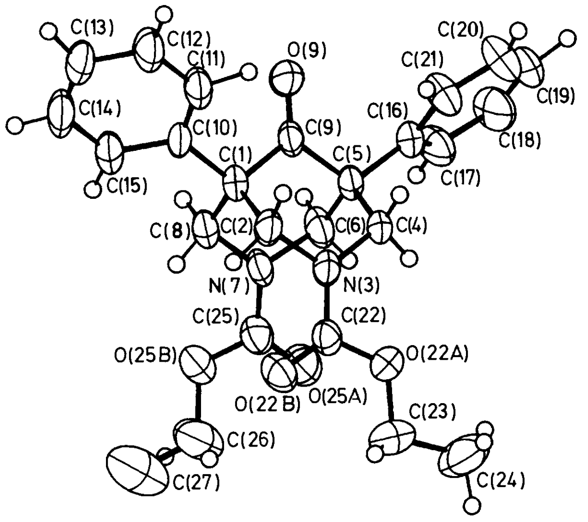
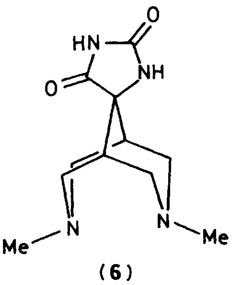
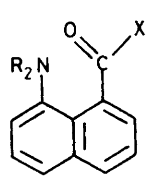


Figure 2. The molecular structure of 3,7-di(ethoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**5**). The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level and the H atoms are represented by spheres of radius 0.1 Å.



(**6**)



(**7**)

Table 1. Comparison of the nucleophile/electrophile interactions in compounds (**4**) and (**7**).

	(4)	(7)
N ··· C/Å	2.665(3)	2.557–2.594
Δ_N(nucleophile)[a]/Å	0.430(2)	0.386–0.402
Δ_C(electrophile)/Å	0.021(3)	0.061–0.088
N ··· C=O/°	98.5(2)	98.6–104.4
N ··· C–OR/°	94.3(2)	92.5–94.4

[a] Δ_N and Δ_C are the displacements of the N and carbonyl C atoms from the planes of their three bonded atoms.

Table 2. Structural details of compounds (**4**) and (**5**).[a]

	(4)		(5)	
	N(3)	N(7)	N(3)	N(7)
Δ_N/Å	0.231	0.430	0.052	0.031
φ/°	26.4	49.6	6.0	3.7
χ_N/°	33.0	—	7.8	5.7
χ_C/°	3.1	—	2.0	0.8
τ/°	0.6	—	5.1	2.4
N–CO/Å	1.361	—	1.338	1.335
N ··· N/Å	2.753	—	2.801	—

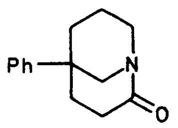
[a] Δ_N Is the displacement of the N atom from the plane of the three atoms bonded to N. φ is the angle between N–C(exocyclic) bond and CH_2–N–CH_2 plane. χ_N, χ_C, and τ are defined in the text.

be described in like terms and a detailed comparison of the nucleophile/electrophile interactions in (**4**) and (**7**) is provided in Table 1. The carbonyl C(22) in (**4**) has less pyramidal character than the carbonyl C atoms in (**7**) and this can be related to the N(7) ··· C(22) separation in (**4**) being a little larger than the corresponding N ··· C separations in (**7**).

Other structural details of (**4**) and (**5**) are listed in Table 2. Atom N(7) in compound (**4**) is displaced by 0.430(2) Å from the C(6)C(8)C(25) plane, equivalent to the N–CH_3 bond being inclined at 49.6° to the CH_2–N–CH_2 plane. For comparison, in 1,3,5-tribenzyl-1,3,5-triazacyclohexane, the N–CH_2Ph bonds are inclined to their CH_2–N–CH_2 planes at 42.9–54.8, mean 48.1°;[6] in NH_3 the out-of-plane angle is 60.3°[7] and in NMe_3 it is *ca.* 56°.[8] The acyl-substituted nitrogen atom in (**4**), N(3), is displaced by 0.231(2) Å from the C(2)C(4)C(22) plane whereas the acyl-substituted nitrogen atoms in (**5**), N(3) and (7), have displacements of 0.052 and 0.031(2) Å which are consistent with the expected planar or nearly planar pattern of bonds at nitrogen in amides and urethanes.

The out-of-plane distortions about the N–C bond in an amide or urethane can be partitioned among out-of-plane bending at the nitrogen (χ_N) and the carbonyl carbon (χ_C) and twisting around the N–CO bond (τ).[9] The parameters for compounds (**4**) and (**5**) are shown in Table 2 and the substantial out-of-plane distortion at N(3) in (**4**) is indicative of an appreciable attractive interaction between C(22) and N(7) in this compound.

The N–CO bond length in (**4**), 1.361(4) Å, is distinctly longer than the N–CO bond lengths of 1.338 and 1.335(4) Å in (**5**), reflecting decreased p–π overlap and the dependence of the radius of N on hybridization. The N atom in the bridgehead amide (**8**) deviates from a coplanar arrangement of bonds to an



(8)

Table 3. Fractional atomic co-ordinates for 3-ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (4), with e.s.d.s in parentheses.

Atom	*x*	*y*	*z*
C(1)	0.697 7(2)	0.083 5(2)	0.374 1(1)
C(2)	0.738 7(2)	0.088 9(2)	0.455 4(1)
C(4)	0.607 0(3)	0.271 6(2)	0.477 2(1)
C(5)	0.559 1(2)	0.274 7(2)	0.396 8(1)
C(6)	0.437 0(3)	0.193 4(2)	0.385 2(2)
C(8)	0.569 9(3)	0.010 2(2)	0.363 5(2)
C(9)	0.663 2(2)	0.215 0(2)	0.348 3(1)
C(10)	0.810 1(2)	0.029 1(2)	0.330 2(1)
C(11)	0.798 7(3)	−0.080 2(3)	0.290 7(2)
C(12)	0.904 1(4)	−0.128 2(3)	0.253 2(2)
C(13)	1.023 3(4)	−0.071 7(3)	0.255 4(2)
C(14)	1.036 4(3)	0.038 6(3)	0.294 1(2)
C(15)	0.930 9(3)	0.087 8(3)	0.330 5(2)
C(16)	0.535 5(3)	0.409 6(2)	0.376 1(1)
C(17)	0.640 9(3)	0.489 0(3)	0.369 9(2)
C(18)	0.622 7(4)	0.612 2(3)	0.351 4(2)
C(19)	0.499 4(4)	0.657 0(3)	0.338 7(2)
C(20)	0.393 6(4)	0.580 7(3)	0.346 0(2)
C(21)	0.411 6(3)	0.456 7(3)	0.365 0(2)
C(22)	0.550 8(3)	0.083 5(3)	0.540 4(1)
C(23)	0.493 7(5)	−0.118 2(3)	0.582 1(3)
C(24)	0.534 2(8)	−0.247 2(4)	0.564 3(4)
C(25)	0.344 3(3)	−0.011 5(3)	0.393 9(2)
N(3)	0.642 8(2)	0.148 6(2)	0.502 9(1)
N(7)	0.461 4(2)	0.063 1(2)	0.403 6(1)
O(9)	0.705 83(17)	0.260 65(16)	0.293 23(10)
O(22A)	0.584 7(2)	−0.036 5(2)	0.545 6(1)
O(22B)	0.454 2(2)	0.127 0(2)	0.568 3(1)

even greater extent, with χ_N 48.8°, and the N–CO bond length in (**8**) is increased to 1.374(7) Å.[10]

Experimental

Compounds (**4**) and (**5**) were prepared by published procedures.[11,12] Compound (**4**) had m.p. 149–150 °C (lit.,[11] 154 °C) (MeOH); M^+, 378; δ_H($CDCl_3$, Perkin-Elmer R32) 1.35 (3 H, t, CH_3), 2.32 (3 H, s, NCH_3), 2.9–3.2 (2 H, m, CH_2), 3.50–3.85 (4 H, m, CH_2), 4.27 (2 H, q, OCH_2), 5.05 (2 H, dd, CH_2), and 7.25–7.45 (10 H, m, Ar); δ_C($CDCl_3$; Varian XL100) 14.9 (q, CH_3), 45.04 (q, NCH_3), 54.42 [s, C(1),C(5)], 56.11 (dd, CH_2), 61.82 (t, OCH_2), 67.09 (t, CH_2), 127.41, 128.09 (d, Ar), 137.39 (s, Ar), 156.81 (s, CO), and 209.9 [s, C(9)].

Compound (**5**) had m.p. 140–141 °C (EtOH), which differed considerably from the literature value, 174–175 °C (EtOH),[12] but gave the following analytical data consistent with the assigned structure: M^+, 436 (Found: C, 68.9; H, 6.35; N, 6.4. $C_{25}H_{28}N_2O_5$ requires C, 68.79; H, 6.47; N, 6.42%); δ_H($CDCl_3$) 1.30 (6 H, t, CH_3), 3.6–3.9 (4 H, m, CH_2), 4.20 (4 H, q, OCH_2), 4.8–5.2 (4 H, m, CH_2), and 7.2–7.5 (10 H, m, Ar); δ_C($CDCl_3$) 14.57 (q, CH_3), 53.06 [s, C(1),C(5)], 55.54 (dd, CH_2), 62.10 (t, OCH_2), 127.47, 127.77, 128.26, 136.15 (Ar), 155.24 (s, CO), and 207.89 [s, C(9)].

Table 4. Fractional atomic co-ordinates for 3,7-di(ethoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5), with e.s.d.s in parentheses.

Atom	*x*	*y*	*z*
C(1)	0.584 4(2)	0.179 3(1)	0.620 0(2)
C(2)	0.469 2(2)	0.224 8(1)	0.612 6(2)
C(4)	0.458 4(2)	0.160 0(1)	0.787 4(2)
C(5)	0.572 9(2)	0.111 7(1)	0.801 7(2)
C(6)	0.514 7(3)	0.052 0(1)	0.703 1(2)
C(8)	0.524 3(3)	0.118 4(1)	0.524 9(2)
C(9)	0.665 7(2)	0.148 9(1)	0.761 6(2)
C(10)	0.673 6(2)	0.223 1(1)	0.585 9(2)
C(11)	0.752 7(3)	0.273 0(1)	0.672 7(2)
C(12)	0.830 0(3)	0.316 5(2)	0.643 1(3)
C(13)	0.827 7(3)	0.310 3(2)	0.522 5(3)
C(14)	0.749 2(3)	0.262 0(2)	0.434 9(3)
C(15)	0.672 6(3)	0.217 9(1)	0.464 9(2)
C(16)	0.648 0(2)	0.087 6(1)	0.946 6(2)
C(17)	0.651 1(3)	0.021 3(1)	0.983 2(3)
C(18)	0.711 9(3)	0.003 5(2)	1.117 8(3)
C(19)	0.768 9(3)	0.050 2(2)	1.215 7(3)
C(20)	0.769 9(3)	0.115 8(2)	1.181 8(2)
C(21)	0.711 3(3)	0.134 6(1)	1.048 5(2)
C(22)	0.248 7(2)	0.182 5(1)	0.571 3(2)
C(23)	0.043 4(3)	0.138 3(2)	0.550 7(3)
C(24)	−0.009 3(3)	0.116 3(2)	0.637 7(4)
C(25)	0.324 2(3)	0.047 9(1)	0.479 1(2)
C(26)	0.134 5(4)	0.049 2(3)	0.261 3(4)
C(27)	0.086 8(6)	0.064 5(4)	0.130 3(5)
N(3)	0.382 95(17)	0.190 64(10)	0.654 90(17)
N(7)	0.447 1(2)	0.073 7(1)	0.563 2(2)
O(9)	0.787 66(16)	0.149 71(9)	0.828 26(16)
O(22A)	0.188 03(16)	0.151 92(9)	0.632 12(16)
O(22B)	0.187 17(16)	0.201 92(9)	0.455 71(15)
O(25A)	0.262 0(2)	0.010 8(1)	0.513 0(2)
O(25B)	0.276 94(18)	0.066 97(9)	0.351 87(15)

Crystal Data.—3-Ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**4**), $C_{23}H_{26}N_2O_3$, $M = 378.5$, orthorhombic, $a = 10.232(2)$, $b = 10.822(2)$, $c = 18.240(2)$ Å, $V = 2\,020$ Å^3, $D_c = 1.24$ g cm^{-3}, $Z = 4$, $F(000) = 808$, μ(Mo-K_α) = 0.89 cm^{-1}, space group $P2_12_12_1$ (No. 19). 3,7-Di(ethoxycarbonyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]-nonan-9-one (**5**), $C_{25}H_{28}N_2O_5$, $M = 436.5$, monoclinic, $a = 11.274(4)$, $b = 19.920(4)$, $c = 11.572(2)$ Å, $\beta = 119.95(5)°$, $V = 2\,252$ Å^3, $D_c = 1.29$ g cm^{-3}, $Z = 4$, $F(000) = 928$, μ(Mo-K_α) = 0.97 cm^{-1}, space group $P2_1/n$ (No. 14).

Crystallographic Measurements.—Cell dimensions were derived from least-squares analysis of the setting angles of 25 reflections measured on an Enraf–Nonius CAD4 diffractometer with Mo-K_α radiation. For compound (**4**), 2 533 reflections were surveyed in the range $\theta < 27°$ and 1 929 satisfied the criterion $I > 2.5\sigma(I)$. For compound (**5**), 4 783 reflections were surveyed in the range $\theta < 27°$ and after averaging 227 pairs of equivalent reflections (merging $R = 0.020$), 3 231 independent reflections satisfied the criterion $I > 2.5\sigma(I)$.

Structure Analyses.—The crystal structures were elucidated by the direct phasing program MITHRIL.[2] After preliminary least-squares adjustment of the co-ordinates and thermal parameters of the C, N, and O atoms, the H atoms, apart from those on a terminal methyl of (**5**), C(27), were located in difference electron-density distributions and included in subsequent least-squares calculations with isotropic thermal parameters. The weighting scheme used was $w = 1/\sigma^2(|F|)$. The calculations converged at $R = 0.039$, $R_w = 0.044$ for compound (**4**) and $R = 0.059$, $R_w = 0.075$ for compound (**5**). The calculations were performed on a SEL 32/27 computer with the GX programs.[13]

Atomic co-ordinates are listed in Tables 3–4. Full details of the molecule geometries and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

References

1 P. H. McCabe, N. J. Milne, and G. A. Sim, *J. Chem. Soc., Chem. Commun.*, 1985, 625.
2 C. J. Gilmore, *J. Appl. Crystallogr.*, 1983, **17**, 42.
3 J. Vilches, F. Florencio, P. Smith-Verdier, and S. García-Blanco, *Acta Crystallogr., Sect. B*, 1981, **37**, 201.
4 W. B. Schweizer, G. Procter, M. Kaftory, and J. D. Dunitz, *Helv. Chim. Acta*, 1978, **61**, 2783.
5 H. Einspahr, J.-B. Robert, R. E. Marsh, and J. D. Roberts, *Acta Crystallogr., Sect. B*, 1973, **29**, 1611; D. Bright, I. E. Maxwell, and J. de Boer, *J. Chem. Soc., Perkin Trans. 2*, 1973, 2101.
6 G. A. Sim, *J. Chem. Soc., Chem. Commun.*, 1987, 1118.
7 P. Helminger, F. C. De Lucia, and W. Gordy, *J. Mol. Spectrosc.*, 1971, **39**, 94.
8 D. R. Lide, Jr. and D. E. Mann, *J. Chem. Phys.*, 1958, **28**, 572.
9 F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169.
10 G. L. Buchanan, D. H. Kitson, P. R. Mallinson, G. A. Sim, D. N. J. White, and P. J. Cox, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1709.
11 G. Settimj, R. Landi-Vittory, F. Gatta, N. Sarti, and S. Chiavarelli, *Gazz. Chim. Ital.*, 1966, 604.
12 S. Chiavarelli and G. Settimj, *Gazz. Chim. Ital.*, 1958, **88**, 1234.
13 P. R. Mallinson and K. W. Muir, *J. Appl. Crystallogr.*, 1985, **18**, 51.

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* See 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

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