Conformations of 3-Azabicyclo[3.3.1]nonane Derivatives

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Unless there is a 7-*endo* substituent, 3-azabicyclo[3.3.1]nonanes exist as twin-chair conformers in which the lone pair of electrons on N(3) strongly repels the C(7)H group, leading to considerable distortion of the cyclohexane ring.

2,4,6,8-Tetra-aryl-3,7-diazabicyclo[3.3.1]nonanes (**1**)[1] and other simpler 3,7-diazabicyclo[3.3.1]nonanes with alkyl or arylsulphonyl substituents at the N atoms[2] adopt the boat–chair conformation rather than the twin-chair conformation commonly observed in bicyclo[3.3.1]nonanes.[3] To obtain additional information about the conformational consequences of lone-pair electrons we have examined the crystal structures of a series of 3-azabicyclo[3.3.1]nonanes.

Compounds (**2**)—(**5**)† were prepared by Mannich condensation of cyclohexanone, aromatic aldehyde, and NH_4OAc.[4]

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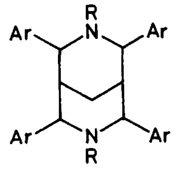
† All crystalline compounds gave satisfactory n.m.r., mass spectral, and microanalytical data: m.p.s.; (**2**) 130.5—132 °C; (**3**) 184—185; (**4**) 130—132; (**5**) 173—175; (**6**) 205—206; (**7**) 209—211; (**8**) 174—175; (**9**) 204—206; (**10**) 159—160.

For (**2**), the 9-keto group was removed by Wolff–Kishner reduction.[4] Condensation of the pyrrolidine enamine of *N*-substituted 4-piperidone with 1,3-dichloro-2-benzoylpropane gave (**8**) and (**9**)[5] and with 1,3-dibromo-2-ethoxycarbonylpropane gave (**10**).[6] Complete epimerisation of (**8**) to (**6**) and of (**9**) to (**7**) was achieved with NaOMe–MeOH.[6] Under the same conditions, (**10**) gave a mixture which was not separated.

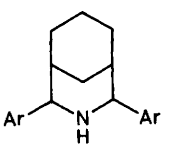
The crystal structures‡ of compounds (**2**)—(**7**) show molecules with the twin-chair conformation and the lone pair of electrons of the N atom in the *endo* (axial) position (see Figure 1); it follows that lone-pair···C–H 3,7-interactions are less repulsive than N–H···C–H 3,7-interactions in (**2**)—(**5**) and lone-pair···lone-pair 3,7-interactions in the twin-chair conformation of (**1**). Compounds (**2**)—(**7**) are conformationally immobile as shown by virtually unchanged ^{1}H n.m.r. spectra over the temperature range −70 to +150 °C.

Compounds (**8**), (**9**), and (**10**) adopt the boat–chair conformation because of the severe interaction that would occur between the *endo* lone pair of electrons at N and the *endo* substituent at position 7 in the twin-chair conformation. The thermodynamically stable C(7)-*exo* epimers (**6**) and (**7**) do not have this interaction and adopt the twin-chair conformation with equatorial C(7)-substituent.

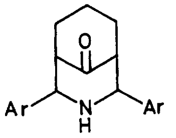
The cyclohexane rings in compounds (**2**)—(**7**) are distorted in the manner observed in carbocyclic bicyclo[3.3.1]nonanes;[3] the mean torsion angle for bonds C(6)–C(7) and C(7)–C(8) is only 45°. The *endo* C(7)–H group apparently experiences appreciable repulsion from the N lone pair and the displacement of the C(7)–H group results in considerable distortion of the cyclohexane ring. The piperidine ring, on the other hand, is very much less distorted, the mean torsion angle for bonds C(2)–N(3) and N(3)–C(4) being 57°. The results demonstrate that though the lone pair of electrons on N(3) strongly repels and displaces the C–H electron density at position 7 a corresponding displacement of the electron density centred at N(3) is avoided, perhaps by some deformation of the lone-pair density.



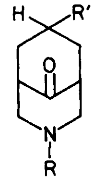
(**1**)



(**2**) Ar = Ph



(**3**) Ar = Ph
(**4**) Ar = p-MeC$_6$H$_4$
(**5**) Ar = p-MeOC$_6$H$_4$



(**6**) R = p-MeC$_6$H$_4$SO$_2$
R' = *exo*-COPh
(**7**) R = p-BrC$_6$H$_4$SO$_2$
R' = *exo*-COPh
(**8**) R = p-MeC$_6$H$_4$SO$_2$
R' = *endo*-COPh
(**9**) R = p-BrC$_6$H$_4$SO$_2$
R' = *endo*-COPh
(**10**) R = p-MeC$_6$H$_4$SO$_2$
R' = *endo*-CO$_2$Et

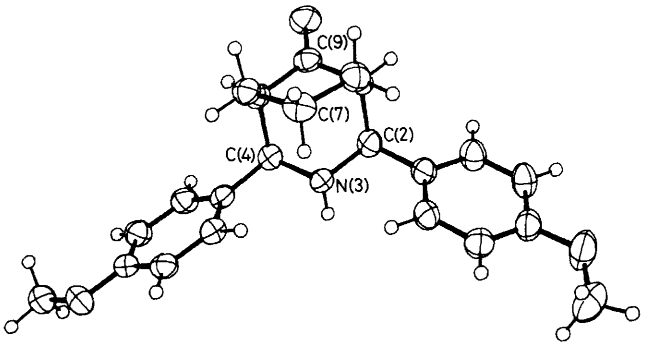


Figure 1. The molecular structure of 2,4-bis(*p*-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (**5**). The thermal ellipsoids are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å.

In all five compounds (**6**)—(**10**), the sulphonyl-substituted N atom has a pyramidal, rather than a planar, arrangement of bonds. The N–S bond is inclined at 32°, on average, to the

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‡ *Crystal data.* (**2**): $C_{20}H_{23}N$, $M = 277.4$, monoclinic, space group $P2_1/c$, $a = 6.398(2)$, $b = 23.880(3)$, $c = 10.664(2)$ Å, $\beta = 107.00(2)°$, $U = 1558$ Å^3, $F(000) = 600$, $Z = 4$, Mo-K_α radiation, $\lambda = 0.71069$ Å, $\mu = 0.73$ cm^{-1}, direct phasing (MITHRIL)[7] for structure solution, followed by least-squares refinement with 2465 reflections for which $I \geq 2.5\sigma(I)$, $R = 0.047$, $R_w = 0.063$, with $w = 1/\sigma^2(|F|)$. (**3**): $C_{20}H_{21}NO$, $M = 291.4$, orthorhombic, space group $Cmc2_1$, $a = 20.826(8)$, $b = 10.508(4)$, $c = 7.244(3)$ Å, $U = 1585$ Å^3, $F(000) = 624$, $Z = 4$, μ(Mo-K_α) = 0.81 cm^{-1}, $R = 0.042$, $R_w = 0.042$ for all 1250 reflections, unit weights. (**4**): $C_{22}H_{25}NO$, $M = 319.5$, monoclinic, space group $P2_1/c$, $a = 6.395(3)$, $b = 21.262(5)$, $c = 13.277(11)$ Å, $\beta = 93.04(6)°$, $U = 1803$ Å^3, $F(000) = 688$, $Z = 4$, μ(Mo-K_α) = 0.77 cm^{-1}, 3031 reflections for which $I \geq 3\sigma(I)$, $R = 0.046$, $R_w = 0.069$, with $w = 1/\sigma^2(|F|)$. (**5**): $C_{22}H_{25}NO_3$, $M = 351.5$, monoclinic, space group $P2_1/c$, $a = 22.525(5)$, $b = 6.479(2)$, $c = 12.751(2)$ Å, $\beta = 101.62(2)°$, $U = 1823$ Å^3, $F(000) = 752$, $Z = 4$, μ(Mo-K_α) = 0.92 cm^{-1}, 2448 reflections for which $I \geq 2.5\sigma(I)$, $R = 0.038$, $R_w = 0.046$, with $w = 1/\sigma^2(|F|)$. (**6**): $C_{22}H_{23}NO_4S$, $M = 397.4$, orthorhombic, space group $P2_12_12_1$, $a = 8.231(4)$, $b = 11.920(4)$, $c = 20.717(5)$ Å, $U = 2033$ Å^3, $F(000) = 840$, $Z = 4$, μ(Mo-K_α) = 1.89 cm^{-1}, $R = 0.066$, $R_w = 0.077$ for all 1874 reflections, with $w = 1/\sigma^2(|F|)$. (**7**): $C_{21}H_{20}NO_4SBr$, $M = 462.4$, monoclinic, space group $C2/c$, $a = 13.164(4)$, $b = 19.350(5)$, $c = 15.484(4)$ Å, $\beta = 96.03(2)°$, $U = 3922$ Å^3, $F(000) = 1888$, $Z = 8$, μ(Mo-K_α) = 23.55 cm^{-1}, 2645 reflections for which $I \geq 2.5\sigma(I)$, $R = 0.045$, $R_w = 0.051$, with $w = 1/\sigma^2(|F|)$. (**8**): $C_{22}H_{23}NO_4S$: $M = 397.4$, monoclinic, space group $P2_1/n$, $a = 6.593(5)$, $b = 14.274(3)$, $c = 21.433(7)$ Å, $\beta = 96.64(7)°$, $U = 2003$ Å^3, $F(000) = 840$, $Z = 4$, μ(Mo-K_α) = 1.91 cm^{-1}, 2644 reflections for which $I \geq 2.5\sigma(I)$, $R = 0.046$, $R_w = 0.059$, with $w = 1/\sigma^2(|F|)$. (**9**): $C_{21}H_{20}NO_4SBr$, $M = 462.4$, monoclinic, space group $P2_1/n$, $a = 6.628(5)$, $b = 14.376(3)$, $c = 21.435(5)$ Å, $\beta = 96.97(4)°$, $U = 2027$ Å^3, $Z = 4$, μ(Mo-K_α) = 22.78 cm^{-1}, $F(000) = 1888$, 1433 reflections for which $I \geq 2.5\sigma(I)$, $R = 0.046$, $R_w = 0.046$, with $w = 1/\sigma^2(|F|)$. (**10**): $C_{18}H_{23}NO_5S$, $M = 365.4$, orthorhombic, space group $P2_12_12_1$, $a = 10.191(3)$, $b = 11.105(3)$, $c = 15.582(5)$ Å, $U = 1763$ Å^3, $F(000) = 776$, $Z = 4$, μ(Mo-K_α) = 2.14 cm^{-1}, 1843 reflections for which $I \geq 2.5\sigma(I)$, $R = 0.036$, $R_w = 0.044$, with $w = 1/\sigma^2(|F|)$. The atomic co-ordinates for this work are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

C(2)–N(3)–C(4) plane. The sulphonyl substituent is clearly different in character from carbonyl, the latter giving a virtually planar bonding pattern at N.[2]

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