diation frequencies was in agreement with experiment. Because of the problems introduced by possible rotation of the aromatic ring holding the CF_3 group, the protons ortho and meta to trifluoromethyl were represented by single stationary protons. The position of the spin representing the ortho proton was adjusted so as to reproduce the contribution of these nuclei to fluorine relaxation that is revealed by selective deuteration experiments;[8a] the spin corresponding to the meta protons was placed 2.48 Å from the pseudo-ortho spin. Similarly, the position of a single spin was adjusted to take into account the relaxation effects of solvent or solvent-derived protons.

Initially the R_{xi} parameters were set to zero, but the need for nonzero values soon became apparent. The values for R_{xi} and R_{2i} given in Table IV could be varied ±10% without substantial effects on the computed $^{19}F\{^1H\}$ NOE curves.

References and Notes

(1) F. A. L. Anet and A, J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965).
(2) T. L. James, "Nuclear Magnetic Resonance in Biochemistry", Academic Press, New York, 1975, p 226.
(3) For recent examples see (a) T. L. James, *Biochemistry*, **15**, 4724 (1976); (b) J. D. Glickson, S. L. Gordon, T. P. Pitner, D. G. Agresti, and R. Walter, *ibid.*, **15**, 5721 (1976); (c) M. Y. Karpeiski and G. I. Yakovlev, *Bioorg. Khim.* **2**, 1221 (1976); (d) A. Kalk and H. J. C. Berendsen, *J. Magn. Reson.*, **24**, 343 (1976); (e) S. J. Leach, G. Nemethy and H. A. Sheraga, *Biochem. Biophys. Res. Commun.*, **75**, 207–215 (1977); (f) N. R. Krishna, D. G. Agresti, J. D. Glickson and R. Walter, *Biophys. J.*, **24**, 791–814 (1978); (g) C. R. Jones, C. T. Sikakana, S. Hehir, M.-C. Kuo, and W. A. Gibbons, *ibid.*, **24**, 815–832 (1978); (h) A. A. Bothner-By and P. E. Johner, *ibid.*, **24**, 779–790 (9178); (i) P. A. Hart, *ibid.*, **24**, 833–848 (1978).
(4) For a review, see J. T. Gerig, "Biochemical Magnetic Resonance", L. J. Berliner and J. Reuben, Eds., Plenum Press, New York, 1978, pp 139–203.
(5) J. T. Gerig, *J. Am. Chem. Soc.*, **99**, 1721 (1977).
(6) J. J. Birktoft and D. M. Blow, *J. Mol. Biol.*, **68**, 187 (1972).
(7) J. T. Gerig and D. C. Roe, *J. Am. Chem. Soc.*, **96**, 233 (1974).
(8) (a) J. T. Gerig, D. T. Loehr, K. F. S. Luk, and D. C. Roe, *J. Am. Chem. Soc.*, in press; (b) M. E. Ando, J. T. Gerig, K. F. S. Luk, and D. C. Roe, *Can. J. Biochem.*, submitted.
(9) G. B. Matson, *J. Magn. Reson.*, **25**, 479 (1977).
(10) R. Freeman and D. H. Whiffen, *Proc. Phys. Soc., London*, **79**, 794 (1962).
(11) R. A. Hoffman and S. Forsen in "High-Resolution Nuclear Magnetic Double and Multiple Resonance", J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Eds., Pergamon Press, Oxford, 1966.
(12) J. T. Gerig, B. A. Halley, and J. A. Reimer, *J. Am. Chem. Soc.*, **99**, 3579 (1977).
(13) T. C. Farrar and E. D. Becker, "Pulse and Fourier Transform NMR", Academic Press, New York, 1971, p 20 ff.
(14) J. T. Gerig, G. B. Matson, and A. D. Stock, *J. Magn. Reson.*, **15**, 382 (1974).
(15) G. R. Conway, N. R. Glass, and J. C. Wilcox, *Ecology*, **51**, 503 (1970).
(16) (a) S. W. Provencher, *Biophys. J.*, **16**, 27 (1976); (b) *J. Chem. Phys.*, **64**, 2772 (1976).
(17) R. L. Vold, *J. Chem. Phys.*, **56**, 3210–3216 (1972).
(18) (a) R. K. Harris and R. H. Newman, *J. Magn. Reson.*, **24**, 449–456 (1976); (b) S. J. Opella, D. J. Nelson, and O. Jardetsky, *J. Chem. Phys.*, **64**, 2533 (1976).
(19) B. D. Sykes, W. E. Hull, and G. H. Snyder, *Biophys. J.*, **21**, 137–146 (1978).
(20) J. J. Led, D. M. Grant, W. J. Horton, F. Sundby, and K. Vilhelmsen, *J. Am. Chem. Soc.*, **97**, 5997 (1975).
(21) A. N. Kuznetsov, B. Ebert, and G. V. Gyul'khandanyan, *Mol. Biol. (Kiev)*, **9**, 871 (1975).
(22) W. L. C. Vaz and G. Schoellmann, *Biochim. Biophys. Acta*, **439**, 206 (1976).
(23) Reference 2, p 242.
(24) P. E. Wilcox, *Methods Enzymol.*, **19**, 64 (1970).
(25) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, 1971, p 44.

Crystal and Molecular Structures of 2,6-*cis*-Dimethylpiperidyl-*N*-phenylacetamidine and 2,6-*cis*-Dimethylpiperidyl-*N*-phenyl-2,2-dimethylpropionamidine. An X-ray Crystallographic Investigation of the C(sp^2)–N(piperidyl) Bond

Gastone Gilli* and Valerio Bertolasi

Contribution from the Istituto Chimico, University of Ferrara,
44100 Ferrara, Italy.

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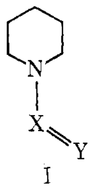
Abstract: The single crystal X-ray analyses of 2,6-*cis*-dimethylpiperidyl-*N*-phenylacetamidine (MA) and 2,6-*cis*-dimethylpiperidyl-*N*-phenyl-2,2-dimethylpropionamidine (TBA) are described. MA crystallizes in the space group $P2_1/c$ with four molecules in the unit cell of dimensions a = 10.238 (2), b = 10.189 (2), c = 12.875 (3) Å, and β = 95.82 (2)°. The structure was solved and refined from 1401 unique observed reflections collected on an automated four-circle diffractometer to final values of the discrepancy indices of R = 0.046 and R_w = 0.058. TBA crystallizes in the space group $P2_1/c$ with eight molecules in the unit cell of dimensions a = 8.470 (2), b = 16.095 (3), c = 24.900 (4) Å, and β = 96.29 (2)°. From 2633 unique observed reflections similarly collected the structure was solved and refined to final values of the discrepancy indices of R = 0.061 and R_w = 0.074. The structure analyses show, in agreement with ^{13}C NMR spectroscopic data, that the two molecules adopt different conformations around the C(sp^2)–N(piperidyl) bond, the amidinic group and the piperidyl ring being approximately coplanar in MA and orthogonal in TBA, respectively. The comparison of the present data with the data in the literature, supported by nonbonded intramolecular potential energy calculations and INDO calculations, allows clarification of the relationship among the torsion angle around the C–N bond, the bond distances in the amidinic group, the pyramidality of the N (piperidyl) atom and the conformation of the 2,6-*cis*-methyl groups in the piperidyl ring.

N-Substituted piperidines of type I have been the subject of several X-ray crystallographic investigations and most of them were found to adopt a nearly planar conformation (that is, with the N—X=Y group lying in the mean plane of the piperidyl ring). Such a conformation would not be preferred in terms of nonbonded interactions alone and is to be ascribed to restricted rotation around the N–X partial double bond, as



I

$$-X{=}Y = \begin{cases} -N{=}O, \textit{N}\text{-nitrosopiperidines} \\ -N{=}N-, \text{ triazenes} \\ -N{=}CR_2, \text{ hydrazones} \\ -Ar \\ -C(R){=}O, \text{ amides} \\ -C(R){=}S, \text{ thioamides} \\ -C(R){=}NR', \text{ amidines} \end{cases}$$

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Table I. Crystal Data

	MA	TBA
formula	$C_{15}H_{22}N_2$	$C_{18}H_{28}N_2$
fw	230.4	272.4
crystal system	monoclinic	monoclinic
cell parameters	a = 10.238 (2) Å	a = 8.570 (2) Å
	b = 10.189 (2) Å	b = 16.095 (3) Å
	c = 12.875 (3) Å	c = 24.900 (4) Å
	β = 95.82 (2)°	β = 96.29 (2)°
ρ_{obsd} (by flotation)	1.17 g cm^{-1}	1.07 g cm^{-1}
μ(Cu Kα)	4.43 cm^{-1}	4.02 cm^{-1}
space group	$P2_1/c$	$P2_1/c$
Z	4	8
ρ_{calcd}	1.15 g cm^{-1}	1.08 g cm^{-1}

can be easily proved by comparing the observed N–X distances with those expected for a pure single bond.

In spite of the relatively high number of X-ray structure investigations, the only systematic study on the preferential ground state conformation of N-substituted piperidines has been carried out by means of ^{1}H and ^{13}C NMR spectroscopy at low temperature.[1-4] These authors have investigated the relative stability of the planar conformation in different derivatives of type I by substitution of the piperidyl ring with 2,6-*cis*-dimethylpiperidyl (DMP) or 2,2,6,6-tetramethylpiperidyl (TMP) rings. They could thus show that the conformations of *N*-nitrosopiperidines,[1] piperidyltriazenes,[3] and piperidylamides[4] were planar regardless of the number of methyl groups on carbons 2 and 6, while only DMP amidines[4] and, probably, DMP hydrazones[1,2] were planar, the corresponding TMP derivatives having adopted an orthogonal conformation; moreover, piperidylamidines were found to be the only class of compounds of type I, whose conformation was affected by a bulky group attached to the amidic moiety of the molecule.

The experimental evidence indicates, therefore, that piperidylamidines are the compounds of type I with the widest potential conformational variability and, consequently, the most promising candidates for the study of the interconnections between the torsion angle around the N–X bond and the other geometrical parameters of the molecule. Accordingly, the present paper reports the crystal structure of two piperidylamidines, 2,6-*cis*-dimethylpiperidyl-*N*-phenylacetamidine (MA) and 2,6-*cis*-dimethylpiperidyl-*N*-phenyl-2,2-dimethylpropionamidine (TBA), for which dynamic ^{13}C NMR studies[4] have suggested planar and orthogonal preferred ground state conformations, respectively. It will be shown that the assigned conformations are confirmed by the X-ray analysis and that the data collected in the present and in other X-ray investigations agree in suggesting an interconversion path between the planar and the orthogonal conformation rather more complicated than usually recognized.

Experimental Section

Crystal Data. The crystals of both compounds were obtained by recrystallization from benzene. The crystals used for the X-ray investigation were small prisms elongated along the a axis and having dimensions of 0.20 × 0.19 × 0.50 mm for MA and 0.16 × 0.25 × 0.55 mm for TBA. The cell dimensions were determined by a least-squares fit to the angular positions of 20 reflections collected on an automatic Siemens AED diffractometer with Ni-filtered Cu K$\bar{\alpha}$ (λ = 1.54178 Å) radiation. Crystal data for the two compounds are given in Table I. Intensity data were collected on the same diffractometer with Ni-filtered Cu Kα radiation and $\omega/2\theta$ scan technique ($\theta \leq 55°$). During the data collection time, the intensity of a standard reflection was monitored after every 20 measurements. The intensities of the standard reflections did not vary for either compound. In all, 1661 independent reflections were collected for MA, out of which 1401 reflections having $I \geq 3\sigma(I)$ were considered observed. For TBA the number of independent reflections was 4278 with 2633 observed. Lorentz and polarization corrections were applied as usual but **no** absorption correction was made.

Table II. Positional (× 10^4) Parameters for MA with esd's in Parentheses

atom	x	y	z
N(1)	7149(2)	4430(2)	3378(2)
N(2)	7378(2)	6195(2)	2311(1)
C(1)	7635(2)	3476(2)	4107(2)
C(2)	7174(2)	3442(3)	5086(2)
C(3)	7546(3)	2462(3)	5793(2)
C(4)	8390(3)	1487(3)	5532(2)
C(5)	8845(3)	1506(2)	4568(2)
C(6)	8470(3)	2485(3)	3865(2)
C(7)	7869(2)	5365(2)	3097(2)
C(8)	9260(3)	5614(3)	3578(2)
C(9)	6027(2)	5942(2)	1828(2)
C(10)	5867(3)	6442(3)	704(2)
C(11)	6315(3)	7843(3)	618(2)
C(12)	7743(3)	7929(3)	1038(2)
C(13)	7974(2)	7487(2)	2170(2)
C(14)	4972(3)	6460(3)	2470(3)
C(15)	7571(4)	8512(3)	2917(3)
H(2)	6535(33)	4069(32)	5226(23)
H(3)	7198(43)	2513(39)	6501(33)
H(4)	8579(28)	787(31)	5931(24)
H(5)	9421(37)	789(40)	4324(24)
H(6)	8733(27)	2480(26)	3212(23)
H(81)	9525(21)	4952(22)	4043(16)
H(82)	9405(25)	6449(23)	3778(22)
H(83)	9950(28)	5373(25)	3102(19)
H(9)	6045(23)	4959(27)	1796(18)
H(101)	6366(27)	5902(27)	189(22)
H(102)	4901(32)	6323(26)	392(24)
H(111)	6146(33)	8136(33)	−53(30)
H(112)	5797(26)	8385(25)	976(20)
H(121)	8084(38)	8925(36)	1043(29)
H(122)	8267(37)	7284(35)	642(28)
H(13)	8943(33)	7351(26)	2357(21)
H(141)	4109(37)	6120(33)	2083(26)
H(142)	4943(33)	7354(35)	2513(26)
H(143)	5126(32)	6098(31)	3181(28)
H(151)	8105(43)	9300(47)	2868(32)
H(152)	7784(36)	8147(37)	3654(34)
H(153)	6585(40)	8699(32)	2796(28)

Structure Determination and Refinement. Structures of both compounds were solved by the system of programs MULTAN 74.[5] All the subsequent calculations were carried out by means of the system of programs SHELX 76[6] and scattering factors for all the atoms were taken from the "International Tables for X-Ray Crystallography".[7]

For the first compound (MA), phases were calculated for 300 reflections having $|E| \geq 1.38$. The E map generated for the set of phases with the highest combined figure of merit (FOM) revealed all the nonhydrogen atoms of the molecule. For TBA, 300 reflections with $|E| \geq 1.84$ were phased and the E map obtained from the set of phases with the highest combined FOM showed all the nonhydrogen atoms of the two independent molecules comprising the asymmetric unit, except the three methyl atoms C(16B), C(17B) and C(18B). These latter atoms were then found by Fourier methods.

MA and TBA were successively refined by full-matrix least-squares methods by assuming isotropic temperature factors. At convergence, the conventional R factor ($R = \Sigma|\Delta F|/\Sigma|F_o|$) was 0.14 for MA and 0.18 for TBA. The difference Fourier maps made after isotropic refinement allowed the positions of all the H atoms to be found for MA but not more than 50% of them for TBA. For this reason, the subsequent refinement was carried out in different ways for the two compounds.

In the case of MA, all the C and N atoms were refined with anisotropic temperature factors and H atoms with isotropic ones; after four cycles of full-matrix least-squares refinement, the conventional R factor was reduced to 0.046 and R_w [$=(\Sigma w|\Delta F|^2/\Sigma w|F_o|^2)^{1/2}$] to

Table III. Positional (× 10^4) Parameters for the Two Independent Molecules of TBA with esd's in Parentheses

	molecule A			molecule B		
atom	*x*	*y*	*z*	*x*	*y*	*z*
N(1)	3479(4)	7301(2)	8677(1)	2375(4)	2660(2)	3722(1)
N(2)	2821(3)	5857(2)	8799(1)	3035(4)	4112(2)	3737(1)
C(1)	1951(5)	7593(2)	8500(2)	3750(5)	2364(2)	3519(2)
C(2)	1098(5)	8003(3)	8866(2)	4869(6)	1941(2)	3864(2)
C(3)	−317(6)	8379(3)	8683(3)	6159(5)	1598(2)	3668(2)
C(4)	−862(6)	8373(3)	8147(3)	6333(5)	1633(2)	3134(2)
C(5)	−14(5)	7979(3)	7788(2)	5218(5)	2022(2)	2785(2)
C(6)	1389(5)	7598(2)	7960(2)	3938(5)	2389(2)	2973(2)
C(7)	3862(4)	6561(2)	8799(1)	2068(4)	3411(2)	3812(1)
C(8)	5602(5)	6407(2)	8977(2)	520(6)	3566(3)	4053(2)
C(9)	1615(5)	5900(2)	9181(2)	4601(5)	4115(3)	4047(2)
C(10)	991(6)	5024(3)	9249(2)	5231(6)	5007(3)	4062(2)
C(11)	334(7)	4640(3)	8724(3)	5273(8)	5376(3)	3511(3)
C(12)	1502(6)	4686(2)	8319(2)	3724(7)	5277(3)	3183(2)
C(13)	2123(5)	5568(2)	8262(1)	3123(5)	4391(2)	3174(2)
C(14)	2278(7)	6254(3)	9728(2)	4589(7)	3782(3)	4609(2)
C(15)	3267(6)	5573(3)	7844(2)	1580(6)	4325(3)	2823(2)
C(16)	5958(6)	5530(3)	9167(2)	241(7)	4476(3)	4175(2)
C(17)	6177(7)	7009(4)	9413(2)	473(8)	3048(4)	4546(3)
C(18)	6563(6)	6589(4)	8508(2)	−851(6)	3283(4)	3654(3)

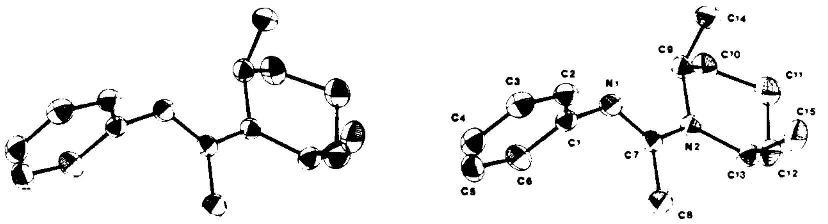


Figure 1. Stereoscopic view of 2,6-*cis*-dimethylpiperidyl-*N*-phenylacetamidine, MA. Thermal ellipsoids are represented at 40% probability level and hydrogen atoms are not shown.

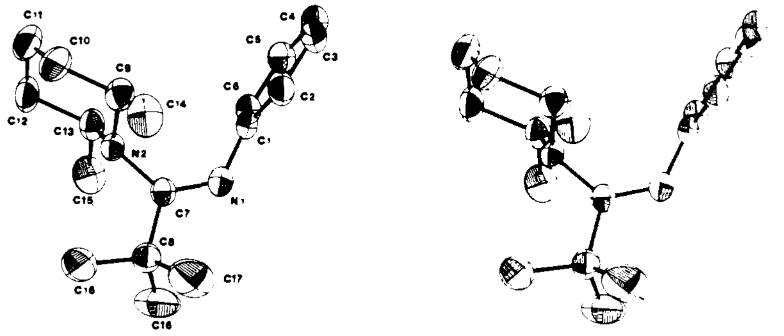


Figure 2. Stereoscopic view of 2,6-*cis*-dimethylpiperidyl-*N*-phenyl-2,2-dimethylpropionamidine (molecule A), TBA(A). Thermal ellipsoids are represented at 40% probability level and hydrogen atoms are not shown.

0.058; the weighting scheme used was of the type $k_1/w = \sigma^2(F_o) + k_2|F_o|^2$, where k_1 and k_2 are constants to be determined. The thermal parameter of one of the H atoms linked to the methyl C(8) atom became very large during the refinement and, therefore, its temperature factor was fixed to the mean value of the other two methyl hydrogens.

For TBA, the structure was refined by a blocked-matrix least-squares method (one block for each independent molecule in the asymmetric unit) with anisotropic temperature factors for all the nonhydrogen atoms and H atoms were assigned calculated positions (C-H bond distance of 1.08 Å) and isotropic temperature factors 20% greater than those of the connected atoms. At convergence, the *R* and R_w factors were respectively 0.061 and 0.074. The weighting scheme was the same as in the previous case.

Final difference maps on both compounds were featureless; final atomic positional parameters are given in Tables II and III. Listings of atomic thermal parameters and of the observed and calculated structure factors for both structures are available (see paragraph on supplementary material at the end of this paper).

Description of the Structures

Both structures consist of discrete molecular units packed without intermolecular distances significantly shorter than the sums of the van der Waals radii. Figures 1 and 2 are ORTEP[8] stereoscopic views of the molecules of MA and TBA(A), showing the numbering scheme and the thermal ellipsoids at 40% probability Bond distances and angles for MA, TBA(A), and TBA(B) are reported in Table IV. Distances and angles for MA involving hydrogen atoms are available (see paragraph on supplementary material).

The two compounds differ in configuration (*E* in MA and *Z* in TBA), and in conformation as far as the piperidyl ring is concerned. In both compounds, the piperidyl ring adopts a "chair" conformation but the two 2,6-*cis*-methyl groups are diaxial in MA and diequatorial in TBA. Moreover the conformation of the two compounds is substantially different as regards the torsion angle around the C(7)-N(2) bond. This

Table IV. Bond Lengths (Å) and Bond Angles for MA and for the Two Independent Molecules of TBA with esd's in Parentheses

	MA	TBA(A)	TBA(B)
N(1)-C(1)	1.406(3)	1.416(5)	1.415(5)
N(1)-C(7)	1.278(3)	1.263(5)	1.262(5)
N(2)-C(7)	1.374(3)	1.441(5)	1.424(5)
N(2)-C(9)	1.480(3)	1.482(5)	1.472(5)
N(2)-C(13)	1.470(3)	1.477(4)	1.482(5)
C(1)-C(2)	1.391(3)	1.395(7)	1.392(6)
C(1)-C(6)	1.378(4)	1.378(6)	1.388(6)
C(2)-C(3)	1.378(4)	1.387(7)	1.372(7)
C(3)-C(4)	1.381(4)	1.365(9)	1.357(7)
C(4)-C(5)	1.369(4)	1.367(8)	1.371(6)
C(5)-C(6)	1.375(4)	1.375(6)	1.373(6)
C(7)-C(8)	1.516(3)	1.529(5)	1.536(6)
C(9)-C(10)	1.528(4)	1.523(6)	1.534(6)
C(9)-C(14)	1.520(4)	1.528(6)	1.499(6)
C(10)-C(11)	1.507(4)	1.498(8)	1.499(9)
C(11)-C(12)	1.509(4)	1.498(8)	1.489(9)
C(12)-C(13)	1.521(4)	1.528(5)	1.515(6)
C(13)-C(15)	1.505(4)	1.506(6)	1.507(6)
C(8)-C(16)		1.509(6)	1.519(7)
C(8)-C(17)		1.498(7)	1.488(8)
C(8)-C(18)		1.529(7)	1.523(7)
C(1)-N(1)-C(7)	122.0(2)	126.6(3)	125.7(3)
C(7)-N(2)-C(9)	117.3(2)	116.0(3)	116.4(3)
C(7)-N(2)-C(13)	121.1(2)	116.0(3)	117.0(3)
C(9)-N(2)-C(13)	119.0(2)	110.7(3)	110.9(3)
N(1)-C(1)-C(2)	119.5(2)	119.1(4)	119.3(4)
N(1)-C(1)-C(6)	122.8(2)	121.3(4)	122.0(3)
C(2)-C(1)-C(6)	117.5(2)	118.8(4)	118.2(4)
C(1)-C(2)-C(3)	121.3(2)	119.5(5)	120.4(4)
C(2)-C(3)-C(4)	119.9(3)	120.8(5)	120.7(4)
C(3)-C(4)-C(5)	119.3(3)	119.5(5)	119.9(4)
C(4)-C(5)-C(6)	120.6(3)	120.8(5)	120.5(4)
C(1)-C(6)-C(5)	121.4(3)	120.5(4)	120.3(4)
N(1)-C(7)-N(2)	119.3(2)	126.6(3)	126.9(4)
N(1)-C(7)-C(8)	123.6(2)	116.2(3)	115.5(4)
N(2)-C(7)-C(8)	117.1(2)	117.2(3)	117.5(4)
N(2)-C(9)-C(10)	110.3(2)	107.8(3)	108.3(3)
N(2)-C(9)-C(14)	113.3(2)	111.9(4)	112.8(4)
C(10)-C(9)-C(14)	112.7(2)	110.4(4)	110.4(4)
C(9)-C(10)-C(11)	112.4(2)	112.9(4)	113.1(4)
C(10)-C(11)-C(12)	108.6(2)	110.6(4)	110.5(5)
C(11)-C(12)-C(13)	112.2(2)	111.9(4)	113.0(4)
N(2)-C(13)-C(12)	111.0(2)	108.6(3)	108.9(3)
N(2)-C(13)-C(15)	113.5(2)	113.1(3)	113.3(4)
C(12)-C(13)-C(15)	112.4(3)	109.2(3)	110.5(4)
C(7)-C(8)-C(16)		113.5(3)	113.4(4)
C(7)-C(8)-C(17)		109.8(4)	109.5(4)
C(7)-C(8)-C(18)		109.7(3)	109.5(4)
C(16)-C(8)-C(17)		109.9(4)	110.9(5)
C(16)-C(8)-C(18)		108.1(4)	107.0(4)
C(17)-C(8)-C(18)		105.6(4)	106.3(5)

is clearly expressed by the angles among the mean planes, called respectively PH, AM, and PIP, through the phenyl, amidinic, and piperidyl groups (Table V). In MA, these three planes undergo a continuous counterclockwise rotation of 14° from PH to AM and of 75° from AM to PIP. In TBA, the three planes are approximately mutually orthogonal.

A selection of the most important torsion angles in MA, TBA(A), and TBA(B) is reported in Table VI.

Bond distances and angles of the two independent molecules of TBA have been compared by means of half-normal probability plots.[9] The plots are nearly linear and their regression parameters for bond distances and angles are respectively: intercept, −0.04 and 0.02; slope, 1.08 and 1.30; correlation coefficients, 0.97 and 0.98, showing that the two sets of values are statistically indistinguishable and that their standard deviations are substantially correct.

Table V. Angles (Degrees) among the Least-Squares Planes through the Phenyl Group (Ph), the Amidinic Group [N(1), N(2), C(7), C(8) (AM)], and the Piperidyl Group [N(2), C(9), C(10), C(11), C(12), C(13) (PIP)]

	MA	TBA(A)	TBA(B)
Ph-AM	74.6	84.6	76.8
AM-PIP	14.1	87.3	84.0
Ph-PIP	86.0	80.3	77.9

Table VI. A Selection of Torsion Angles (Degrees)

	MA	TBA(A)	TBA(B)
C(2)-C(1)-N(1)-C(7)	111.7	101.5	107.8
C(6)-C(1)-N(1)-C(7)	−74.4	−88.8	−80.4
C(1)-N(1)-C(7)-N(2)	173.9	−1.9	−0.9
N(1)-C(7)-N(2)-C(9)	−0.4	−62.6	−59.4
N(1)-C(7)-N(2)-C(13)	161.4	69.8	75.1
C(7)-N(2)-C(9)-C(10)	−152.6	−162.8	−161.7
C(7)-N(2)-C(9)-C(14)	80.0	−41.3	−39.0
C(7)-N(2)-C(13)-C(12)	153.1	162.3	161.3
C(7)-N(2)-C(13)-C(15)	−79.3	40.9	37.9
N(2)-C(9)-C(10)-C(11)	−51.1	−57.1	−55.9
N(2)-C(13)-C(12)-C(11)	51.2	57.1	56.7
C(9)-C(10)-C(11)-C(12)	59.2	52.5	51.1
C(13)-C(12)-C(11)-C(10)	−59.0	−52.0	−51.4

All the bond distances and angles are quite normal and similar in the two compounds, with the exception of those of the amidinic group. The values of the C(7)-N(2) and C(7)-N(1) bond distances indicate different bond orders for the two C-N bonds in TBA and MA. In TBA, the C(7)-N(1) bond length of (on average) 1.262 Å corresponds well to that of a pure double bond and the C(7)-N(2) bond length of (on average) 1.433 Å corresponds to the value of 1.43 Å usually taken as that of a single $C(sp^2)$-$N(sp^3)$ bond, while the values of the corresponding bond distances in MA [C(7)-N(1) = 1.278; C(7)-N(2) = 1.374 Å] are both intermediate between those of a single and a double bond. The different double bond contribution to C(7)-N(2) is paralleled by the different pyramidality of the piperidyl N atom, as the distances from the plane C(7), C(9), C(13) of the N(2) atom are respectively 0.36, 0.34, and 0.13 Å in TBA(A), TBA(B), and MA. The different degree of pyramidality is reflected by the mean value of the bond angles at the piperidyl N(2) atom, the value of which is 114.2° in TBA(A), 114.8° in TBA(B), and 119.1° in MA.

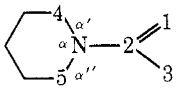
Conversely, the bond distances N(1)-C(1) are not significantly different in MA and TBA, suggesting that the phenyl π orbitals are decoupled from the π system of the amidinic group, which is to be expected as in both compounds the phenyl group is nearly perpendicular to the amidinic group plane. The endocyclic phenyl angle C(2)-C(1)-C(6) is similar [118.8, 118.2, and 117.5° in TBA(A), TBA(B), and MA, respectively] in both compounds and significantly displaced from 120°. As is well known,[10] the contraction of this endocyclic angle can be taken as a measure of the electron-releasing properties of the substituent when, as in the present case, conjugative effects are absent. A comparison of the average value of 118.2° obtained for the present compounds with the values tabulated[11] for other substituents allows us to classify the group $-N{=}C(R)NR_2$ as one of the strongest electron-releasing groups for pure inductive effect.

Discussion of the Structures

An analysis of the differences between the two compounds suggests that they could be rationalized according to the following general scheme;

(a) The piperidyl ring, by itself, tends to be coplanar with

Table VII.[13] Geometry around the N Atom in Piperidine Derivatives and Other Related Groups[a]



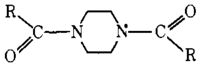
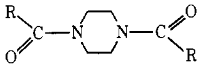
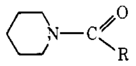
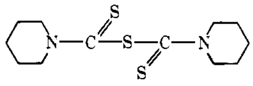
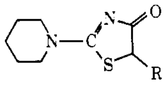
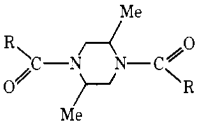
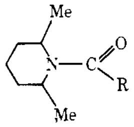
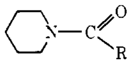
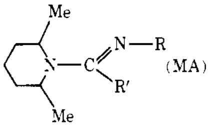
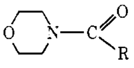
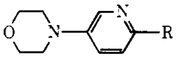
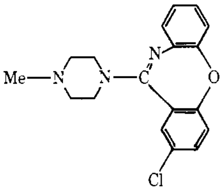
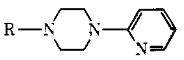
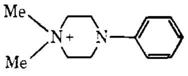
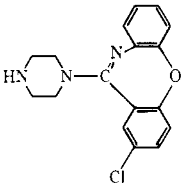
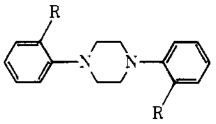
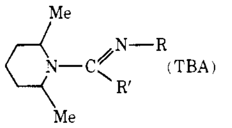
	T	d	α	$\bar{\alpha}$	ref
	2.2[b]	1.345	112.0	119.5	14
	1.2[b]	1.316	113.1	120.0	15
	3.3[c]	1.342	113.5	119.9	16
	4.1[b] 5.3[b]	1.289 1.344	113.0 111.0	120.0 120.0	17
	5.3[c]	1.314	114.2	119.7	18
	5.6[c] 9.5[c]	1.350 1.353	115.3 116.3	120.0 119.9	19
	7.2[c]	1.349	119.3	119.8	20
	8.1[c]	1.350	114.2	119.9	21
	9.7[c]	1.374	119.0	119.1	this work
	11.3[c]	1.343	113.6	118.9	22
	17.4[c]	1.383	114.3	117.0	23
	19.4[c]	1.381	113.0	116.7	24
	20.0[c]	1.383	111.2	116.1	25
	25.0[c]	1.41	112.0	114.0	26
	25.1[c]	1.394	112.0	115.3	24
	48.0[c] 68.6[c]	1.430 1.427	110.0 109.8	113.5 112.9	27

Table VII. (*Continued*)

	T	d	α	$\bar{\alpha}$	ref
 (TBA)	66.2[c]	1.441	110.7	114.2	
	67.2[c]	1.424	110.9	114.8	this work

[a] Distances in Å and angles in degrees. [b] Angle between the planes 1,2,3,N and 2,N,4,5. [c] Mean value of the torsion angles 1,2,N,4 and 1,2,N,5.

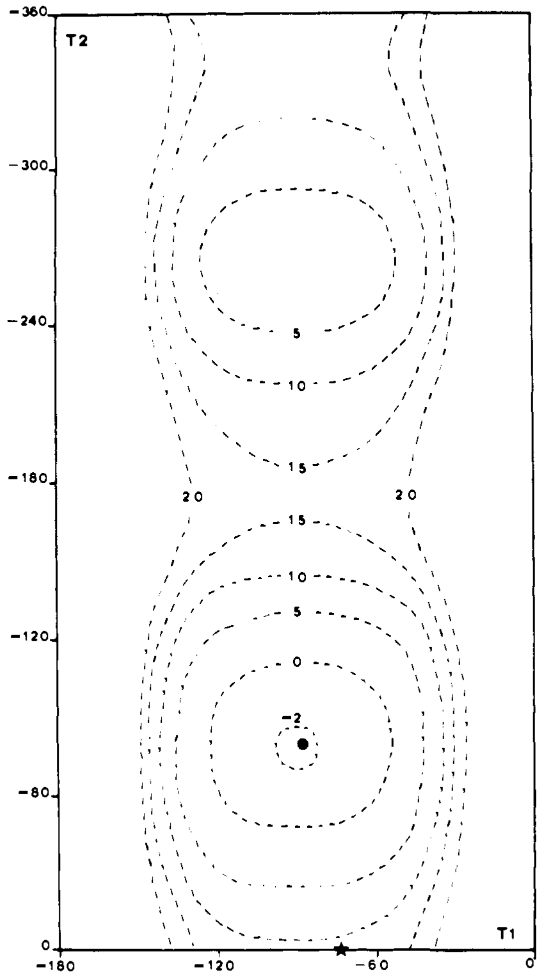


Figure 3. Intramolecular potential energy (kcal/mol) calculated for MA as a function of the torsion angles T1 = C(6)-C(1)-N(1)-C(7) and T2 = N(1)-C(7)-N(2)-C(9). Calculated and experimental minima are indicated by a circle and a star, respectively.

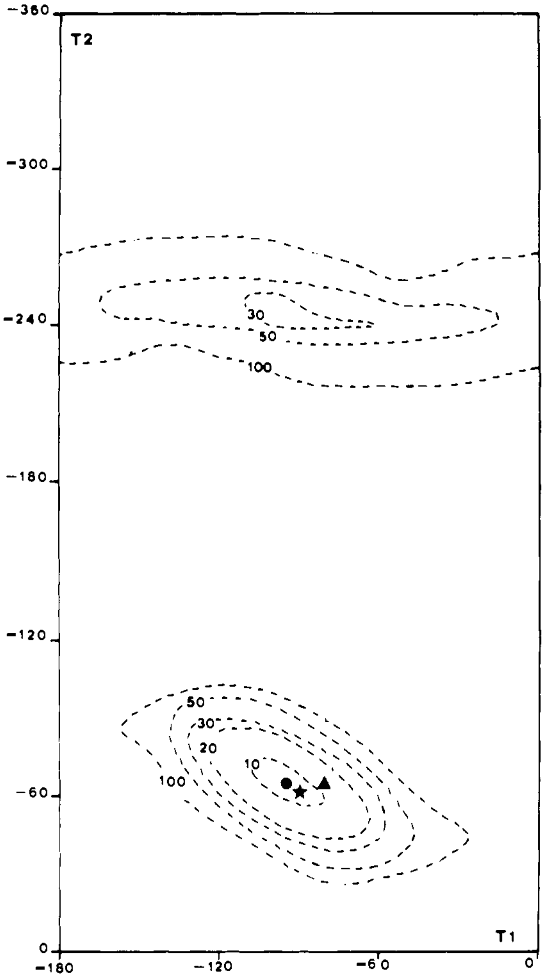


Figure 4. Intramolecular potential energy (kcal/mol) calculated for TBA(A) as a function of the torsion angles T1 = C(6)-C(1)-N(1)-C(7), T2 = N(1)-C(7)-N(2)-C(9) and T3 = N(1)-C(7)-C(8)-C(16). The section shown is that displaying the absolute minimum of energy and corresponds to T3 = 180.7°. The calculated minimum and the experimental minima for TBA(A) and TBA(B) are indicated by a circle, a star, and a triangle, respectively.

the amidinic moiety owing to the partial double bond character of the C(7)-N(2) bond.

(b) Only in extreme cases, as in TBA, can the steric hindrance of the substituent groups force a conformation in which the two moieties are nearly orthogonal, producing therefore a total decoupling between the π system of the amidinic group and the p_z orbital of the N(2) atom.

(c) The different bond order of the C(7)-N(2) bond determines, accordingly, the C(7)-N(2) and C(7)-N(1) bond distances and the degree of pyramidality of the N(2) atom.

(d) The rather unusual diaxial conformation of the two 2,6-*cis*-methyl groups on the piperidyl ring, observed in MA, is likely to be produced by the fact that the axial-to-axial repulsion between the two methyl groups is smaller than the repulsion between equatorial methyl groups and substituent groups when the piperidyl and amidinic moieties are nearly coplanar.

The role played by the partial double bond character of the C(7)-N(2) bond in flattening the molecule can be proved, in the present case, by the following simple arguments. The torsion angles C(6)-C(1)-N(1)-C(7) = T1 and N(1)-C(7)-N(2)-C(9) = T2 for MA and TBA(A) and the additional angle N(1)-C(7)-C(8)-C(16) = T3 for TBA(A) have been estimated by minimizing the nonbonded intramolecular potential energy U of the free molecules by using semiempirical atom-atom potential curves.[12] The map U(T1,T2) for MA is shown in Figure 3, and in Figure 4 is reported the section of the map U(T1,T2,T3), calculated for TBA(A) for T3 = 180.7°, the value which corresponds to the section with the lowest absolute value of energy and which is not far from the experi-

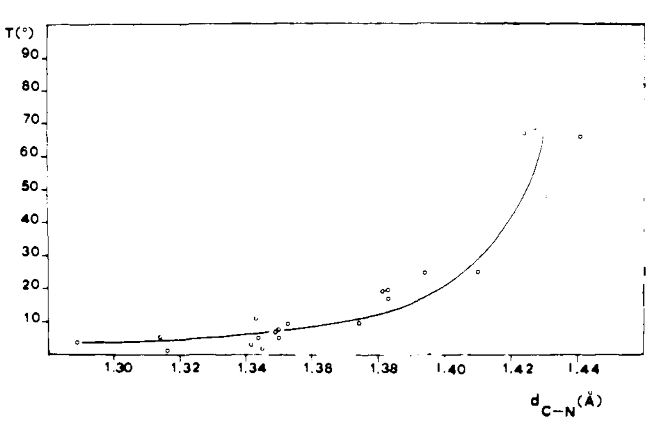


Figure 5. Plot of the torsion angle around the C(7)–N(2) bond, *T*, *vs.* the bond distance C(7)–N(2), *d*, for all the data of Table VII. The continuous line shows the least-squares curve calculated assuming a hyperbolic dependence of *d* on *T*.

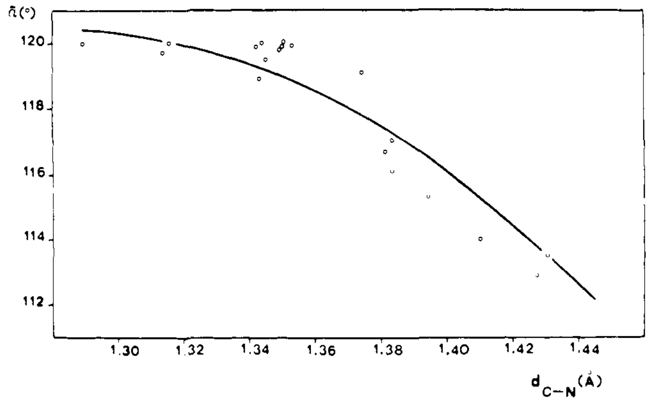


Figure 6. Plot of the mean bond angle at the N(2) atom, $\bar{\alpha}$, vs. the bond distances C(7)–N(2), *d*, for all the data of Table VII. The continuous line shows the least-squares curve calculated assuming a parabolic dependence of $\bar{\alpha}$ on *d*.

mental value of T3 = 174.5°. The absolute minima are found at T1 = −88.9 and T2 = −80.6° for MA and at T1 = −94.4 and T2 = −64.9° for TBA(A). Both the calculated and the experimental values are marked in Figures 3 and 4, and their comparison reveals that the preferred conformation of the piperidyl group is always that nearly perpendicular to the amidinic group, as far as the nonbonded interactions alone are acting on the molecule, showing that the different conformation found experimentally for MA (piperidyl and amidinic groups nearly coplanar) is caused by a different factor, which can be tentatively identified in the partial double bond character of the C(7)–N(2) bond.

Arguments supporting points a, b, and c given above can be obtained from a general analysis of the structural parameters of molecules having a C(sp^2)–N(piperidyl) bond, mainly amides, thioamides, dithioamides, amidines, and molecules where the N (piperidyl) atom is linked to an aromatic carbon. These molecules are listed in Table VII together with the parameters of interest, that is, the values of the torsion angle around C(7)–N(2), *T*, bond distance C(7)–N(2), *d*, endocyclic angle at N(2), α, and the mean value of the three bond angles at N(2), $\bar{\alpha}$. The $\bar{\alpha}$ value can be taken as a measure of the degree of pyramidality of the piperidyl nitrogen; this parameter was chosen as the alternative parameter, the distance of N(2) from the plane of the three bonded atoms, was seldom given in the referenced literature. The data of the table are rearranged in Figures 5 and 6 as plots $T = f(d)$ and $\bar{\alpha} = f(d)$, respectively.

Figure 5 shows that the bond distance C–N is dependent on the torsion angle *T* and that values of *d* approaching a pure

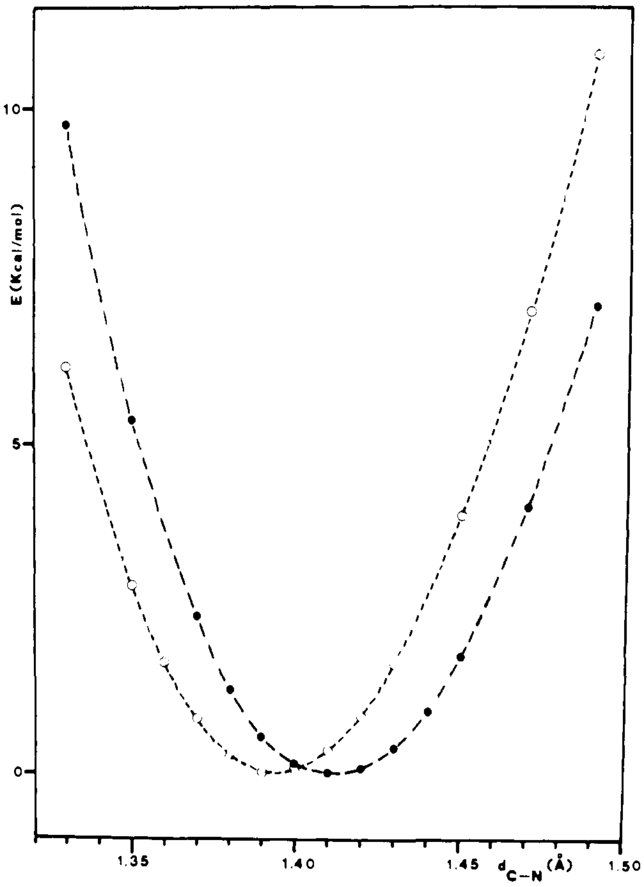
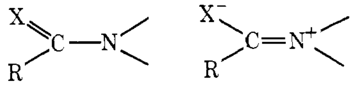


Figure 7. Total energy (kcal/mol) of the molecule calculated in the INDO[29,30] approximation for MA (open circles) and TBA(A) (full circles) as a function of the internuclear distance C(7)–N(2).

single bond C(sp^2)–N(sp^3) can be observed only when the torsion angle *T* tends to 90°. The observed value of *T* appears to be determined by the balance of two opposing forces, one arising from the double bond contribution to the C–N bond and the other arising from the steric hindrance of the substituents. In spite of the fact that such a delicate balance could be affected by the field of the crystal forces, the data of Table VII indicate, in agreement with the expectation, that the values of *T* increase with the increasing steric hindrance of the substituents *and* with the decreasing contribution of the polar form B to the ground state of the molecule. This model fits the experimental evidence that amides (the compounds of the series known to have the highest contribution of the polar form B) tend to be planar irrespective, within the due limits, of the steric hindrance of the substituents[28] and fits, moreover, the intuitive concept that the wide range (1.29 + 1.38 Å) of bond distances observed for the small interval 0° ≤ *T* ≤ 10° (see Figure 5) could be hardly interpreted only in terms of a functional dependence of *d* on *T*. In fact, the difference of π energy associated with a rotation of only 10° is small, as can be estimated computing the overlap integral between two p orbitals on adjacent C and N atoms as a function of the torsion angle; the variation of such an integral is determined by the cosine of the torsion angle and amounts only to 1.5% for a rotation from 0 to 10°.



A B

X = O, S, NR, CHR

The variation in pyramidality of the N(2) atom expressed as mean value, $\bar{\alpha}$, of the bond angle at N(2) as a function of the

C(7)-N(2) bond distance, *d*, is shown in Figure 6 for all the data of Table VII. The flattening of the bonds at N(2) increases with decreasing *d* and therefore with the increasing double bond character of the C(7)-N(2) bond. As the $\overline{\alpha}$ value ranges from 120 to 112.9° while the C-N distance changes from a double to a single bond length, the plot can be interpreted in terms of a continous variation of the state of hybridization of the piperidyl N atom from sp^2 to sp^3. Conversely, the value of the endocyclic angle, α, cannot be taken as a good indicator of the state of hybridization of the N atom. In fact, a weak dependence of α on *d* is observed only for those compounds not having nonequatorial 2,6-cis substituents in the piperidyl ring, while rings in a chair conformation with diaxial 2,6-cis substituents (MA and compound of ref 20) display endocyclic angles far smaller then expected, and an intermediate behavior is observed in case of 2,6 substituents in twisted-boat rings.[19]

A more direct proof of the intercorrelations among the different geometrical parameters would be obtained by minimizing the total energy of the molecule by means of "ab initio" or semiempirical quantum-mechanical calculations. Unfortunately, the interconversion path from the conformation in which the amidinic and piperidyl moieties are coplanar to that in which they are orthogonal appears to be rather complicated; it has been shown in the present paper that it implies the variation of at least five different parameters, that is, the torsion angle around the C(7)-N(2) bond, the bond distances C(7)-N(2) and C(7)-N(1), the pyramidality of the N(2) atom, and the switching of the 2,6-*cis*-methyl groups from a diaxial to a diequatorial conformation. Moreover, this last process could imply a transition state in which the piperidyl ring itself is twisted. As a minimization, accounting for all the degrees of freedom of the molecule appeared to be a difficult problem to deal with; a simple minimization of the energy as a function of the C(7)-N(2) bond distance, all other geometrical factors remaining constant, has been undertaken for the two molecules MA and TBA(A). The starting coordinates were those of Tables II and III and the calculations were carried out in the INDO[29,30] approximation. A plot of the total energy (expressed in kcal/mol above the absolute minima) as a function of the internuclear C(7)-N(2) distance for MA and TBA(A) is reported in Figure 7. The plot confirms the idea of a shorter internuclear equilibrium C-N distance in MA than in TBA(A), in spite of a certain discrepancy between the calculated [1.394 Å in MA and 1.414 Å in TBA(A)] and experimental values [1.374 Å in MA and (on average) 1.433 Å in TBA].

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Supplementary Material Available: Anisotropic thermal parameters, bond distances and angles involving hydrogen atoms, and observed and calculated structure factor amplitudes (29 pages). Ordering information is given on any current masthead page.

References and Notes

(1) L. Lunazzi, G. Cerioni, and K. U. Ingold, *J. Am. Chem. Soc.*, **98**, 7484 (1976).

(2) L. Lunazzi, G. Placucci, and G. Cerioni, *J. Chem. Soc., Perkin Trans. 2*, 1666 (1977).

(3) L. Lunazzi, G. Cerioni, E. Foresti, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 686 (1978).

(4) L. Lunazzi, D. Macciantelli, D. Tassi, and A. Dondoni, *J. Chem. Soc., Perkin Trans. 2*, in press.

(5) P. Main, M. M. Woolfson, L. Lessinger, G. Germain, and J. P. Declercq, "MULTAN 74. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", University of York, England, and Louvain, Belgium, 1974.

(6) G. Sheldrick, "SHELX 76. Program for Crystal Structure Determination", University of Cambridge, England, 1976.

(7) "International Tables for X-Ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974, p 73.

(8) C. K. Johnson, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1971.

(9) S. C. Abrahams and E. T. Keve, *Acta Crystallogr., Sect. A*, **27**, 157 (1971).

(10) A. Domenicano, A. Vaciago, and C. A. Coulson, *Acta Crystallogr., Sect. B*, **31**, 221 (1975).

(11) A. Domenicano, P. Mazzeo, and A. Vaciago, *Tetrahedron Lett.*, **13**, 1029 (1976).

(12) G. Giglio, *Nature (London)*, **222**, 339 (1969).

(13) The six-membered ring adopts a chair conformation in all the compounds reported in Table VII but that corresponding to ref 19, where a twisted-boat conformation is adopted. The C(sp^2) atom is always linked to the ring in equatorial position. The 2,6-*cis*-methyl groups of the compound of ref 20 are in diaxial conformation.

(14) L. Olansky and J. W. Moncrief, *Acta Crystallogr., Sect. B*, **29**, 357 (1973).

(15) T. M. Ko and J. W. Moncrief, *Acta Crystallogr., Sect. B*, **31**, 2544 (1975).

(16) D. Tranqui, D. T. Cromer, and A. Boucherle, *Acta Crystallogr., Sect. B*, **30**, 2237 (1974).

(17) P. L. Johnson and I. C. Paul, *J. Chem. Soc. B*, 1296 (1970).

(18) A. F. Cameron and N. J. Hair, *J. Chem. Soc. B*, 1733 (1971).

(19) T. Sakurai, D. T. Nakamaru, S. Tsuboyama, and K. Tsuboyama, *Acta Crystallogr., Sect. B*, **33**, 3568 (1977).

(20) E. Arte, J. Feneau-Dupont, J. P. Declercq, G. Germain, and M. van Meerssche, *Cryst. Struct. Commun.*, **6**, 773 (1977).

(21) E. Arte, J. Feneau-Dupont, J. P. Declercq, G. Germain, and M. van Meerssche, *Cryst. Struct. Commun.*, **6**, 493 (1977).

(22) E. Arte, J. Feneau-Dupont, J. P. Declercq, G. Germain, and M. van Meerssche, *Cryst. Struct. Commun.*, **6**, 767 (1977).

(23) J. N. Brown and K. C. Agrawal, *Acta Crystallogr., Sect. B*, **34**, 1002 (1978).

(24) D. B. Cosulich and F. M. Lovell, *Acta Crystallogr., Sect. B*, **33**, 1147 (1977).

(25) M. H. J. Koch, G. Germain, J. P. Declercq, and M. van Meerssche, *Acta Crystallogr., Sect. B*, **33**, 1975 (1977).

(26) C. Chothia and P. Pauling, *Acta Crystallogr., Sect. B*, **34**, 2986 (1978).

(27) P. B. Donaldson, C. G. Griggs, and P. A. Tasker, *Cryst. Struct. Commun.* **6**, 597 (1977).

(28) This statement is substantially correct when referred to piperidyl and 2,6-substituted piperidylamides (see ref 4). However, relevant departures from planarity have been observed in other classes of amides having bulky substituents, e.g., in benzoylphenylhydrazones [S. A. Puckett, M. K. Greensley, I. C. Paul, and D. Y. Curtin, *J. Chem. Soc., Perkin Trans. 2*, 847 (1977), and references therein].

(29) P. Dobosh and N. S. Ostlund, "CNINDO/74", Quantum Chemical Program Exchange, Vol. 10, 1974, p 281.

(30) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, 1970.