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The Absolute Configuration of Pyrazidole

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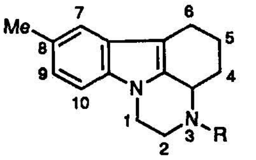
The absolute configuration of 8-methyl-3-(-*S*-α-phenylethyl)-2,3,3a-*S*,4,5,6-hexahydro-1*H*-pyrazino-[3,2,1-*jk*]carbazole has been established on the basis of the stereospecificity of its ^{1}H and ^{13}C NMR parameters, which, taking into account the synthetic scheme, provides evidence for an *S*-configuration of the aymmetric C-3a atom in the original (+)-pyrazidole.



1; R = H
2; R = (*S*)-Ph(Me)CH—

Pyrazidole, the racemate of 2,3,3a,4,5,6-hexahydro-8-methyl-1*H*-pyrazino-[3,2,1-*jk*]carbazole chlorohydrate (1 HCl), is a well-known medicinal preparation: an antidepressant that acts as a highly selective inhibitor of A-type monoaminooxidase.[1] Its UV and ^{13}C NMR spectra have been measured and an X-ray crystallographic analysis has been carried out.[2,3] Recently, pyrazidole has been separated into enentiomers,[4,5] the pharmacological activity of which has been investigated.[5] Thus, it is of interest to determine the absolute configuration of pyrazidole.

In the present work, a diastereoisomerically pure derivative of pyrazidole **2** {m.p. 121–122°C, $[\alpha]_D + 48$ (*c* 0.5, CHCl$_3$)}, hydrogenolysis of which yields the base pyrazidole (+)-**1**,[4,5] was studied.

In order to establish the absolute configuration we used the method of ref. 6, based on the stereospecificity of the ^{1}H and ^{13}C NMR parameters relative to the lone electron pair of the nitrogen atom. First, we carried out a population analysis of the N—CH(Ph)Me bond rotamers using the molecular mechanics MM2 method[7] for the two possible configurations of the C-3a centre using a modified MM2/MMP2(85) program[8] and taking into account the effective dielectric permeability of the medium (CDCl$_3$ solvent).[9] In this case, conformers with an antiperiplanar orientation of the lone pair of the nitrogen atom N-3 and the proton at C-3a were computed from the magnitude of the directly bonded carbon–proton spin–spin coupling constant, ^1J(C-3a, H-3a), and its stereospecificity relative to the nitrogen lone pair.[6] As far as the phenyl substituent is concerned, we conclude that it has an equatorial orientation, based on the $^2J_{2a2e}$ value and the stereospecificity of the geminal $^2J_{HH}$ coupling relative to the nitrogen long pair.[10] As shown in Fig. 1, the 3a-*S*,3′-*S*(**a**) and 3a-*R*,3′-*S*(**b**) rotamers are the most energetically preferable ones. According to the NMR data,† the magnitudes of the chemical shifts, δ_H and δ_C, and also the $^1J_{CH}$ and $^1J_{CC}$ values for the phenyl residue taking into account the boundary values, given in ref. 6, provide evidence for a rotamer with an antiperiplanar orientation of the methyl substituent relative to the nitrogen lone pair. It follows that the C-3a centre in **2**, and hence also in **1**, has an *S*-configuration.

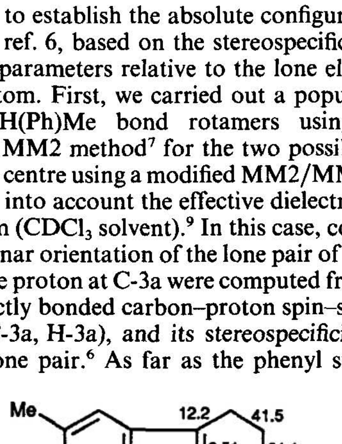


Fig. 1 Energies for various conformations of the N—CH(Ph)Me bond rotamers (**a**, **b**, **c**) of **2** calculated using the MM2 method

From published data on the conformational analysis of cyclohexenes and their heteroatomic analogues,[3,11] one may suppose that the cyclohexenic residue of molecule **2** in solution is characterized by a 'half-chair' conformation. A similar conformation can also be expected for the piperazine ring of molecule **2**, bearing in mind the planar conformation of the pyrrole residue. The numerical results of the MM2 computations confirm the preference for 'half-chair' conformations in the six-membered rings (Fig. 2).

The J_{HH} values measured correspond to the calculated conformations. Using dihedral angles determined by the MM2 method, $^3J_{HH}$ coupling constants were computed according to the modified Karplus-type equations proposed in refs. 12 and 13. Good agreement was found between 14 of the pairs of

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† NMR spectra were measured using a Bruker WM-400 spectrometer with a working frequency of 400 MHz for ^{1}H nuclei and 100.6 MHz for ^{13}C ones. In order to determine the NMR parameters with high accuracy (±0.02–0.1 Hz), narrow spectral ranges were chosen.

^{1}H NMR data for compound **2**: (CDCl$_3$, J/Hz) δ 2.84 (1H, H$_{1a}$, $^2J_{1a1e}$, −11.75, $^3J_{1a2a}$ 11.70, $^3J_{1a2e}$ 3.74), 2.87 (1H, H$_{1e}$, $^3J_{1e2a}$ 5.41, $^3J_{1e2e}$ 1.61), 3.56 (1H, H$_{2a}$, $^2J_{2a2e}$ −10.53), 3.98 (1H, H$_{2e}$), 4.79 (1H, N—CH, $^3J_{CH,Me}$ 6.71), 1.60 [3H, N—CH(Ph)Me], 3.90 (1H, H$_{3a}$, $^3J_{3a4a}$ 10.68, $^3J_{3a4e}$ 4.88, $^5J_{3a6a}$ 2.35, $^5J_{3a6e}$ 1.75), 1.63 (1H, H$_{4a}$, $^2J_{4a4e}$ −11.75, $^3J_{4a5a}$ 13.65, $^3J_{4a5e}$ 2.59), 2.43 (1H, H$_{4e}$, $^3J_{4e5a}$ 2.44, $^3J_{4e5e}$ 4.27), 1.97 (1H, H$_{5a}$, $^3J_{5a5e}$ −13.65, $^3J_{5a6a}$ 11.60, $^3J_{5a6e}$ 6.41), 2.28 (1H, H$_{5e}$, $^3J_{5e6a}$ 5.95, $^3J_{5e6e}$ 1.53), 2.77 (1H, H$_{6a}$, $^2J_{6a6e}$ −15.72), 2.87 (1H, H$_{6e}$); 7.45–7.70 (5H, Ph), 2.71 (3H, 8-CH$_3$).

^{13}C NMR data for **2**: (CDCl$_3$ J/Hz) 42.73 (C$_1$, $^1J_{CH_a}$ 131.1, $^1J_{CH_e}$ 135.4), 43.10 (C$_2$, $^1J_{CH_a}$ 138.8, $^1J_{CH_e}$ 140.7), 53.55 (C$_{3''}$ $^1J_{CH}$ 135.4, $^1J_{C_{3'}C_{3''}}$ 35.2), 8.14 (C$_{3'''}$ $^1J_{CH}$ 125.4), 55.30 (C$_{3a}$, $^1J_{CH}$ 131.1), 27.80 (C$_4$, $^1J_{CH_a}$ 127.8, $^1J_{CH_e}$ 128.3), 22.21 (C$_5$, $^1J_{CH_a}$ 125.9, $^1J_{CH_e}$ 129.7), 20.57 (C$_6$, $^1J_{CH_a}$ 126.4, $^1J_{CH_e}$ 128.8), 106.56 (C$_{6a}$), 128.04 (C$_{6b}$), 118.00 (C$_7$, $^1J_{CH}$ 155.0), 135.99 (C$_8$), 21.50 (C$_{8''}$ $^1J_{CH}$ 125.4), 121.92 (C$_9$, $^1J_{CH}$ 156.2), 108.52 (C$_{10}$, $^1J_{CH}$ 157.8), 135.69 (C$_{10a}$), 128.26 (C$_{11a}$), 143.48 (C$_q$, $^1J_{C_qC_3}$, 47.9), 126.41–127.80 (Ph).

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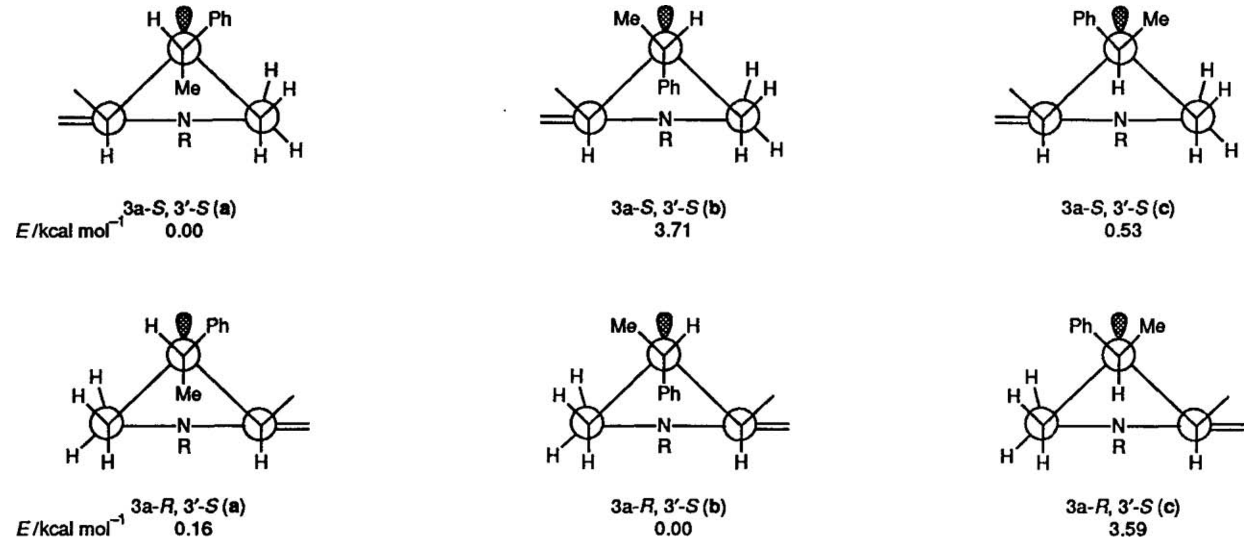

3a-*S*, 3′-*S* (a) *E*/kcal mol⁻¹ 0.00

3a-*S*, 3′-*S* (b) 3.71

3a-*S*, 3′-*S* (c) 0.53

3a-*R*, 3′-*S* (a) *E*/kcal mol⁻¹ 0.16

3a-*R*, 3′-*S* (b) 0.00

3a-*R*, 3′-*S* (c) 3.59

Fig. 2 MM2 calculated torsional angles for **2**; 1 cal = 4.184 J

experimental and theoretical ${}^3J_{HH}$ values, the latter having a r.m.s. deviation of 0.6 Hz from the Haasnoot–de Leeuw–Altona equation[10] and 0.9 Hz from the Imai–Osawa equation,[11] indicating that the ‘half-chair’ conformation of the six-membered rings is conserved in solution ($CDCl_3$). A major deviation was found for ${}^3J_{3a4e}$ (${}^3J^{dev}_{3a4e} = 2.8$ Hz) in the case of the Imai–Osawa equation. This is thought to be caused by the absence of an appropriate term in the latter equation to express the contribution of the π-orbitals from adjacent double bonds to ${}^3J_{HH}$.

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