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2-(1-Naphthylmethyl)-2-imidazoline Hydrochloride (Naphazoline Hydrochloride), $C_{14}H_{15}N_2^+.Cl^-$, an α-Adrenergic Agonist

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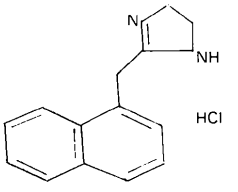
Abstract. $M_r = 246{\cdot}73$, monoclinic, $P2_1/c$, $a = 11{\cdot}895\ (3)$, $b = 9{\cdot}228\ (2)$, $c = 12{\cdot}820\ (3)$ Å, $\beta = 117{\cdot}18\ (2)°$, $V = 1252$ Å^3, $Z = 4$, $D_m = 1{\cdot}30$, $D_x = 1{\cdot}29$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 2{\cdot}48$ mm^{-1}, $F(000) = 524$, $T = 277\ (1)$ K. Final $R = 0{\cdot}040$ for 1291 observed reflections. The folded conformation of the molecule is different from the extended one usually preferred by similar biologically active compounds.

Introduction. Naphazoline exhibits many of the pharmacological activities of epinephrine. However, its chemical structure differs considerably from that of the usual sympathomimetic amines. The skeleton of most of the sympathomimetic amines is comprised of a benzene ring and an ethylamine side chain attached to it, whereas in naphazoline, the ethylamine side chain becomes a part of the heterocyclic ring. Naphazoline is an α-adrenergic agonist and powerful hypertensive vasoconstrictor of low toxicity. The outstanding cardiovascular action of naphazoline is to constrict peripheral blood vessels, although it is used chiefly as a nasal and ocular decongestant. It is a powerful α-receptor stimulant, but naphazoline differs from other sympathomimetic amines in that it depresses instead of stimultes the CNS (Weiner, 1980).



Experimental. Single crystals grown by slow evaporation of an aqueous solution at room temperature (301 K), density determined by flotation in a mixture of bromoform and benzene, cell dimensions first determined from rotation and Weissenberg photographs and later more accurately on a diffractometer kept at 277 (1) K by centring 15 reflections in range $45 < 2\theta < 67°$; systematic absences $0k0$ for k odd and $h0l$ for l odd indicated space group $P2_1/c$; data collected with a crystal 0·25 × 0·20 × 0·40 mm, ω–2θ scan mode, Syntex $P\bar{1}$ diffractometer, graphite-monochromatized Cu $K\alpha$, 1503 independent reflections measured in range $2\theta \leq 120°$, 1291 of these considered observed with $I > 3\sigma(I)$; three standard reflections measured after 97 reflections showed no significant change in intensity; data corrected for geometrical factors but not for absorption; structure solved by direct methods with *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1978); full-matrix least-squares refinement of positional coordinates and isotropic temperature factors of all non-H atoms reduced R to 0·115, quantity minimized $w(|F_o| - |F_c|)^2$, unit weights used throughout refinement; H atoms fixed in calculated positions ($B = 4{\cdot}0$ Å^2) and refinement completed by block-diagonal least-squares cycles with anisotropic temperature factors for non-H atoms; in last cycle $R = 0{\cdot}040$ and $S = 0{\cdot}92$ and parameter shifts were less than their standard deviation; the highest coordinate shift-to-error ratio was 0·42, while the average shift to error = 0·14; final Fourier map featureless; scattering factors from *International Tables for X-ray Crystallography* (1974); *XRAY ARC* (1971) program system used for calculation.

Discussion. The atomic coordinates are given in Table 1* and the atoms are labelled in Fig. 1.

The bond lengths and angles are given in Table 2. In the imidazoline ring, C(8)–N(1) and C(8)–N(2) bonds are short and indicative of double-bond character. N(2) is protonated and both N(1) and N(2) participate in hydrogen bonding. N(1)–H···Cl($x,\frac{1}{2}-y,\frac{1}{2}+z$) = 3·092 (3) Å and N(2)–H···Cl($-x,1-y,1-z$) = 3·133 (3) Å. The H···Cl distances are 2·33 (5) Å and the N–H···Cl angles are 173·7 (5) and 176·8 (5)° respectively. Thus each Cl atom is involved in two intermolecular hydrogen bonds of the form N(1)–H···Cl···H–N(2), that link the molecules into continuous chains parallel to **b** (Fig. 2).

Both the naphthalene and imidazoline rings are planar. The dihedral angle between these two planes is 94·1°. The interesting feature of the present compound

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38278 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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is its molecular conformation when compared to similar biologically active amines. It is to be noted that naphazoline has sympathomimetic properties and a phenethylamine skeleton [C(1) to C(6) as the phenyl ring and C(6)–C(7)–C(8)–N as the side chain] can be thought to be hidden in the molecule. The structure and conformation of a number of conformationally mobile active phenethylamines have been studied and it has been observed that with a few exceptions most of these compounds adopt an extended *trans* conformation (Carlström, Bergin & Falkenberg, 1973; Hebert, 1979; Duax, 1978). This would require the torsion angles τ_1 and τ_2 involving atoms C(1)–C(6)–C(7)–C(8) and C(6)–C(7)–C(8)–N in the present structure to be around ± 90 and $\pm 180°$ respectively. As a result the distance (D_N) of the amino nitrogen from the centre of the benzene ring in phenethylamines is found to be around 5 Å. This distance is thought to be of considerable significance (Horn, 1974; Carlström, 1973; Hebert, 1979). In naphazoline hydrochloride τ_1 and τ_2 are found to be $-176{\cdot}8\,(6)$ and $85{\cdot}4\,(6)°$ respectively which is just the reverse. This indicates that the side chain is almost in the plane of the naphthalene ring and is in the folded form instead of being maximally extended. The conformation is then markedly different from that of most of the other sympathomimetic amines. Since the side chain is folded, the distance D_N of the protonated N atom from the centre of the adjacent phenyl ring in the present compound is 4·30 (1) Å which is much less than the usual value of 5·1 to 5·2 Å obtained for most of the sympathomimetic compounds studied so far. Adrenaline hydrogen tartrate (Carlström, 1973) is an example where the conformation is seen to be different ($\tau_1 = -3°$) but the side chain is extended ($\tau_2 = 179°$) and the distance D_N here is maintained at 5·18 Å. There are, however, some examples of phenethylamines and related compounds where this distance is less than 5 Å (lying between 3·89 to 4·07 Å) but they exhibit the *gauche* ($\tau_2 = 60°$) conformation in the crystal structures (Baker, Chothia, Pauling & Weber, 1973; Ernst & Cagle, 1973; Kennard, Giacovazzo, Horn, Mongiorgi & Riva di Sanseverino, 1974; Grunewald, Walters, Flynn, Atwood & Greese, 1978). It is also interesting to note that like naphazoline, another α-adrenergic agonist, clonidine, differs from the conventional chemical structure of sympathomimetic amines. Clonidine, however, conforms nicely with the preferred conformation of sympathomimetic compounds (Cody & DeTitta, 1979) while naphazoline has an altogether

Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors with their e.s.d.'s in parentheses*

B_{eq} is calculated by the expression $B_{eq} = \frac{4}{3}\sum_i\sum_j \beta_{ij}(a_i a_j)$.

	x	y	z	B_{eq}(Å^2)
Cl	0·1291 (1)	0·2223 (1)	0·5183 (1)	4·0 (1)
N(1)	0·1494 (3)	0·4207 (3)	0·8094 (2)	3·8 (2)
N(2)	0·0778 (3)	0·5738 (3)	0·6644 (3)	3·9 (2)
C(1)	−0·2896 (3)	0·3986 (4)	0·6504 (3)	3·3 (3)
C(2)	−0·3814 (3)	0·3024 (4)	0·5700 (3)	3·9 (3)
C(3)	−0·3480 (4)	0·2104 (5)	0·5011 (3)	4·7 (3)
C(4)	−0·2296 (4)	0·2100 (4)	0·5117 (3)	4·7 (3)
C(5)	−0·1374 (4)	0·3056 (4)	0·5910 (3)	3·9 (3)
C(6)	−0·1656 (3)	0·3988 (4)	0·6588 (3)	3·2 (3)
C(7)	−0·0683 (3)	0·5050 (4)	0·7434 (3)	3·9 (3)
C(8)	0·0536 (3)	0·5005 (4)	0·7393 (3)	3·4 (3)
C(9)	0·2581 (4)	0·4386 (4)	0·7846 (3)	4·0 (3)
C(10)	0·2079 (4)	0·5479 (4)	0·6831 (3)	4·0 (3)
C(11)	−0·3245 (4)	0·4894 (4)	0·7202 (3)	4·1 (3)
C(12)	−0·4441 (5)	0·4847 (5)	0·7091 (4)	5·3 (3)
C(13)	−0·5339 (4)	0·3901 (6)	0·6305 (4)	6·1 (4)
C(14)	−0·5037 (4)	0·3019 (5)	0·5621 (4)	5·5 (3)

Table 2. *Bond distances* (Å) *and bond angles* (°) *with their e.s.d.'s in parentheses*

N(1)–C(8)	1·309 (4)	C(3)–C(4)	1·352 (6)
N(1)–C(9)	1·475 (5)	C(4)–C(5)	1·413 (5)
N(2)–C(8)	1·310 (5)	C(5)–C(6)	1·369 (5)
N(2)–C(10)	1·473 (5)	C(6)–C(7)	1·526 (5)
C(1)–C(2)	1·419 (5)	C(7)–C(8)	1·475 (5)
C(1)–C(6)	1·429 (5)	C(9)–C(10)	1·535 (5)
C(1)–C(11)	1·424 (5)	C(11)–C(12)	1·362 (6)
C(2)–C(3)	1·407 (5)	C(12)–C(13)	1·391 (7)
C(2)–C(14)	1·411 (5)	C(13)–C(14)	1·360 (7)

C(8)–N(1)–C(9)	111·3 (3)	C(1)–C(6)–C(7)	118·4 (3)
C(8)–N(2)–C(10)	111·3 (3)	C(5)–C(6)–C(7)	121·9 (3)
C(2)–C(1)–C(6)	118·7 (3)	C(6)–C(7)–C(8)	113·3 (3)
C(2)–C(1)–C(11)	118·5 (3)	N(1)–C(8)–N(2)	112·3 (3)
C(6)–C(1)–C(11)	122·7 (3)	N(1)–C(8)–C(7)	123·6 (3)
C(1)–C(2)–C(3)	119·3 (3)	N(2)–C(8)–C(7)	124·1 (3)
C(1)–C(2)–C(14)	118·7 (4)	N(1)–C(9)–C(10)	102·5 (3)
C(3)–C(2)–C(14)	122·0 (4)	N(2)–C(10)–C(9)	102·6 (3)
C(2)–C(3)–C(4)	121·2 (4)	C(1)–C(11)–C(12)	120·3 (4)
C(3)–C(4)–C(5)	120·1 (4)	C(11)–C(12)–C(13)	121·2 (5)
C(4)–C(5)–C(6)	121·0 (4)	C(12)–C(13)–C(14)	120·1 (5)
C(1)–C(6)–C(5)	119·7 (3)	C(2)–C(14)–C(13)	121·3 (4)

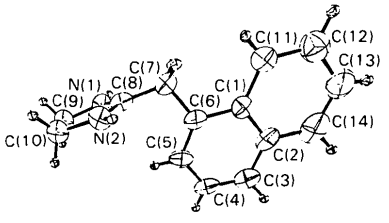

Fig. 1. An *ORTEP* drawing (Johnson, 1965) of the molecule with the atom-numbering scheme. The thermal ellipsoids are recorded at the 50% probability level.

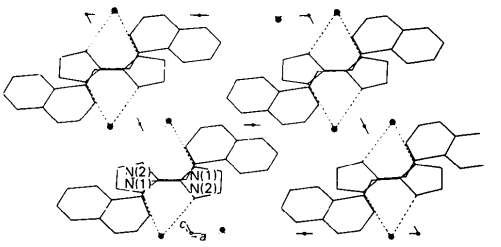

Fig. 2. Projection of the crystal structure down the *b* axis.

different conformation. This conformational difference in naphazoline is of interest particularly in visualizing the complementary α-adrenergic receptor sites.

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Structure du Méthyl-2 Phényl-5 Aza-1 Bicyclo[2.1.0]pentanedicarboxylate-2,4 de Diméthyle, $C_{15}H_{17}NO_4$: Un Premier Exemple de Aza-1 Bicyclo[2.1.0]pentane

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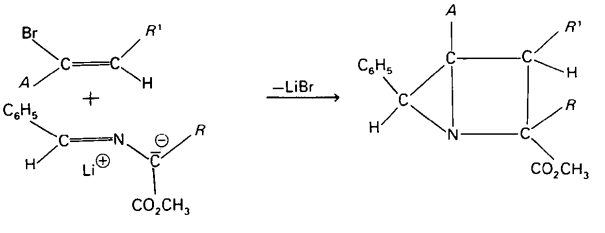
Abstract. $M_r = 275{\cdot}3$, monoclinic, $P2_1/c$, $a = 12{\cdot}127\ (3)$, $b = 11{\cdot}706\ (2)$, $c = 10{\cdot}781$ Å, $\beta = 109{\cdot}3\ (2)°$, $V = 1444$ Å^3, $Z = 4$, $D_x = 1{\cdot}266$ Mg m^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, μ(Mo $K\alpha$) $= 0{\cdot}086$ mm^{-1}, $T = 293$ K, $F(000) = 584$, $R = 0{\cdot}049$ for 960 observations $[I > 0{\cdot}6\sigma(I)]$. This compound is the first example of a 1-azabicyclo[2.1.0]pentane and the X-ray analysis was necessary to confirm such a structure and for stereochemical studies.

Introduction. La formation des aza-1 bicyclo-[2.1.0]pentanes résulte de la réaction des anions d'imines dérivées d'amino-acides avec des alcènes portant sur le même atome de carbone un groupement électroattracteur et un groupement nucléofuge (Fouchet, Joucla & Hamelin, 1981):



A = CN, CO_2R; R' = H, CH_3, C_6H_5; R = CH_3, C_6H_5

L'originalité de ce type de composé ainsi que le problème stéréochimique soulevé par cette réaction ont rendu nécessaire l'étude à l'aide de rayons X.

Partie expérimentale. Les cristaux ont été préparés par évaporation lente d'une solution dans un mélange

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