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Structural Researches on H_2 Agonists: the Structures of the Dipicrates of 2-(2-Amino-4-imidazolyl)ethylamine, its 5-Methyl Derivative and *N,N*-Dimethyl-2-(2-amino-1,3-thiazol-5-yl)ethylamine*

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Abstract. To acquire structural information for understanding the effect of the amino group in 2-aminohistamine derivatives, the structures of the dipicrates of 2-(2-amino-4-imidazolyl)ethylamine (I), its 5-methyl analogue (II) and *N,N*-dimethyl-2-(2-amino-1,3-thiazol-5-yl)ethylamine (III) have been studied. Crystal data are: (I) $C_5H_{10}N_4.2C_6H_3N_3O_7.H_2O$, $M_r = 602{\cdot}4$, $P2_1/c$, $a = 21{\cdot}897\ (4)$, $b = 5{\cdot}107\ (1)$, $c = 21{\cdot}769\ (11)$ Å, $\beta = 104{\cdot}34\ (1)°$, $V = 2358\ (1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}696$ Mg m^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 1{\cdot}2719$ mm^{-1}, $F(000) = 1240$, $T = 293\ (2)$ K, $R = 0{\cdot}0410$ for 2739 reflections. (II) $C_6H_{12}N_4.2C_6H_3N_3O_7.\frac{1}{2}C_2H_6O$, $M_r = 621{\cdot}4$, $Fdd2$, $a = 25{\cdot}044\ (4)$, $b = 40{\cdot}178\ (5)$, $c = 10{\cdot}143\ (2)$ Å, $V = 10{\cdot}206\ (3)$ Å^3, $Z = 16$, $D_x = 1{\cdot}618$ Mg m^{-3}, Cu $K\bar{\alpha}$, $\mu = 1{\cdot}1794$ mm^{-1}, $F(000) = 5136$, $T = 293\ (2)$ K, $R = 0{\cdot}0381$ for 1480 reflections. (III) $C_7H_{13}N_3S.2C_6H_3N_3O_7$, $M_r = 629{\cdot}5$, $P\bar{1}$, $a = 13{\cdot}074\ (4)$, $b = 13{\cdot}853\ (6)$, $c = 8{\cdot}206\ (4)$ Å, $\alpha = 105{\cdot}88\ (11)$, $\beta = 103{\cdot}36\ (3)$, $\gamma = 64{\cdot}90\ (2)°$, $V = 1283\ (1)$ Å^3, $Z = 2$, $D_x = 1{\cdot}629$ Mg m^{-3}, Cu $K\bar{\alpha}$, $\mu = 1{\cdot}8916$ mm^{-1}, $F(000) = 648$, $T = 293\ (2)$, $R = 0{\cdot}0497$ for 1958 reflections. In all these compounds the cation is formed by protonation of a ring N atom and the side-chain amine group. π conjugation along the guanidine and isothiourea systems makes the *juxta*-NH_2 group coplanar with the ring. The conformation of the side chain is heavily influenced by the presence of the methyl group at the 5-imidazole position in the case of (II), and by the presence of sulfur in the ring and methyls on the side-chain amino N atom in the case of (III).

Introduction. The study of imidazolylalkylamine chemical properties, related to their histaminergic activity, has confirmed that the amidine component of the heterocycle is a fundamental part of the H_2-agonistic structure. Likewise it was shown that the factors promoting the formation of the monoprotonated base τ-NH tautomer in the ionic equilibrium are also able to cause the pharmacological dissociation between the H_1 and H_2 properties, making the molecule suitable in general for H_2 activity and in particular as gastric-acid-secretion stimulant (Black, Duncan, Durant, Ganellin & Parsons, 1972; Durant, Emmett & Ganellin, 1973; Durant, Ganellin & Parsons, 1975; Vitali, Bertaccini, Impicciatore & Plazzi, 1972, 1979; Durant, Emmett, Ganellin, Roe & Slatter, 1976; Hepp, Dziuron & Schunack, 1979; Vitali, Impicciatore, Plazzi, Bordi & Vitto, 1984). These properties are observed even when the amidine group is not included in a ring system, so substances like *S*-(aminoalkyl)-isothioureas can still stimulate the H_2 receptors and, in this case, their action is not connected with the

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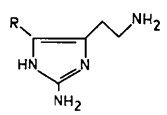
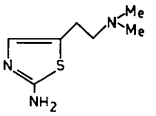
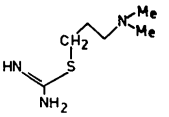
contracturant effects as they do not contain pyridine nitrogen which is considered essential for H_1 activities. In agreement with these observations, *S*-(3-dimethylaminopropyl)isothiourea (dimaprit, IV) is a pure H_2 agonist (Parsons, Owen, Ganellin & Durant, 1977; Vitali, Bertaccini & Coruzzi, 1978; Impicciatore, Plazzi, Chiavarini & Razzetti, 1980), while the H_2-stimulating properties of 2-(5-methyl-4-imidazolyl)-ethylamine (5-methylhistamine) prevail over the H_1 ones, and the opposite is observed with 2-(2-methyl-4-imidazolyl)ethylamine (2-methylhistamine).



(I): R = H
(II): R = Me



(III)



(IV)

Research, developed on the basis of these considerations, has recently shown that 2-(2-amino-4-imidazolyl)ethylamine (2-aminohistamine, I) is a potent H_2 agonist, as is dimaprit, and the hypothesis has been put forward that the *juxta*-nuclear NH_2 group in some way participates in the proton-transfer process necessary for the activation of the H_2 receptors.

Nevertheless, responses different from those expected have been obtained with 2-(2-amino-5-methyl-4-imidazolyl)ethylamine (II) and particularly with *N,N*-dimethyl-2-(2-amino-5-thiazolyl)ethylamine (III) whose potent effects on the stimulation of the gastric-acid secretion and the relaxant effects on gall-bladder smooth muscle are not competitively inhibited by the H_2 antagonists (nor by atropin).

These facts show that the geometrical features of the heterocyclic moiety are relevant in making the molecule suitable for the receptorial space. To this end the crystal structures of compounds (I), (II) and (III) have been studied and the present paper reports the results of these analyses.

Experimental. The compounds have been prepared and the pharmacological properties of their hydrochloride derivatives have been tested as described elsewhere (Vitali, Impicciatore, Plazzi, Bordi & Morini, 1986).

The relevant data concerning the crystal structure analyses are summarized in Table 1. All the reflections were corrected for Lorentz and polarization effects; those of (I) and (II) were corrected for extinction following Zachariasen (1963) using the values $0{\cdot}36\,(1)\times10^{-7}$ and $0{\cdot}202\,(4)\times10^{-8}$ for the g parameter, respectively. Absorption and extinction effects for (III) were corrected with the Walker & Stuart (1983) method (absorption: min. 0·849, max. 1·171; extinction: min. 0·939, max. 1·036). The structures were solved using *MULTAN*74 (Main, Woolfson, Lessinger, Germain & Declercq, 1974) and refined by least squares using *SHELX*76 (Sheldrick, 1976). In (II) the ethanol molecule is distributed in two positions about a twofold axis with 0·5 occupancy factors. All the H atoms were located from difference Fourier syntheses and refined isotropically except those of the C8 methylene and N9 ammonium groups of (I) which were put in calculated positions and those of the ethanol molecule in (II) which were not considered. The atomic scattering factors and the anomalous-scattering coefficients are from *International Tables for X-ray Crystallography* (1974). The final atomic coordinates are given in Table 2.*

Table 1. *Experimental data for the crystallographic analyses*

	(I)	(II)	(III)
Reflections for lattice parameters			
number	24	19	19
θ range (°)	15–33	17–50	13–30
Crystal data			
radiation	Cu $K\alpha_1$	Cu $K\alpha_1$	Cu $K\alpha_1$
wavelength (Å)	1·540562	1·540562	1·540562
Crystal size (mm)	0·84×0·10×0·05	0·20×0·16×0·13	0·20×0·13×0·05
Diffractometer	Siemens AED	Siemens AED	Siemens AED
Scan speed (° s^{-1})	0·2–0·05	0·2–0·05	0·2–0·05
Scan width (°)	1·20+0·33tanθ	1·20+0·33tanθ	1·20+0·33tanθ
θ range (°)	3–70	3–70	3–65
h range	0/26	0/30	−13/14
k range	0/6	0/48	−16/15
l range	26/25	0/12	0/8
Standard reflection	431	040	141
Intensity variation	None	None	None
Scan mode	θ–2θ	θ–2θ	θ–2θ
Number of measured reflections	4889	2676	3919
Condition for observed reflections	$I \geq 2{\cdot}5\sigma(I)$	$I \geq 3\sigma(I)$	$I \geq 3\sigma(I)$
Number of reflections used in refinement	2739	1480	1958
Anisotropic LS on F	Block diagonal	Block diagonal	Block diagonal
Mean LS shift to e.s.d. ratio	0·136	0·606	0·083
Min./max. height in final $\Delta\rho$ (e $Å^{-3}$)	−0·16/0·26	−0·11/0·12	−0·21/0·14
Number of refined parameters	441	463	464
R	0·0410	0·0381	0·0497
wR	0·0641	0·0573	0·0721
S	0·8711	0·8219	0·6098
k,g $\{w=k/[\sigma^2(F_o)+gF_o^2]\}$	1·0000, 0·0036	0·0315, 0·0712	0·2215, 0·0185

The calculations were carried out on the Cyber 76 computer of the 'Consorzio per la gestione del Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord-Orientale (CINECA, Casalecchio, Bologna)' with the financial support of the University of Parma, and the Gould-SEL 32/77 computer of the 'Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma)'. In addition to the quoted programs, *LQPARM* (Nardelli & Mangia, 1984), *PARST* (Nardelli, 1983), *ABSORB* (Ugozzoli, 1983), *THMV* (Trueblood, 1984), *ORTEP* (Johnson, 1965), *PLUTO* (Motherwell & Clegg, 1976) have been used.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and all bond lengths and angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43463 (58 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Final atomic coordinates* ($\times 10^4$) *of non-*H *atoms and isotropic B equivalent* (Å^2)

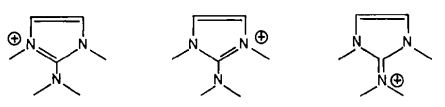
	x	y	z	B_{eq}		x	y	z	B_{eq}
Compound (I)									
O1*A*	−1468 (1)	692 (5)	8442 (1)	4·23 (7)	O61*B*	3502 (1)	13608 (6)	5464 (1)	5·55 (8)
O21*A*	−901 (1)	−644 (5)	7527 (1)	4·45 (7)	O62*B*	4204 (2)	14064 (7)	4955 (1)	6·98 (10)
O22*A*	108 (1)	−809 (4)	7906 (1)	3·72 (6)	N2*B*	4385 (1)	5782 (5)	6968 (1)	3·24 (7)
O41*A*	1083 (1)	6663 (5)	9034 (1)	4·92 (8)	N4*B*	6086 (1)	9400 (7)	6186 (1)	4·67 (9)
O42*A*	593 (1)	8972 (5)	9592 (1)	4·90 (8)	N6*B*	4006 (1)	13013 (5)	5369 (1)	3·51 (7)
O61*A*	−1433 (1)	6462 (6)	9762 (1)	5·29 (8)	C1*B*	4115 (1)	9328 (6)	6146 (1)	2·77 (7)
O62*A*	−1914 (1)	3122 (6)	9291 (1)	5·33 (8)	C2*B*	4579 (1)	7603 (6)	6534 (1)	2·82 (7)
N2*A*	−413 (1)	56 (5)	7909 (1)	2·97 (7)	C3*B*	5203 (1)	7564 (7)	6537 (1)	3·15 (8)
N4*A*	617 (1)	7155 (6)	9231 (1)	3·59 (7)	C4*B*	5422 (1)	9338 (7)	6163 (1)	3·40 (8)
N6*A*	−1468 (1)	4642 (6)	9395 (1)	3·34 (7)	C5*B*	5023 (1)	11073 (7)	5772 (1)	3·26 (8)
C1*A*	−1010 (1)	2197 (6)	8615 (1)	2·66 (7)	C6*B*	4396 (1)	11052 (6)	5768 (1)	2·85 (7)
C2*A*	−449 (1)	2033 (6)	8379 (1)	2·64 (7)	N1	7857 (1)	8076 (5)	2716 (1)	2·94 (6)
C3*A*	73 (1)	3564 (6)	8584 (1)	2·79 (7)	N3	7079 (1)	10338 (5)	2872 (1)	3·56 (7)
C4*A*	66 (1)	5493 (6)	9028 (1)	2·85 (7)	N6	7393 (1)	6662 (6)	3540 (1)	4·05 (8)
C5*A*	−450 (1)	5870 (6)	9275 (1)	2·86 (8)	N9	7415 (1)	8731 (7)	868 (1)	5·15 (9)
C6*A*	−964 (1)	4253 (6)	9082 (1)	2·70 (7)	C2	7444 (1)	8269 (6)	3074 (1)	3·01 (7)
O1*B*	3542 (1)	9241 (5)	6130 (1)	3·98 (6)	C4	7273 (1)	11502 (7)	2380 (2)	3·60 (8)
O21*B*	4648 (1)	3651 (5)	7055 (1)	4·62 (7)	C5	7759 (1)	10122 (6)	2281 (1)	3·00 (7)
O22*B*	3989 (1)	6487 (6)	7239 (1)	5·57 (9)	C7	8153 (2)	10482 (7)	1816 (2)	3·68 (9)
O41*B*	6283 (1)	10988 (7)	5868 (2)	7·26 (11)	C8	8048 (2)	8482 (7)	1295 (2)	4·18 (9)
O42*B*	6435 (1)	7828 (7)	6534 (1)	5·91 (9)	O*W*	2644 (1)	8717 (5)	4815 (1)	4·49 (7)
Compound (II)									
O1*A*	799 (2)	5944 (1)	8487 (5)	4·60 (12)	O62*B*	4999 (2)	7918 (1)	5967 (6)	6·51 (16)
O21*A*	382 (3)	5367 (1)	9182 (6)	8·82 (21)	N2*B*	5101 (2)	9219 (1)	4989 (5)	3·88 (14)
O22*A*	722 (3)	4943 (1)	8302 (8)	10·34 (27)	N4*B*	5856 (2)	8992 (2)	9297 (5)	4·54 (15)
O41*A*	1393 (2)	4967 (1)	3954 (5)	5·71 (14)	N6*B*	5358 (2)	8052 (1)	6566 (5)	3·98 (13)
O42*A*	1592 (2)	5433 (1)	3012 (6)	6·63 (16)	C1*B*	5163 (2)	8618 (1)	5711 (5)	3·04 (14)
O61*A*	1576 (2)	6433 (1)	5591 (5)	4·93 (13)	C2*B*	5244 (2)	8970 (1)	5969 (6)	3·01 (13)
O62*A*	953 (2)	6489 (1)	7036 (6)	5·35 (13)	C3*B*	5459 (2)	9084 (2)	7112 (6)	3·51 (16)
N2*A*	634 (2)	5236 (1)	8309 (7)	5·83 (18)	C4*B*	5631 (2)	8862 (2)	8074 (6)	3·57 (15)
N4*A*	1421 (2)	5272 (1)	3940 (6)	4·38 (15)	C5*B*	5597 (2)	8523 (1)	7886 (6)	3·50 (16)
N6*A*	1232 (2)	6316 (1)	6327 (5)	3·54 (12)	C6*B*	5368 (2)	8408 (1)	6748 (6)	3·12 (14)
C1*A*	919 (2)	5795 (1)	7462 (6)	3·42 (15)	N1	9772 (2)	8525 (1)	7050 (4)	3·66 (12)
C2*A*	858 (2)	5437 (1)	7264 (6)	3·60 (15)	N3	9507 (2)	8538 (1)	5043 (4)	3·46 (11)
C3*A*	1019 (2)	5276 (2)	6129 (7)	3·78 (16)	N6	9675 (3)	9056 (1)	6057 (6)	5·42 (16)
C4*A*	1249 (2)	5453 (2)	5125 (6)	3·37 (14)	N9	9081 (2)	8049 (1)	9233 (5)	3·56 (11)
C5*A*	1319 (2)	5792 (2)	5199 (7)	3·53 (16)	C2	9656 (2)	8730 (1)	6048 (5)	3·61 (13)
C6*A*	1156 (2)	5957 (1)	6316 (6)	3·20 (14)	C4	9535 (2)	8203 (1)	5390 (5)	3·44 (13)
O1*B*	4951 (2)	8502 (1)	4686 (4)	4·45 (12)	C5	9692 (2)	8194 (1)	6651 (5)	3·37 (13)
O21*B*	4827 (2)	9138 (1)	4031 (5)	4·82 (12)	C7	9783 (2)	7906 (1)	7566 (5)	3·49 (13)
O22*B*	5248 (2)	9506 (1)	5180 (6)	6·55 (16)	C8	9296 (2)	7787 (1)	8332 (5)	3·48 (13)
O41*B*	5866 (2)	9288 (1)	9455 (5)	6·11 (15)	C10	9392 (4)	7934 (2)	4454 (7)	5·43 (21)
O42*B*	6031 (2)	8792 (1)	10100 (5)	6·72 (18)	O14	7934 (4)	2762 (2)	4078 (12)	6·96 (26)
O61*B*	5724 (2)	7892 (1)	7032 (6)	6·96 (17)	C13	7786 (3)	2522 (2)	4657 (9)	7·38 (22)
Compound (III)									
O1*A*	5097 (3)	3025 (3)	4204 (5)	4·09 (16)	O62*B*	1431 (4)	2338 (4)	1428 (7)	7·07 (20)
O21*A*	5439 (4)	1860 (5)	928 (6)	6·53 (24)	N2*B*	−2431 (4)	5153 (4)	−819 (6)	3·58 (18)
O22*A*	4087 (4)	1307 (4)	−285 (5)	6·35 (24)	N4*B*	−517 (4)	7097 (4)	3778 (7)	4·32 (20)
O41*A*	2852 (4)	−327 (4)	2762 (6)	5·75 (20)	N6*B*	1208 (4)	3169 (4)	2517 (7)	4·22 (20)
O42*A*	3136 (4)	−36 (3)	5531 (7)	5·07 (18)	C1*B*	−644 (4)	4067 (4)	781 (7)	3·11 (19)
O61*A*	4016 (4)	3362 (3)	8209 (5)	4·99 (18)	C2*B*	−1497 (4)	5118 (4)	548 (6)	2·72 (18)
O62*A*	5718 (4)	2826 (4)	7610 (5)	5·27 (18)	C3*B*	−1454 (5)	6077 (5)	1463 (7)	3·20 (20)
N2*A*	4660 (5)	1602 (4)	984 (6)	4·45 (21)	C4*B*	−569 (4)	6073 (4)	2756 (7)	2·95 (19)
N4*A*	3191 (4)	125 (4)	4155 (8)	3·92 (19)	C5*B*	273 (5)	5110 (5)	3093 (7)	3·32 (22)
N6*A*	4749 (4)	2836 (4)	7285 (6)	3·37 (18)	C6*B*	250 (4)	4148 (4)	2136 (7)	3·13 (19)
C1*A*	4716 (4)	2310 (4)	4126 (7)	3·13 (19)	S	−240 (1)	9585 (1)	6911 (2)	4·24 (5)
C2*A*	4432 (4)	1608 (4)	2630 (7)	3·12 (20)	N3	399 (4)	11081 (4)	8636 (6)	3·98 (17)
C3*A*	3915 (4)	918 (4)	2640 (7)	3·09 (20)	N6	−1585 (4)	11669 (4)	8167 (6)	4·21 (19)
C4*A*	3705 (4)	867 (4)	4159 (7)	2·93 (19)	N9	3528 (4)	6449 (3)	6968 (5)	3·12 (15)
C5*A*	3975 (4)	1487 (4)	5693 (8)	2·82 (20)	C2	−545 (4)	10898 (4)	8007 (6)	3·46 (19)
C6*A*	4476 (4)	2168 (4)	5658 (6)	2·72 (17)	C4	1403 (5)	10194 (4)	8239 (8)	4·42 (22)
O1*B*	−673 (3)	3197 (3)	−129 (6)	5·31 (16)	C5	1209 (4)	9315 (4)	7314 (7)	3·60 (19)
O21*B*	−2835 (3)	4466 (4)	−1102 (5)	4·96 (18)	C7	2089 (5)	8258 (4)	6539 (8)	4·02 (22)
O22*B*	−2780 (4)	5886 (4)	−1609 (5)	5·16 (18)	C8	2545 (5)	7418 (4)	7668 (7)	3·55 (20)
O41*B*	−1276 (4)	7938 (3)	3450 (6)	5·86 (19)	C11	3213 (7)	5796 (6)	5341 (9)	5·12 (27)
O42*B*	278 (4)	7059 (4)	4932 (7)	6·46 (20)	C12	4166 (6)	5760 (6)	8278 (9)	4·96 (27)
O61*B*	1784 (4)	3244 (3)	3928 (6)	5·33 (18)					

Throughout the paper an averaged value is a weighted mean with weights equal to the reciprocal of the squares of the e.s.d.'s and, when two values are compared, the ratio between their difference and the e.s.d. of the difference, Δ/σ, is considered.

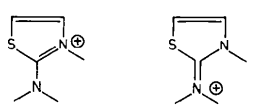
Discussion. The structures of the cations are shown in the *ORTEP* drawings of Fig. 1. Selected bond distances and angles of the cations are given in Table 3. Bond distances and angles of the picrate anions are collected in Table 4 where the values obtained after correction for librational thermal motion are given in square brackets. This motion was analysed by the rigid-body **TLS** method of Schomaker & Trueblood (1968), considering also the internal motion according to the one-parameter model of Dunitz & White (1973) for all cases except that of the cation of (III), where acceptable results were obtained by considering as a rigid body the segment remaining after disregarding the terminal part of the side chain. The results of the analyses are quite acceptable [cations: $wR_U = 0.067$ for (I), 0·093 for (II), 0·060 for (III)] even in the case of the picrate anions which give poorer wR_U values [anions: $wR_U = 0.087$ for (I*A*), 0·091 for (I*B*), 0·120 for (II*A*), 0·143 for (II*B*), 0·087 for (III*A*), 0·120 for (III*B*)] but are generally in good agreement with those found by a similar treatment for picric acid in the adduct it forms with anthracene (Herbstein & Kaftory, 1976).

Description of the structures. The crystals of the three compounds consist of packings of diprotonated cations and picrate anions held together by hydrogen bonds involving the amino groups of the cations, O atoms of the anions and water molecules in the case of (I) and ethanol molecules in the case of (II). As shown by the drawings of the cations in Fig. 1, protonation involves an N atom of the ring and the amine group of the side chain, while the amine group attached to the ring becomes planar as a consequence of π conjugation with the ring.

From the bond distances and angles quoted in Table 3, it appears quite evident that one double bond tends to be delocalized along the N6–C2(N1)–N3 (or N6–C2–N3 in the case of the thiazole ring) system, while the other tends to be localized at the C4–C5 bond, so that, of the all possible resonance structures, the following ones seem to be the most important:



for the 2-aminoimidazole and



for the 2-aminothiazole system.

The other possible resonance structures involving formal separation of charges, or a positive charge at S in the case of thiazole, seem to be less important but not negligible.

In agreement with this description, the five-atom ring is practically planar in all three compounds, as indicated by the following parameters [Q is the Cremer & Pople (1975) total puckering amplitude, d is the perpendicular distance of the atom from the plane]:

	$\sum(\Delta/\sigma)^2$	Q (Å)	d(max.) (Å)	atom
(I)	10·7	0·011 (3)	0·007 (3)	C2
(II)	10·3	0·015 (2)	0·010 (5)	C4
(III)	5·4	0·012 (5)	0·009 (6)	C2

and by the tendency N6 has to lie in that plane, its perpendicular distance from it being only 0·001 (4) for (I), 0·007 (6) for (II) and 0·083 (6) Å for (III). It is possible that this last displacement, which is significant, is also real and due to the presence of the bulky S atom in the ring. The same effect produces a more relevant displacement for C7 from the ring plane which is 0·139 (7) Å for the sulfur derivative and 0·015 (4), 0·029 (5) Å for (I) and (II), respectively. Supporting this view are the intramolecular non-bonded contacts S···N6 = 2·719 (5) Å and S···C7 = 2·849 (6) Å, which are shorter than the sum of the van der Waals radii.

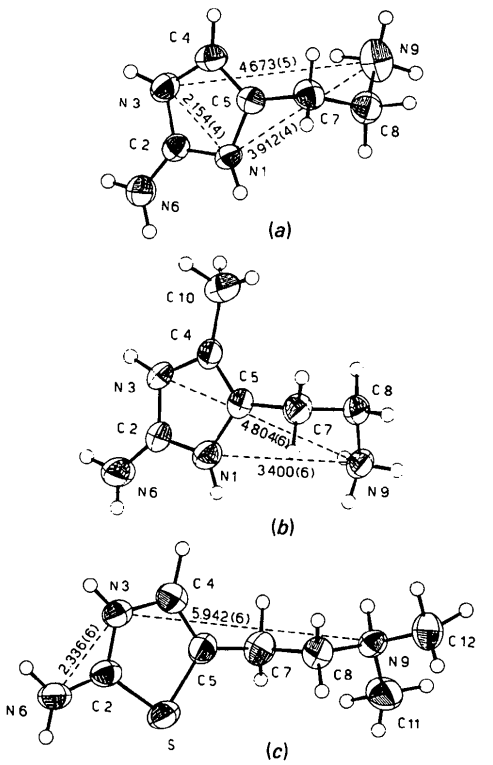


Fig. 1. *ORTEP* drawings of the cation (*a*) in (I), (*b*) in (II), (*c*) in (III). Ellipsoids at 50% probability.

Also, the methyl C10 at the imidazole position 5 in (II) is coplanar with the ring, its displacement, 0·004 (10) Å, not being significant. Its presence produces only small changes in the endocyclic angles at C4 and N3, if comparison is made with compound (I), the other endocyclic angles not being significantly different in the two compounds. On the contrary, the presence of sulfur in the thiazole ring produces relevant changes in the endocyclic distances and angles owing to the lengthening of the S–C distances and the narrowing of the angle at sulfur.

Bond distances and angles in the side chain are as expected, but the conformation of the chain changes in the three compounds owing to the presence of the methyl at position 5 in (II) and the two methyls at the ammonium terminal group in the thiazole derivative. These conformations are illustrated by the Newman projections of Fig. 2, which show that the orientation of the C8–N9 bond, with respect to the C7–C5 one, changes from (+)synclinal in (I) (Fig. 2*b*) to (–)-synclinal in (II) (Fig. 2*d*) as a consequence of the presence of the C10 methyl group, and becomes antiperiplanar in (III) (Fig. 2*f*). In connection with the side-chain conformation, the distance between the N atom of the ring and that of the side chain in (III) is much longer [5·942 (6) Å] than the corresponding ones in (I) [4·673 (5) Å] and (II) [4·804 (6) Å].

Picrate anions. In each picrate compound there are two independent picrate anions, the cations being doubly protonated. It appears that there are no significant differences between corresponding bond distances and angles of the two anions, except for the angles involving the adjacent O atoms of the phenol and *o*-nitro groups and the torsions about the C–N bonds of these substituents.

If the rotations of the *o*-nitro groups about the C–N bond are disregarded, there is a local pseudo-mirror running through C1···C4 in the benzene ring and the values of bond distances and angles are averaged with this assumption in Table 4. From these values it appears that π delocalization is not equally distributed in the ring: the double-bond character increases from C1–C2 to C3–C4 and C2–C3, in agreement with the trend present in other picrates [*e.g. N*-(*p*-chlorophenyl)-*S*,*S*-dimethylsulfimidium picrate (Cameron,

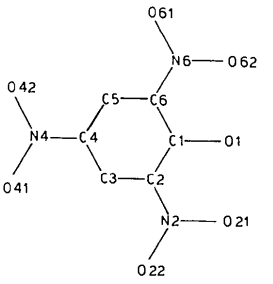
Table 3. *Selected bond distances* (Å), *bond angles* (°) *and torsion angles* (°) *in the cations*

The values in square brackets are corrected for rigid-body librational motion.

	(I)		(II)		(III)	
N1–C2	1·337 (4)	[1·341]	1·339 (7)	[1·341]	—	—
S–C2	—	—	—	—	1·712 (5)	[1·722]
C2–N3	1·332 (4)	[1·339]	1·331 (7)	[1·334]	1·324 (8)	[1·341]
N3–C4	1·380 (4)	[1·384]	1·394 (6)	[1·396]	1·396 (6)	[1·399]
C4–C5	1·338 (4)	[1·344]	1·339 (7)	[1·342]	1·338 (8)	[1·352]
N1–C5	1·391 (4)	[1·397]	1·407 (7)	[1·409]	—	—
S–C5	—	—	—	—	1·735 (6)	[1·752]
C2–N6	1·330 (4)	[1·334]	1·313 (6)	[1·315]	1·334 (6)	[1·339]
C5–C7	1·495 (5)	[1·499]	1·500 (7)	[1·502]	1·508 (7)	[1·511]
C7–C8	1·501 (5)	[1·507]	1·524 (7)	[1·527]	1·522 (9)	—
C8–N9	1·471 (4)	[1·479]	1·494 (7)	[1·498]	1·497 (6)	—
N9–C11	—	—	—	—	1·474 (8)	—
N9–C12	—	—	—	—	1·494 (9)	—
C4–C10	—	—	1·484 (9)	[1·487]	—	—
N1–C2–N3	107·6 (3)		106·7 (4)		—	
S1–C2–N3	—		—		111·0 (5)	
C2–N3–C4	108·9 (3)		110·5 (4)		114·7 (6)	
N3–C4–C5	108·0 (3)		106·5 (4)		112·4 (6)	
C4–C5–N1	106·3 (3)		106·8 (4)		—	
C4–C5–S1	—		—		111·0 (5)	
C5–N1–C2	109·2 (3)		109·4 (4)		—	
C5–S1–C2	—		—		91·0 (3)	
N1–C2–N6	126·6 (3)		126·9 (5)		—	
S1–C2–N6	—		—		125·9 (5)	
N3–C2–N6	125·8 (3)		126·4 (5)		123·0 (6)	
N1–C5–C7	122·4 (3)		122·1 (4)		—	
S1–C5–C7	—		—		122·8 (5)	
C4–C5–C7	131·3 (3)		131·1 (5)		126·0 (6)	
C5–C7–C8	114·9 (3)		115·8 (4)		112·4 (5)	
C7–C8–N9	111·3 (3)		112·3 (4)		110·1 (5)	
N3–C4–C10	—		122·0 (5)		—	
C5–C4–C10	—		131·4 (5)		—	
C8–N9–C11	—		—		114·1 (6)	
C8–N9–C12	—		—		110·3 (5)	
C11–N9–C12	—		—		111·1 (6)	
C4–C5–C7–C8	–109·1 (5)		–87·8 (7)		95·7 (8)	
N1–C5–C7–C8	70·6 (4)		92·5 (6)		—	
S1–C5–C7–C8	—		—		–91·2 (7)	
C5–C7–C8–N9	67·3 (4)		–62·6 (6)		–171·9 (5)	
C7–C8–N9–C11	—		—		–68·8 (7)	
C7–C8–N9–C12	—		—		165·3 (6)	

Table 4. *Averages and ranges of bond distances* (Å) *and angles* (°) *in the picrate anions*

The values in square brackets are corrected for rigid-body librational motion. The averages are calculated assuming a pseudo-mirror symmetry (see text).



	Av.		Min.		Max.	
C1–O1	1·247 (3)	[1·251]	1·237 (7)	[1·241]	1·266 (8)	[1·269]
C1–C2	1·446 (2)	[1·449]	1·426 (8)	[1·430]	1·461 (8)	[1·465]
C2–C3	1·368 (2)	[1·372]	1·352 (8)	[1·359]	1·387 (10)	[1·391]
C3–C4	1·379 (2)	[1·382]	1·363 (9)	[1·366]	1·391 (9)	[1·394]
C2–N2	1·454 (2)	[1·455]	1·443 (7)	[1·448]	1·466 (6)	[1·470]
C4–N4	1·452 (3)	[1·460]	1·444 (4)	[1·451]	1·470 (8)	[1·475]
N2–O21	1·223 (2)	[1·229]	1·208 (9)	[1·213]	1·233 (7)	[1·236]
N2–O22	1·219 (2)	[1·222]	1·197 (7)	[1·200]	1·233 (7)	[1·239]
N4–O41	1·223 (2)	[1·226]	1·201 (8)	[1·205]	1·232 (9)	[1·235]
O1–C1–C2	124·0 (4)		120·3 (5)		127·2 (5)	
C1–C2–C3	124·2 (2)		122·6 (5)		124·8 (5)	
C2–C3–C4	119·0 (2)		117·8 (6)		120·3 (6)	
C3–C4–C5	121·6 (2)		120·6 (6)		122·5 (6)	
C6–C1–C2	112·0 (2)		111·7 (3)		112·8 (5)	
C1–C2–N2	119·4 (2)		117·5 (5)		120·8 (5)	
C3–C2–N2	116·4 (2)		115·8 (3)		117·7 (6)	
C3–C4–N4	119·2 (2)		118·3 (5)		120·1 (6)	
C2–N2–O21	119·3 (2)		117·0 (5)		121·2 (5)	
C2–N2–O22	118·1 (2)		117·1 (6)		118·9 (3)	
C4–N4–O41	118·3 (1)		117·5 (6)		119·5 (5)	
O21–N2–O22	122·6 (3)		121·2 (5)		124·3 (5)	
O41–N4–O42	123·3 (2)		122·3 (4)		124·1 (7)	

Freer & Maltz, 1981), dimethylammonium picrate (Walkinshaw, 1986), 10,10-dimethyladeninium picrate (Dahl, 1986)]. In terms of resonance this trend is justified by an increased importance of the quinonic structures.

Bond distances and angles in the nitro groups do not differ significantly, while relevant differences are observed for the orientation of these groups with respect to the benzene ring: the *p*-nitro group is nearly coplanar with the ring, but the planes of the *o*-nitro groups are rotated with respect to the ring by angles ranging from 50·6 (3) to 6·7 (1)°. These distortions are caused by the steric hindrance between the phenol and adjacent *o*-nitro group O atoms, which is also responsible for the asymmetry of the C—C—N exocyclic angles formed by this group. In this respect it is worth noticing that these angles are practically equal in the case of the *p*-nitro group.

Hydrogen-bonding interactions, involving the O atoms of the *o*-nitro groups, justify the differences observed for these distortions in the different compounds.

Packing and hydrogen bonding. In all three compounds, packing is mainly determined by hydrogen bonds involving the N atoms of the cations, the O atoms of the anions and, if present, the solvent molecules, as shown in Table 5 and Fig. 3. In general, there is a tendency for the cations to form regular systems of bifurcated hydrogen bonds in which the imine and amine H atoms of the aminoimidazole moieties are shared by the phenolic and *o*-nitro O atoms of two adjacent picrate anions.

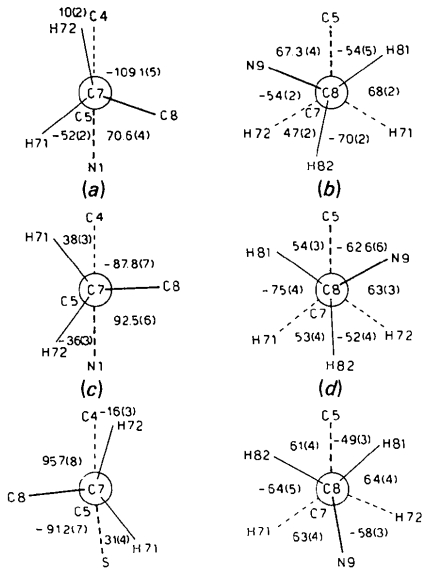


Fig. 2. Newman projection along C7—C5 and C8—C7: (*a*) and (*b*) for (I); (*c*) and (*d*) for (II); (*e*) and (*f*) for (III).

This regular situation is present on both sides of the cation ring of (I), while in (II) and (III) it is observed only on one side of the ring. On the other side this regular sequence of hydrogen bonds is destroyed by the insertion of the $N9H_3$ ammonium terminal group in (II) and by the presence of sulfur in (III).

In (I), the water molecule of crystallization joins, through hydrogen bonds, the side-chain ammonium group with two picrate anions and one more NH···O hydrogen bond connects that group with the nitro O atom of another picrate. In (II) the side-chain ammonium group forms hydrogen bonds with three picrate anions, while in (III) there is only one H atom in the methylated ammonium group available for a bifurcated hydrogen bond with a picrate anion.

The results of the structural analyses suggest that the different biological behaviour of the imidazolylethylamines and the thiazole derivative can be ascribed to the different geometrical features of these systems. In particular, even if the *juxta*-nuclear NH_2 group is

Table 5. *Hydrogen bonds*

D—H···*A*	*D*—H (Å)	*D*···*A* (Å)	H···*A* (Å)	∠*D*—H···*A* (°)
Compound (I)				
N1—H1N···O1*A*^{i}	0·82 (3)	2·689 (3)	1·98 (3)	144 (3)
N1—H1N···O21*A*^{i}	0·82 (3)	3·108 (4)	2·43 (4)	140 (3)
N3—H3N···O1*B*^{ii}	0·89 (5)	2·843 (4)	2·06 (5)	146 (4)
N3—H3N···O22*B*^{ii}	0·89 (5)	2·807 (4)	2·13 (4)	132 (4)
N6—H61N···O61*B*^{ii}	0·87 (4)	3·266 (5)	2·43 (4)	160 (4)
N6—H61N···O1*B*^{ii}	0·87 (4)	3·133 (4)	2·48 (4)	132 (3)
N6—H62N···O1*A*^{i}	0·90 (4)	2·825 (4)	2·11 (5)	135 (4)
N6—H62N···O62*A*^{i}	0·90 (4)	3·118 (4)	2·29 (4)	152 (4)
N9—H91N···O61*B*^{iii}	1·08	3·091 (4)	2·57	109
N9—H91N···O*W*^{iii}	1·08	2·947 (5)	1·91	160
N9—H92N···O*W*^{iv}	1·08	2·935 (5)	1·86	180
N9—H93N···O42*B*^{v}	1·08	2·981 (4)	1·96	157
O*W*—H1*W*···O1*B*	0·82 (5)	3·057 (3)	2·33 (5)	148 (5)
O*W*—H1*W*···O61*B*	0·82 (5)	3·232 (4)	2·79 (5)	116 (4)
O*W*—H2*W*···O62*A*^{vi}	1·04 (9)	2·826 (4)	1·82 (9)	162 (7)

Symmetry code: (i) $x+1, \frac{1}{2}-y, z-\frac{1}{2}$; (ii) $1-x, 2-y, 1-z$; (iii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iv) $1-x, y+\frac{1}{2}, \frac{1}{2}-z$; (v) $x, \frac{3}{2}-y, z-\frac{1}{2}$; (vi) $-x, \frac{1}{2}+y, \frac{3}{2}-z$

Compound (II)				
N1—H1N···O1*B*^{i}	0·85 (6)	2·713 (6)	1·94 (6)	150 (4)
N1—H1N···O21*B*^{i}	0·85 (6)	3·183 (6)	2·52 (5)	136 (4)
N3—H3N···O1*A*^{ii}	0·93 (6)	2·719 (6)	1·88 (5)	148 (5)
N3—H3N···O62*A*^{ii}	0·93 (6)	3·262 (7)	2·51 (6)	138 (4)
N6—H61N···O21*B*^{i}	0·83 (7)	3·058 (8)	2·41 (8)	136 (5)
N6—H62N···O1*A*^{ii}	0·92 (6)	2·865 (8)	2·17 (6)	132 (4)
N6—H62N···O21*A*^{ii}	0·92 (6)	3·000 (8)	2·16 (6)	152 (5)
N9—H91N···O1*B*^{i}	0·94 (7)	2·876 (6)	2·06 (6)	145 (6)
N9—H91N···O62*B*^{i}	0·94 (7)	2·941 (7)	2·32 (7)	124 (5)
N9—H92N···O61*A*^{iii}	0·89 (5)	2·992 (6)	2·54 (6)	112 (4)
N9—H92N···O41*B*^{iv}	0·89 (5)	2·996 (7)	2·28 (6)	136 (4)
N9—H93N···O41*A*^{v}	0·82 (7)	3·097 (7)	2·33 (7)	156 (5)
N9—H93N···O14^{vi}	0·82 (7)	3·100 (11)	2·74 (6)	109 (6)

Symmetry code: (i) $x+\frac{1}{2}, y, z+\frac{1}{2}$; (ii) $1-x, \frac{1}{2}-y, z-\frac{1}{2}$; (iii) $1-x, \frac{1}{2}-y, z+\frac{1}{2}$; (iv) $\frac{1}{4}+x, \frac{7}{4}-y, z-\frac{1}{4}$; (v) $x+\frac{3}{4}, \frac{5}{4}-y, z+\frac{3}{4}$; (vi) $x, y+\frac{1}{2}, z+\frac{1}{2}$

Compound (III)				
N3—H3N···O1*B*^{i}	0·94 (7)	2·670 (6)	1·87 (6)	142 (6)
N3—H3N···O62*B*^{i}	0·94 (7)	2·913 (7)	2·17 (7)	135 (6)
N6—H61N···O1*B*^{i}	0·97 (7)	2·759 (8)	1·95 (8)	139 (6)
N6—H62N···O41*A*^{ii}	0·92 (6)	2·835 (9)	2·07 (7)	139 (5)
N6—H62N···O62*A*^{iii}	0·92 (6)	3·173 (6)	2·50 (5)	130 (4)
N9—H9N···O21*A*^{iv}	0·95 (7)	3·112 (8)	2·54 (5)	119 (4)
N9—H9N···O1*A*^{iv}	0·95 (7)	2·643 (8)	1·73 (7)	162 (5)

Symmetry code: (i) $x, y+1, z+1$; (ii) $-x, 1-y, 1-z$; (iii) $x-1, y+1, z$; (iv) $1-x, 1-y, 1-z$

planar in all three compounds as a consequence of conjugative effects, the conformation of the side chain is heavily influenced by the presence of the methyl group at position 5 in (II) and by the presence of the hetereocyclic S atom and methyl groups at N in (III).

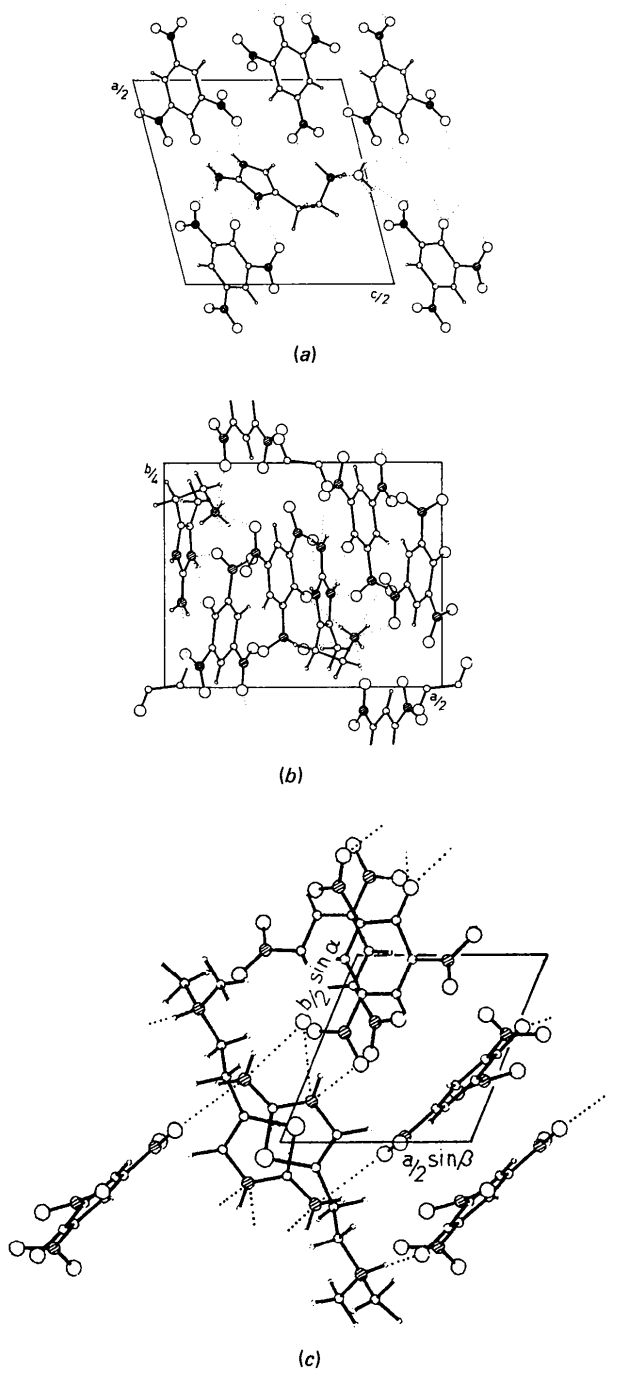


Fig. 3. Hydrogen bonding and packing (*a*) in (I), (*b*) in (II), (*c*) in (III).

As a consequence, the distance between the N atom of the ring and that of the chain in (III) is much longer [5·942 (6) Å] than in (I) [4·673 (5) Å]. Moreover, the distance [2·336 (6) Å] between the *juxta*-nuclear N atom and the ring N atom in (III) is different from the distance [2·154 (4) Å] between the two ring N atoms in (I), suggesting that the amidine group in (III) is not a pharmacophore equivalent to the amidine group in (I) for its H_2-receptorial interaction. In (II) the presence of the methyl substituent produces changes of the N(ring)···N(chain) distances [3·400 (6) and 4·804 (6) Å] with respect to the corresponding ones in (I) [3·912 (4) and 4·673 (5) Å], with the consequent loss of activity.

These facts implicitly support the hypothesis that the molecular flexibility of dimaprit is a fundamental feature of its activity. So the biological properties of 2-aminohistamine, in comparison with those of 2-methylhistamine, could be ascribed to the existence, in the H_2 receptor, of a hydrophilic area suitable to receive the *juxta*-nuclear NH_2, rather than to a direct involvement of this group in the amidinic activation.

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Structures of 3-Cyanohexahydronaphth[2,3-*e*][1,2]oxazines. 1

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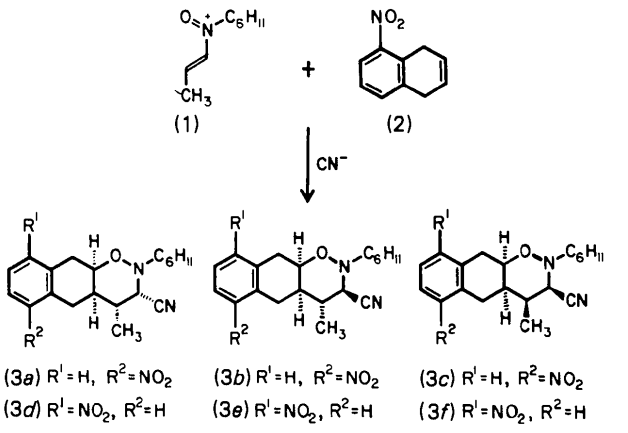
Abstract. 2-Cyclohexyl-4α-methyl-3,4,4aα,5,10,10aα-hexahydro-6-nitronaphth[2,3-*e*][1,2]oxazine-3β-carbonitrile, $C_{20}H_{25}N_3O_3$, $M_r = 355{\cdot}43$, monoclinic, $P2_1/n$, $a = 13{\cdot}375$ (9), $b = 11{\cdot}601$ (8), $c = 12{\cdot}725$ (8) Å, $\beta = 109{\cdot}49$ (6)°, $V = 1861{\cdot}32$ Å^3, $Z = 4$, $D_x = 1{\cdot}268$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 6·15 cm^{-1}, $F(000) = 760$, room temperature, final $R = 0{\cdot}052$, $wR = 0{\cdot}058$ for 2742 unique observed [$I > 0$] reflections. In this nitro-substituted derivative the tetrahydrooxazine ring is in a distorted chair conformation with exceptionally large endocyclic torsion angles about the C(1*A*)—O(1) and O(1)—N(2) bonds [71·4 (2) and −76·6 (2)°, respectively]. Both the methyl and the cyano substituents are in axial positions.

Introduction. This investigation forms part of a study of the cycloaddition reactions of the *N*-cyclohexyl-*N*-propenylnitrosonium ion (1) (Kempe, Das Gupta, Blatt, Gygax, Felix & Eschenmoser, 1972) with 5-substituted 1,4-dihydronaphthalenes (Holzapfel, Koekemoer & Van Dyk, 1985). The reaction of 5-nitro-1,4-dihydronaphthalene (2) with (1) furnished four isomeric iminium ions which on treatment with potassium cyanide yielded the corresponding cyanide adducts (3*a*–3*f*). The stereochemistry of the *cis*-fused *B*/*C* ring system of these hexahydronaphthoxazines (assignment based on an analysis of the ^{1}H NMR spectra) can be described as 3α,4α, 3β,4α and 3β,4β with respect to the cyano and methyl substituents. The 3α,4α- and 3β,4α-stereoisomers with the same regiochemistry are chemically interconvertible (Van Dyk, 1986). In order to establish the regioselectivity of the cycloaddition reaction the unambiguous structure determination of at least one isomer with a 4α-methyl and one with a 4β-methyl substituent was required.



In addition, the stereochemistry and conformation deduced on the basis of ^{1}H NMR implied that both the cyano and methyl substituents in the 3β,4α-isomers are in sterically crowded axial positions. This result can be compared with the ^{1}H NMR-based conclusion of Riediker & Graf (1979) that 2-cyclohexyl-3β-cyano-4α-mesyloxymethyl-4aα,8aα-perhydro-1,2-benzoxazine has a preferred conformation in which the β-cyano and α-mesyloxymethyl substituents are in axial positions, a finding that was interpreted in terms of a generalized anomeric effect operating in the α-cyano-hydroxylamine-ether structural unit.

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