played by this bridging position is remarkedly demonstrated by the complete isomorphism between the structures of tetrasodium pyrophosphate dodecahydrate and imidodiphosphate.[28] A further example is provided by the recent observation[24] of the nearly complete isomorphism between disodium dihydrogen phosphate hexahydrate and disodium dihydrogen phosphonate hexahydrate which does not have a bridge oxygen.

(28) M. Larsen, R. Willett, and R. G. Yount, *Science*, **166**, 1510 (1969).

On the other hand, the nonbridging oxygen atoms in both polyphosphate and orthophosphate ions normally exhibit strong interactions (ionic and hydrogen bonding) with the neighboring atoms. Thus, the relative inertness of the bridging oxygens in forming hydrogen bonds in crystals is consistent with the observation that the polyphosphates have lower solvation energies in aqueous solutions than do their hydrolysis products.

Acknowledgment. We wish to acknowledge the helpful comments and suggestions of Dr. L. Pauling.

Crystal and Molecular Structure of the Antihistamine 2-[(2)-Dimethylaminoethyl-2-thenylamino]pyridine Hydrochloride

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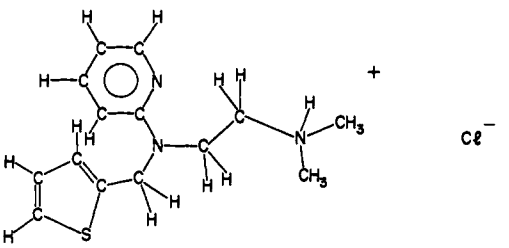
Abstract: The crystal structure of the antihistamine 2-[(2)-dimethylaminoethyl-2-thenylamino]pyridine hydrochloride has been determined using three-dimensional diffractometer data. The colorless plates are monoclinic, of space group $P2_1/c$. The unit cell containing eight molecules has dimensions $a = 10.936 \pm 0.003$, $b = 10.417 \pm 0.003$, and $c = 28.256 \pm 0.008$ Å, $\beta = 106.21 \pm 0.02°$. The structure was solved by using a Patterson synthesis and an E map to locate one sulfur and two chlorine atoms. Positions for the remaining atoms were deduced from subsequent electron density syntheses. Thirty-seven of the 40 hydrogen atoms were located and their positions and isotropic temperature factors refined along with the positional and anisotropic thermal parameters for the other atoms. The final residual R was 0.055 for 2983 observed reflections. The two independent molecules assume different geometries. In addition, the thiophene ring in one molecule is physically disordered. Equivalent bond lengths in the two molecules are equal, except for those involving the disordered thiophene group. The nitrogen atom at the center of the molecule is in the sp^2 hybridization state. Both molecules adopt the trans configuration about the carbon–carbon bond of the ethylamine side chain (as was found for histamine itself), thus adding support for the competitive site-occupancy theory of antihistaminic activity.

Although the mechanism of antihistamine activity has not been clearly established, one view is that antihistamines compete with histamine for a receptor site.[1,2] Nearly all antihistamines are alkylamines and can be classified into seven different groups on the basis of the other substituents.[1] If competition between histamine and antihistamines exists, then we might expect a structural or conformational similarity to exist between these two species. Therefore, structural studies of histamine and several antihistamines were undertaken to provide data on these important molecules. Our results on histamine have been reported,[3] as well as a preliminary report[4] on the antihistamine Histadyl,[5] 2-[(2)-dimethylaminoethyl- 2- thenylamino]-pyridine hydrochloride (I).



I

Experimental Section

A sample of 2-[(2)-dimethylaminoethyl-2-thenylamino]pyridine hydrochloride, $C_{14}H_{20}N_3S \cdot HCl$, $M = 297.85$, was generously supplied by Eli Lilly and Co. The compound was recrystallized as transparent colorless plates on [001] by cooling from a hot isopropyl alcohol solution. Preliminary investigations by Rose and Williams[6] had found the monoclinic space group $P2_1/n$, with $a = 27.35$, $b = 10.38$, and $c = 10.96$ Å, $\beta = 96°$, $Z = 8$, $\rho_{obsd} = 1.273$ g cm^{-3}. For the present study the equivalent space group $P2_1/c$ (no. 14) was chosen and the cell dimensions were redetermined. A small crystal (0.10 × 0.05 × 0.05 mm) was mounted on the

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(1) R. E. Wilhelm, *Med. Clin. N. Amer.*, **45**, 887 (1961).

(2) C. Botre', M. Marchetti, C. Del Vecchio, G. Lionetti, and A. Memoli, *J. Med. Chem.*, **12**, 832 (1969).

(3) M. V. Veidis, G. J. Palenik, R. Schaffrin, and J. Trotter, *J. Chem. Soc. A*, 2659 (1969).

(4) G. R. Clark and G. J. Palenik, *J. Amer. Chem. Soc.*, **92**, 1777 (1970).

(5) Histadyl is the registered trade name for the compound 2-[(2)-dimethylaminoethyl-2-thenylamino]pyridine hydrochloride.

(6) H. A. Rose and J. G. Williams, *J. Amer. Pharm. Ass.*, **48**, 487 (1959).

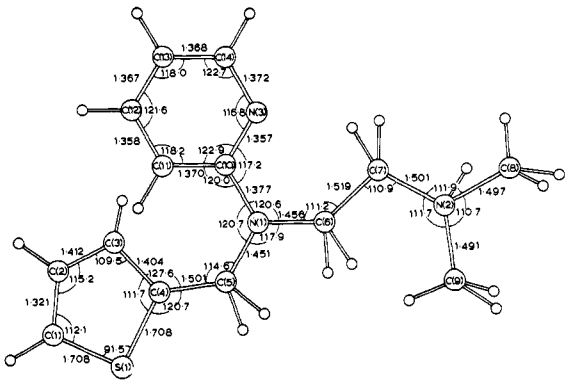

Figure 1. The atomic numbering and average bond distances and angles in the 2-[(2)-dimethylaminoethyl-2-thenylamino]pyridinium ion. The values for the thiophene ring are the values found in the ordered ring.

orienter of a Datex automated General Electric XRD-6 diffractometer and aligned so that the [100] direction was parallel to and coincident with the ϕ axis of the orienter. The observed 2θ values for 20 reflections in the range 23.15–49.71° were then measured using a narrow beam (1° take-off angle) of Cu Kβ X-radiation (λ = 1.39217 Å). The cell dimensions obtained by a least-squares procedure and their estimated standard deviations are a = 10.936 ± 0.003, b = 10.417 ± 0.003, and c = 28.256 ± 0.008 Å, β = 106.21 ± 0.02°. The cell volume is 3199.9 Å^3. The density calculated for eight molecules per cell is 1.236 g cm^{-3}.

Intensity data were collected using the same crystal. The maximum and minimum μR values were 0.2 and 0.1, respectively, which could introduce a maximum error of 15% in some cases. However, the negligible variation of the intensity as a function of φ at χ equal to 90° suggests that the error was much less. Furthermore, any absorption errors will have only a slight effect on the conformation or distances in the molecule. A thin nickel filter (0.35 mil) and a combination linear amplifier–pulse height selector ensured a monochromatic beam of X-rays. Angular settings were computed for the Cu Kα_1 wavelength (1.54051 Å). Each reflection was counted for 20 sec with crystal and scintillation counter stationary. A unique set of reflections was measured to the limit 2θ = 135° followed by a measurement of those reflections within the limit 2θ = 100° in the hemisphere defined by the diffractometer geometry. Four reflections with representative ϕ values were selected as standards and were recounted after every 100 measurements to monitor the stability of the crystal alignment and its behavior under radiation. The counts for these standards were very constant throughout the data collection, with the maximum variation of only 3% being attributable to random counting fluctuations. Before the crystal was removed from the orienter, an empirical background curve was derived by the systematic measurement of regions of reciprocal space which were known to contain no reflections. All data were then corrected for their appropriate background values, and for α_1–α_2 splitting effects. When all equivalent reflections had been averaged, the 13,436 measurements reduced to 3023 observed independent reflections. A further 2512 reflections were less than 1.2 times their threshold value and were considered to be unobserved. All data were then reduced to structure amplitudes in the usual manner.

Determination and Refinement of the Structure. Since there are two molecules in the asymmetric unit, the initial step was to locate the two sulfur and two chlorine atoms. However, in a three-dimensional sharpened Patterson function, the observed vector array was consistent with only three of these four heavy atoms and two of the atoms were related by the factor [1/2 0 1/2]. Direct methods of phase determination were attempted and an E map computed from the most likely combination of signs showed the same three peaks. A Patterson superposition map could not unambiguously position the remaining heavy atom since it contained several maxima consistent with maxima in the E map. Eventually, an electron density synthesis was computed with phases determined by the three atoms. A further 28 of the 38 nonhydrogen atoms could be located but the position of the remaining heavy atom was not established. Another electron density synthesis then revealed the remaining thiophene ring and two previously unplaced methyl carbon atoms. Bond lengths in this second thiophene ring were poor and the peak heights in the two α positions were almost identical. Apparently this ring was disordered and had adopted two possible orientations which were related by a twist of 180° about the carbon–carbon bond external to the ring. There appeared to be equal occupancy of each orientation. Refinement was commenced with individual isotropic thermal parameters using full-matrix least-squares techniques. The function minimized was $\Sigma w|F_{obsd} - F_{calcd}|^2$, where w was defined by $\sqrt{w} = F_{obsd}/a$ if $F_{obsd} < a$, $\sqrt{w} = 1$ if $a < F_{obsd} < b$, $\sqrt{w} = b/F_{obsd}$ if $F_{obsd} > b$. Values selected for a and b were 20 and 150, respectively. Initially all atoms of the pyridine groups were assigned carbon scattering factors. One atom in the α position of each pyridine ring had an isotropic temperature factor which was significantly lower than those of the other atoms of the rings, and these two were subsequently assumed to be nitrogen atoms.

Several trial cycles were also computed to decide upon the best-fitting model for the disordered thiophene ring in molecule 2. Models attempted were: (a) the atoms of molecule 2 arbitrarily labeled S-1 and C-3 were assigned carbon scattering curves, (b) the atom labeled S-1 was assigned sulfur and that labeled C-3 was assigned carbon scattering curves, (c) the atom labeled S-1 was assigned carbon and that labeled C-3 was assigned sulfur scattering curves, and (d) both S-1 and C-3 were assigned average [(S + C)/2] values. The isotropic temperature factors (Å^2) found after two full-matrix least-squares cycles are shown in Table I. These indicated

Table I. Isotropic Temperature Factors (Å^2)

	Model			
	a	b	c	d
S-1	0.19	9.87	0.15	6.34
C-3	0.52	0.34	10.59	5.99

that model d should be adopted. The site occupancy was considered to be sufficiently close to 50% so that refinement of an occupancy number was not required. For consistency with the thiophene ring in molecule 1 the atomic numbering scheme using the labels S-1 and C-3 was retained although they represent equivalent atom types. To further check the proposed model, a difference synthesis was then computed omitting thiophene ring 2. The electron density map was examined closely to see if the ring could be established as two overlapped but slightly displaced half-weighted rings. However, no peak could be resolved into a doublet although all except C-4 were distended in the expected directions.

The residual R was 0.13 after the isotropic refinement on model d. All atoms were assigned anisotropic thermal parameters and four least-squares cycles were computed using the block diagonal approximation to the full matrix and applying 0.5 of all calculated shifts. The earlier weighting scheme was retained throughout. A difference synthesis was then computed. All hydrogen atoms were located as well-resolved peaks except for the three on thiophene ring 2 which were quite diffuse and hence were omitted entirely. A further six cycles were then computed refining the 37 isotropic hydrogen atoms along with the other 38 anisotropic atoms. The hydrogen atoms were initially assigned isotropic temperature factors of 4.0 Å^2, and after the six cycles these ranged from 1.3 to 8.9 Å^2, with most lying at about 6 Å^2. After the two final cycles, in which the hydrogen atoms were maintained constant, and approximately 40 weak reflections with $F_{calcd} < 0.5F_{obsd}$ were given zero weight, refinement was terminated. The maximum shifts in positional and thermal parameters were, respectively, 0.1 and 0.2 of their calculated errors. The final residual for all observed reflections was 0.055. The atomic scattering factors for Cl, S, and N were from the usual source[7] with the values for C and H taken from the tabulation using Hartee–Fock–Slater wave functions.[8] The final atomic parameters for the nonhydrogen atoms are given in Table II, with the hydrogen atom parameters listed in Table III.[9]

(7) "International Tables for X-Ray Crystallography," Vol. III, The Kynoch Press, Birmingham, England, 1962, p 201.

(8) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).

(9) A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JACS-72-4005. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Table II. Final Positional and Thermal Parameters (× 10^4) and Their Estimated Standard Deviations in Parentheses[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
				Molecule 1					
Cl-(1)	1953 (1)	0489 (1)	4684 (0)	75 (1)	81 (1)	15 (0)	40 (2)	16 (1)	2 (1)
S-1	1555 (1)	1677 (2)	6737 (1)	130 (2)	137 (2)	24 (0)	−37 (3)	48 (1)	−38 (1)
N-1	2568 (3)	−0442 (3)	6248 (1)	73 (4)	78 (4)	14 (1)	2 (7)	2 (2)	0 (3)
N-2	0079 (3)	−2475 (3)	5374 (1)	71 (4)	76 (4)	14 (1)	28 (7)	8 (3)	−9 (3)
N-3	3174 (4)	−2282 (4)	6734 (1)	119 (5)	102 (5)	18 (1)	−4 (8)	26 (3)	12 (3)
C-1	1452 (5)	3291 (6)	6823 (2)	137 (7)	165 (8)	28 (1)	48 (13)	10 (5)	−61 (6)
C-2	2069 (5)	3959 (5)	6566 (2)	171 (8)	103 (6)	23 (1)	24 (11)	−43 (5)	−11 (5)
C-3	2674 (5)	3222 (5)	6277 (2)	152 (7)	97 (6)	10 (1)	−12 (10)	−4 (4)	−3 (3)
C-4	2437 (4)	1913 (4)	6332 (2)	79 (5)	97 (5)	10 (1)	0 (8)	1 (3)	0 (3)
C-5	2825 (4)	0800 (4)	6070 (2)	108 (5)	108 (6)	10 (1)	22 (9)	11 (3)	2 (3)
C-6	1323 (4)	−1007 (4)	6026 (2)	81 (5)	104 (6)	15 (1)	1 (9)	11 (3)	−18 (4)
C-7	1346 (4)	−1836 (4)	5585 (2)	69 (4)	87 (5)	12 (1)	−17 (8)	11 (3)	−7 (3)
C-8	−0117 (5)	−3583 (5)	5678 (2)	117 (6)	93 (6)	22 (1)	−46 (10)	26 (4)	−1 (4)
C-9	−0078 (5)	−2864 (5)	4852 (2)	105 (6)	136 (7)	17 (1)	27 (10)	4 (4)	−26 (4)
C-10	3456 (4)	−1069 (4)	6617 (2)	88 (5)	78 (5)	11 (1)	3 (8)	20 (3)	−3 (3)
C-11	4577 (4)	−0482 (4)	6839 (2)	78 (4)	77 (5)	15 (1)	−1 (8)	−4 (3)	−9 (3)
C-12	5451 (5)	−1132 (5)	7195 (2)	108 (6)	141 (7)	17 (1)	−1 (10)	9 (4)	−30 (4)
C-13	5230 (5)	−2339 (6)	7335 (2)	143 (7)	168 (8)	15 (1)	74 (12)	6 (4)	9 (5)
C-14	4085 (5)	−2892 (5)	7102 (2)	168 (8)	112 (6)	19 (1)	33 (11)	32 (5)	29 (4)
				Molecule 2					
Cl-1	7081 (1)	0420 (1)	9725 (1)	76 (1)	82 (1)	25 (0)	11 (2)	28 (1)	6 (1)
S-1*	2085 (2)	−1408 (2)	8778 (1)	146 (3)	138 (3)	26 (1)	27 (5)	66 (2)	26 (2)
N-1	3084 (3)	1046 (3)	8441 (1)	93 (4)	74 (4)	14 (1)	8 (7)	17 (3)	−6 (3)
N-2	4971 (3)	2340 (3)	9679 (1)	70 (4)	78 (4)	13 (1)	−14 (6)	14 (2)	−2 (3)
N-3	1856 (4)	2897 (4)	8362 (1)	138 (5)	91 (5)	16 (1)	26 (8)	31 (3)	4 (3)
C-1	2108 (5)	−2899 (6)	8880 (2)	128 (7)	178 (9)	24 (1)	−78 (13)	0 (5)	50 (5)
C-2	2829 (6)	−3557 (6)	8658 (2)	204 (9)	126 (7)	26 (1)	−7 (14)	−26 (6)	3 (5)
C-3*	3498 (2)	−2768 (2)	8353 (1)	159 (3)	110 (3)	21 (0)	48 (5)	33 (2)	0 (2)
C-4	3037 (4)	−1347 (4)	8449 (2)	89 (5)	84 (5)	15 (1)	−3 (8)	1 (3)	−2 (4)
C-5	3383 (5)	−0142 (4)	8224 (2)	115 (6)	95 (6)	18 (1)	19 (9)	37 (4)	−3 (4)
C-6	4109 (4)	1708 (5)	8799 (2)	76 (5)	125 (6)	14 (1)	−24 (9)	13 (3)	−12 (4)
C-7	3850 (4)	1793 (4)	9298 (2)	73 (4)	92 (5)	13 (1)	−34 (8)	14 (3)	−1 (3)
C-8	4755 (4)	2331 (5)	10181 (2)	113 (6)	144 (7)	11 (1)	−34 (11)	15 (3)	−1 (4)
C-9	5307 (4)	3659 (5)	9555 (2)	109 (6)	102 (6)	18 (1)	−71 (9)	29 (4)	−11 (4)
C-10	1944 (4)	1660 (4)	8231 (2)	106 (5)	75 (5)	13 (1)	12 (8)	27 (3)	0 (3)
C-11	0951 (4)	1011 (5)	7909 (2)	106 (6)	97 (6)	14 (1)	−23 (9)	0 (3)	−9 (4)
C-12	−0155 (5)	1659 (6)	7717 (2)	129 (6)	176 (8)	16 (1)	−42 (12)	3 (4)	2 (5)
C-13	−0285 (5)	2917 (6)	7837 (2)	117 (6)	190 (9)	21 (1)	73 (12)	19 (4)	39 (5)
C-14	0728 (5)	3512 (5)	8157 (2)	148 (7)	112 (6)	20 (1)	48 (11)	37 (4)	8 (4)

[a] The temperature factor for an atom is of the form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$. [b] An asterisk denotes disordered atoms in the thiophene ring,

Discussion

Since there are two molecules per asymmetric unit, the molecular geometry has been determined twice. The distances and angles in the two molecules are tabulated in Table IV, with the average values (except for the C–S bonds in the disordered thiophene ring) and the atomic numbering given in Figure 1. A comparison of the distances in Table IV shows that the largest difference in chemically equivalent bonds is 0.015 Å, about two standard deviations. The bonds in the disordered thiophene ring involved S-1, C-3, and C-4. Values ranged from 1.519 to 1.611 Å (1.57 Å average), which is close to the average of a C–S and C–C single bond of 1.56 Å. The similarity of these averaged bond lengths suggests that the assumption of an occupancy factor of 0.5 was reasonable.

The C–S distances in the ordered thiophene ring of 1.708 (6) Å for S-1–C-1 and 1.708 (5) Å for S-1–C-4 are in excellent agreement with the values found in other thiophene rings where resonance does not perturb the ring; 1.717 (4) Å in thiophene,[10] 1.71 (2) Å in tetracyanothiophene.[11] However, if the thiophene is substituted and resonance with a side chain is important, the two C–S bond lengths become unequal, *i.e.*, 1.722 (3) and 1.706 (4) Å in 2-formylthiophene thiosemicarbazone.[12] These results suggest that the C–S distances in thiophene compounds may be reasonable indicators of resonance interaction with the substituent groups, although more studies would be helpful.

Except for the C-10–C-11 bond and the distances involving N-1, all other bond lengths in the two molecules are identical and have the usual values. The two C-10–C-11 distances are significantly different from each other, although not significantly different from the mean value of 1.370 Å. The latter value is reasonable in terms of the usual distances found in pyridine rings. The N-1–C-5 and N-1–C-6 distances are equal but somewhat shorter than the values one expects for an sp^3-N to an sp^3-C atom (compare the distances around N-2 which average 1.496 (7) Å). The N-1–C distances together with the sum of the angles about N-1, 360.0° for molecule 1 and 358.4° for molecule 2, suggest that N-1 is sp^2 hybridized. Furthermore, the N-1–C-10 distance of 1.377 (6) Å is significantly shorter than the N-1–C-5 or N-1–C-6 distances (average 1.453 (6) Å), indicating a strong interaction between N-1 and the pyridine ring. The double-bond character in the N-1–

(10) W. R. Harshbarger and S. H. Bauer, *Acta Crystallogr., Sect. B.*, **26**, 1010 (1970).

(11) V. Rychnovsky and D. Britton, *ibid., Sect. B*, **24**, 725 (1968).

(12) M. Mathew and G. J. Palenik, *ibid., Sect. B*, **24**, 59 (1971).

Table III. Probable Hydrogen Positions[a]

Atom bonded to		x	y	z	B, Å²	Distance, Å
			Molecule 1			
H-1	C-1	104	351	706	6.5	0.93
H-2	C-2	213	485	652	6.8	0.94
H-3	C-3	316	340	612	1.4	0.80
H-4	C-5	236	084	570	1.9	1.03
H-5	C-5	371	082	610	1.8	0.95
H-6	C-6	077	−029	593	3.8	0.95
H-7	C-6	110	−151	629	2.3	0.99
H-8	C-7	166	−126	537	3.0	0.98
H-9	C-7	205	−260	569	2.1	1.09
H-10	N-2	−053	−184	538	2.0	0.95
H-11	C-8	−009	−324	604	3.4	1.08
H-12	C-8	−088	−394	556	4.8	0.88
H-13	C-8	070	−430	571	6.0	1.15
H-14	C-9	−101	−332	471	4.6	1.09
H-15	C-9	060	−339	483	4.1	0.94
H-16	C-9	−005	−206	461	5.6	1.07
H-17	C-11	464	018	679	5.2	0.71
H-18	C-12	633	−071	738	5.6	1.05
H-19	C-13	587	−289	762	9.0	1.07
H-20	C-14	378	−384	716	5.9	1.08
			Molecule 2			
H-4	C-5	291	−014	780	2.2	1.17
H-5	C-5	434	−014	829	2.0	1.01
H-6	C-6	429	260	867	3.3	1.04
H-7	C-6	494	121	882	1.4	1.03
H-8	C-7	369	090	942	2.0	1.03
H-9	C-7	306	238	928	2.6	1.04
H-10	N-2	578	170	968	5.3	1.11
H-11	C-8	454	135	027	5.9	1.10
H-12	C-8	556	262	043	4.8	1.01
H-13	C-8	406	294	016	5.2	0.99
H-14	C-9	559	368	923	2.3	1.05
H-15	C-9	457	424	948	3.1	0.98
H-16	C-9	604	400	982	4.5	0.99
H-17	C-11	107	025	780	6.7	0.88
H-18	C-12	−089	115	749	6.4	1.03
H-19	C-13	−113	338	770	6.2	1.02
H-20	C-14	069	448	826	4.8	1.05

[a] The hydrogen atom is given followed by the atom to which it is bonded, the position parameters × 10^3, the isotropic thermal parameter used in the calculations, and the corresponding C–H or N–H distance.

Table IV. Bond Distances and Bond Angles in the Two Cations with the Estimated Standard Deviations Given in Parentheses

Bond	Distance 1, Å	Distance 2, Å
Cl-1–N-2	3.007 (5)	3.029 (4)
S-1–C-1	1.708 (6)	1.579 (7)
S-1–C-4	1.708 (5)	1.580 (5)
N-1–C-5	1.444 (6)	1.458 (6)
N-1–C-6	1.455 (6)	1.456 (6)
N-1–C-10	1.375 (6)	1.379 (6)
N-2–C-7	1.502 (6)	1.500 (6)
N-2–C-8	1.489 (6)	1.504 (6)
N-2–C-9	1.492 (6)	1.489 (6)
N-3–C-10	1.363 (6)	1.351 (6)
N-3–C-14	1.378 (7)	1.367 (7)
C-1–C-2	1.321 (9)	1.326 (9)
C-2–C-3	1.421 (8)	1.519 (7)
C-3–C-4	1.404 (7)	1.611 (5)
C-4–C-5	1.499 (6)	1.502 (7)
C-6–C-7	1.522 (6)	1.516 (6)
C-10–C-11	1.357 (6)	1.383 (7)
C-11–C-12	1.358 7)	1.358 (7)
C-12–C-13	1.362 (8)	1.371 (9)
C-13–C-14	1.368 (8)	1.367 (8)
Bond	**Angle 1, deg**	**Angle 2, deg**
C-1–S-1–C-4	91.5 (3)	99.7 (3)
C-5–N-1–C-6	117.5 (3)	118.3 (4)
C-5–N-1–C-10	121.6 (4)	119.7 (4)
C-6–N-1–C-10	120.9 (4)	120.4 (4)
C-7–N-2–C-8	112.4 (3)	111.3 (3)
C-7–N-2–C-9	110.5 (3)	112.9 (3)
C-8–N-2–C-9	111.4 (4)	110.0 (3)
C-10–N-3–C-14	116.5 (4)	117.1 (4)
S-1–C-1–C-2	112.1 (5)	113.8 (5)
C-1–C-2–C-3	115.2 (5)	115.7 (5)
C-2–C-3–C-4	109.5 (4)	100.3 (3)
S-1–C-4–C-3	111.7 (3)	110.5 (3)
S-1–C-4–C-5	120.7 (3)	124.6 (4)
C-3–C-4–C-5	127.6 (4)	124.7 (4)
N-1–C-5–C-4	114.3 (4)	114.8 (4)
N-1–C-6–C-7	110.8 (4)	111.5 (4)
N-2–C-7–C-6	110.6 (3)	111.2 (4)
N-1–C-10–N-3	117.7 (4)	116.7 (4)
N-1–C-10–C-11	119.5 (4)	120.4 (4)
N-3–C-10–C-11	122.8 (4)	122.9 (4)
C-10–C-11–C-12	118.5 (4)	117.9 (5)
C-11–C-12–C-13	122.0 (5)	121.2 (5)
C-12–C-13–C-14	117.5 (5)	118.4 (5)
N-3–C-14–C-13	122.8 (5)	122.5 (5)

Table V. Displacement of Pyridine Ring Atoms (Å)

	C-11	C-12	C-13	C-14	N-3	N-1
Molecule 1	0.08	0.06	−0.04	−0.12	−0.12	−0.01
Molecule 2	0.16	0.06	−0.19	−0.34	−0.24	0.10

C-10 bond is also reflected in the displacement of the pyridine ring atoms from the plane defined by C-5, C-6, and C-10, as given in Table V. The displacement of N-1 from the plane would be 0.00 for an sp^2 configuration and 0.46 for a tetrahedral sp^3 hybridization. Therefore, the distances and planarities about N-1 are consistent for an sp^2 hybridization for this atom.

Each cation contains one hydrogen atom, H-10, on the dimethylamino group which is capable of forming a hydrogen bond. In both cations a relatively strong hydrogen bond to the Cl^- ion is formed by this hydrogen atom. The N···Cl distance is 3.007 (4) and 3.029 (4) Å, the H-10···Cl distance is 2.06 and 1.93 Å, and the H–H–Cl angle is 4.3 and 4.7° for cations 1 and 2, respectively. Although all the remaining distances < 3.9 Å were calculated and carefully surveyed, no unusual intermolecular distances were observed. Therefore, the crystal appears to be composed of hydrogen-bonded cation–anion moieties packed into the unit cell.

Biological Significance. The two obvious features of the structure which may influence the biological activity of the antihistamine, 2-[(2)-dimethylaminoethyl-2-thenylamino]pyridine hydrochloride, are the conformation of the molecule and the planarity around the N-1 atom. The remaining molecular parameters are in good agreement with the values found in other organic molecules, suggesting that the biological activity of this compound is not a result of unusual electronic effects.

The conformation down the C–C bond of the dimethylaminoethyl side chain of the two molecules is shown in Figure 2. We see that although the conformations are not identical, in both cases the dimethylamino group is trans to the substituent on the second carbon atom of the ethyl group. Because of the similarity to the conformation found in histamine,[3] the action of antihistamines was related to this conformational similarity.[4] This hypothesis has been viewed as unlikely since histamine exists as both the trans and gauche isomers in

solution.[13] However, since at least 25–45% of the histamine cation is in the trans conformation, this conformer could still be the reactive species. Furthermore, the recent crystal-structure study of *dl*-bromopheniramine maleate, a potent antihistamine, has also revealed a trans conformation about the C–C bond of the dimethylaminoethyl group.[14] Therefore, the hypothesis that the trans conformation is essential to antihistamine activity appears very reasonable. In addition, the dimethylamino group is more basic than the NH_2 group in histamine, allowing the antihistamine to displace or to compete favorably with histamine for a receptor site. The biological response caused by histamine is then related to the imidazole group, not the dimethylaminoethyl chain. The bulky groups found in most antihistamines are therefore selected to prevent the response triggered by the imidazole ring. Other structural studies of antihistamines and related compounds are planned to further explore these hypotheses.

The biological activity of the cephalosporins[15] was related to the planarity of the β-lactam nitrogen atom. Although I contains a planar tertiary amine nitrogen atom, the biological activity of the drug is probably not related to this function. The conformational arguments presented above, together with the fact that other potent antihistamines lack this group, suggest that a planar tertiary nitrogen is not essential for antihistamine activity. However, the present results together with the cephalosporin studies indicate that planarity may be a good indication of resonance interaction.

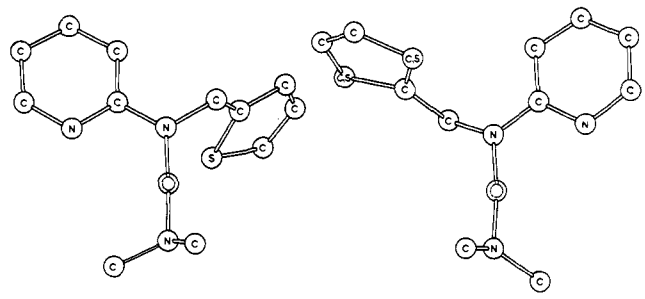

Figure 2. A view down the C–C bond of the dimethylaminoethyl side chain in the two molecules in the asymmetric unit. The disordered thiophene ring atoms are labeled CS.

Acknowledgment. We wish to thank Eli Lilly and Co. for the sample of Histadyl. Financial support was provided by the U. S. Public Health Services, National Institute of Allergies and Infectious Diseases, and the National Research Council of Canada. The research was carried out at the University of Waterloo, Waterloo, Ontario, Canada.

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Protein Folding

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Received September 17, 1971

Abstract: We have developed simple computer routines for locating regions in which the peptide backbone of globular proteins is folded back on itself. These programs have been used to locate "turns" in carboxypeptidase and α-chymotrypsin. The following generalizations can be made. (1) Turns occur on the surface of the protein molecules. (2) Turn segments are less hydrophobic than the protein as a whole. (3) Uninterrupted sequences of 3–8 hydrophilic residues are frequently associated with folding of the peptide chain.

Although more than ten protein crystal structures have been determined, the principles by which these molecules develop secondary and tertiary structure are not yet well understood. The considerations discussed to date have been rather general and nonrestrictive.[1,2] One approach to this problem is to focus on local structural features such as α helices and β-pleated sheets. Recently, attention has been drawn to the turning points of the peptide chain. "Hairpin" and 3–10 turns have been predicted theoretically[2,3] and identified as common features of globular protein structures.[4] We have developed computer procedures for determining the location of "hairpin" and other turns, given the protein coordinates. We report here some initial results on three characteristics of the turns in globular proteins. (1) Turns occur on the surface of the protein molecules. (2) The amino acid composition of these regions is considerably less hydrophobic than the composition of the proteins as a whole or the helical and β sections. (3) The occurrence of a turn or corner is very frequently associated with an uninterrupted sequence of 3–8 hydrophilic residues.

Methods and Results

Our observations are based on the following sources of data: (1) the atomic coordinates[5] and a Phillips–

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