Stereochemistry of Anticholinergic Agents. IX.* Crystal and Molecular Structure of 3-(2-Methylpiperidino)-1-phenylpropyl 2-Tolyl Ether Methiodide

By T. A. Hamor

Chemistry Department, The University, Birmingham B15 2TT, England

The title compound crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 11.77$ (1), $b = 10.33$ (1), $c = 18.04$ (2) Å, $Z = 4$. The structure was refined to $R = 4.7\%$ for 1860 observed counter amplitudes. Estimated standard deviations for bond lengths, bond angles and torsion angles average 0.02 Å, 1.2 and 1.6°. The structure is very similar to that of the corresponding phenyl ether methiodide. Certain bond angle distortions in the ether group are compared with analogous distortions observed in other aromatic ethers.

Introduction

Guy & Hamor (1975) described the crystal structure of 3-(2-methylpiperidino)-1-phenylpropyl phenyl ether methiodide (henceforth MPP), an anticholinergic agent with activity of *ca* 46% of that of atropine sulphate in inhibiting acetylcholine-induced spasms of isolated guinea pig ileum (Yoshida, Morita & Ogawa, 1973*a*). The corresponding 2-tolyl ether methiodide (henceforth MPT) is an even more potent anticholinergic with an activity of 66.6% of that of atropine sulphate (Yoshida, Morita & Ogawa, 1973*b*). The present paper describes the crystal structure of MPT.

It was hoped that any differences in the overall geometries of the two cations, due to the presence of the extra methyl group in MPT, could be correlated with its somewhat greater biological activity. This would be of value in obtaining a better understanding of anticholinergic drug mechanism. However, during the course of the structure determination, it gradually became clear that the crystal structures of MPP and MPT were virtually identical, and that the extra methyl group had only a marginal effect on the conformation. It seemed, nevertheless, worth while to continue with the refinement to obtain an independent measure of bond lengths and angles, especially in the ether grouping, which in the MPP structure appeared to differ from standard values.

Experimental

Crystals suitable for X-ray analysis were supplied by Dr A. Yoshida. After initial examination by photographic methods, final cell dimensions and intensities were measured on a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo $K\alpha$ radiation. The crystal, $0.5 \times 0.5 \times 0.3$ mm, was set about z. From 2537 reflexions scanned in the range $0.1 \le \sin \theta/\lambda \le 0.6$, 1860, for which $I > 2.5\sigma(I)$, were con-

* Part VIII: Hamor (1976).

sidered to be observed and were used in the structure analysis. The ω-scan method was employed with 130 steps of 1s at intervals of 0.01° for each reflexion on layers $hk0$ to $hk5$. Reflexions on the higher layers were measured by a variable scan-range technique (Guy & Hamor, 1974). Backgrounds were measured for 30s at each end of the scan. Three reflexions were re-measured after each layer to monitor the stability of the system. No significant variation of intensity was observed. Absorption corrections were not applied.

Crystal data

$C_{23}H_{32}INO$, $M = 465.4$. Orthorhombic, $a = 11.77$ (1), $b = 10.33$ (1), $c = 18.04$ (2) Å, $U = 2193.4$ Å³, $Z = 4$, $D_c = 1.409$ g cm⁻³, $F(000) = 952$. Systematic absences: $h00$, h odd; $0k0$, k odd; $00l$, l odd. Space group $P2_12_12_1$. Mo $K\alpha$ radiation, $\lambda = 0.71069$ Å; μ(Mo $K\alpha$) = 14.9 cm⁻¹.

Determination of the structure

Comparison of the crystal data with those of MPP ($a = 11.41$, $b = 10.24$, $c = 17.92$ Å, space group $P2_12_12_1$) suggested that the two structures might be similar. A Patterson synthesis showed that the I⁻ ion occupied virtually the same position in the unit cell. The structure was determined by using the atomic coordinates for MPP to phase a difference synthesis which contained only one maximum at a chemically reasonable site for the extra methyl group known to be present in MPT. Least-squares refinement of coordinates and thermal parameters (isotropic for C, N and O; anisotropic for I⁻) resulted in an R of 7.6%. The lighter atoms were now allowed to vibrate anisotropically and H atoms were introduced in their theoretical positions but their parameters were not refined. The H atoms of methyl group C(23) were not included as there seemed to be no reliable method of calculating their positions. Attempts to locate them from a difference synthesis were not successful. Refinement was ter-

minated when all calculated shifts in the atomic parameters were $<0.1\sigma$ and R 4·7% for the 1860 observed structure amplitudes.* Final atomic coordinates are in Table 1 and the thermal parameters in Table 2.† A stereoscopic view of the cation is shown in Fig. 1.

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* A list of observed and calculated structure amplitudes has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31581 (17 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

† Owing to the limitations of computer storage, the structure was refined in two blocks for the anisotropic least-squares calculations. The standard deviations derived from the least-squares totals may therefore be underestimates, and have been increased by 50 % to give more realistic values.

Table 1. *Fractional atomic coordinates* ($\times 10^4$) *with estimated standard deviations in parentheses*

	x	y	z
C(1)	5522 (10)	2810 (12)	−169 (7)
C(2)	4857 (10)	2673 (14)	474 (7)
C(3)	5004 (14)	3491 (19)	1054 (9)
C(4)	5830 (17)	4494 (17)	1006 (11)
C(5)	6454 (13)	4613 (19)	359 (14)
C(6)	6308 (13)	3787 (14)	−209 (10)
C(7)	6184 (10)	36 (11)	−200 (6)
C(8)	7293 (9)	363 (11)	−301 (6)
C(9)	8144 (12)	−343 (14)	66 (7)
C(10)	7849 (12)	−1300 (14)	532 (8)
C(11)	6738 (14)	−1625 (13)	640 (8)
C(12)	5886 (12)	−977 (13)	276 (8)
C(13)	5379 (10)	1887 (13)	−808 (7)
C(14)	4230 (11)	2062 (14)	−1238 (7)
C(15)	4271 (9)	3302 (12)	−1664 (6)
C(16)	3229 (10)	2420 (12)	−2795 (7)
C(17)	2177 (12)	2645 (15)	−3275 (8)
C(18)	1092 (12)	2818 (19)	−2849 (9)
C(19)	1214 (12)	3846 (14)	−2281 (10)
C(20)	2213 (10)	3576 (15)	−1782 (7)
C(21)	3583 (17)	4786 (14)	−2561 (10)
C(22)	4288 (13)	2290 (16)	−3253 (9)
C(23)	4638 (15)	−1312 (19)	393 (12)
N	3322 (8)	3494 (11)	−2215 (5)
O	5280 (7)	576 (9)	−564 (5)
I	7500 (1)	3538 (1)	−2365 (1)

Table 1 (*cont.*)

	x	y	y
H(2)	4223	1920	513
H(3)	4521	3377	1559
H(4)	5916	5155	1464
H(5)	7107	5346	336
H(6)	6807	3925	−710
H(8)	7523	1157	−664
H(9)	9024	−89	−21
H(10)	8512	−1831	814
H(11)	6539	−2384	1034
H(13)	6111	2010	−1186
H¹(14)	3538	2076	−843
H²(14)	4131	1249	−1628
H¹(15)	4238	4101	−1256
H²(15)	5089	3348	−1962
H(16)	3153	1478	−2518
H¹(17)	2081	1811	−3645
H²(17)	2323	3526	−3604
H¹(18)	875	1901	−2558
H²(18)	396	3075	−3223
H¹(19)	439	3910	−1943
H²(19)	1357	4780	−2564
H¹(20)	2062	2651	−1496
H²(20)	2278	4358	−1370
H¹(21)	3654	5530	−2115
H²(21)	4376	4739	−2868
H³(21)	2880	5074	−2933
H¹(22)	4387	3180	−3577
H²(22)	4160	1463	−3632
H³(22)	5022	2124	−2908

The weighting scheme was $w^{1/2} = 1$ if $|F_o| < 30{\cdot}0$, and $w^{1/2} = 30{\cdot}0/|F_o|$ if $|F_o| > 30{\cdot}0$. Scattering factors for C, I, N and O were taken from Hanson, Herman, Lea &. Skillman (1964), those for H from Stewart, Davidson & Simpson (1965). The real and imaginary components of the anomalous dispersion correction for I were from *International Tables for X-ray Crystallography* (1962). The final weighted R (Hamilton, 1965) was 0·069 for the enantiomer depicted in Fig. 1, and 0·075 for the centrosymmetrically related configuration.

The major part of the computations was carried out on the CDC 7600 at the University of Manchester
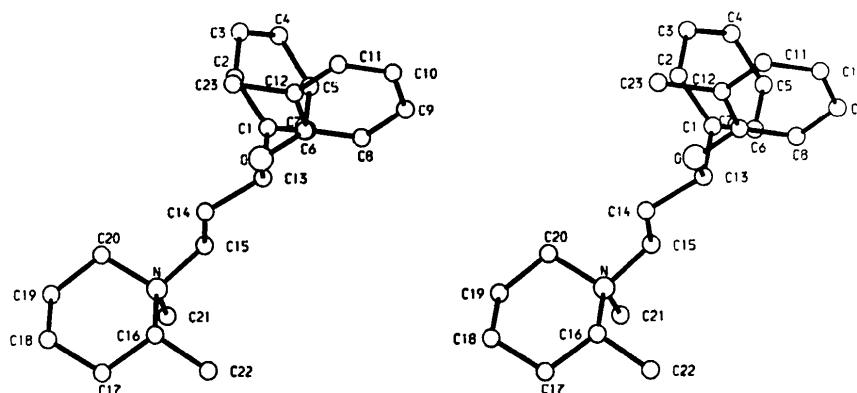

Fig. 1. Stereoscopic view of the MPT cation along the y axis.

Table 2. Anisotropic thermal parameters ($\times 10^4$) for the heavier atoms

Temperature factors are in the form
$$T = \exp\left[-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{12}hka^*b^* + \ldots)\right].$$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	459	512	558	118	−35	72
C(2)	538	568	614	131	−48	−32
C(3)	808	894	644	364	−26	120
C(4)	943	717	1001	324	−347	−475
C(5)	538	800	1362	7	−225	−256
C(6)	625	578	944	18	−33	5
C(7)	554	382	358	7	−45	−64
C(8)	451	424	417	−8	4	−48
C(9)	619	517	532	128	−42	−101
C(10)	786	492	648	242	−146	−39
C(11)	960	335	629	−15	−100	111
C(12)	668	481	602	−143	106	−23
C(13)	428	663	452	21	−13	79
C(14)	512	575	640	−40	−169	125
C(15)	490	487	475	−12	−112	30
C(16)	599	475	483	36	27	74
C(17)	658	749	627	4	−173	−51
C(18)	587	1104	695	122	−228	−125
C(19)	551	665	874	90	−78	44
C(20)	516	740	560	−4	26	−54
C(21)	1123	516	795	−282	−21	107
C(22)	643	797	837	170	66	−20
C(23)	744	975	1255	−380	161	366
N	564	505	496	−102	−68	199
O	500	569	563	−83	−114	−7
I	646	664	839	−90	259	−15

Regional Computer Centre with the X-RAY 72 system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

Discussion

Molecular dimensions are in Table 3. Estimated standard deviations average 0·02 Å for lengths and 1·2 and 1·6° for bond and torsion angles. The results of mean plane calculations are in Table 4. The atomic numbering scheme, shown in Fig. 1, is the same as for the structure of MPP (Guy & Hamor, 1975).

Table 3. Molecular dimensions

(a) Bonded distances (Å) with standard deviations in parentheses

C(1)—C(2)	1·407 (19)	C(1)—C(13)	1·505 (18)
C(2)—C(3)	1·356 (22)	C(13)-O	1·429 (16)
C(3)—C(4)	1·424 (25)	O——C(7)	1·368 (15)
C(4)—C(5)	1·385 (30)	C(13)-C(14)	1·569 (18)
C(5)—C(6)	1·344 (28)	C(14)-C(15)	1·495 (18)
C(6)—C(1)	1·371 (19)	C(15)-N	1·508 (15)
C(7)—C(8)	1·361 (16)	N——C(16)	1·528 (16)
C(8)—C(9)	1·404 (18)	C(16)-C(17)	1·529 (19)
C(9)—C(10)	1·343 (19)	C(17)-C(18)	1·501 (21)
C(10)-C(11)	1·365 (22)	C(18)-C(19)	1·483 (24)
C(11)-C(12)	1·372 (21)	C(19)-C(20)	1·507 (19)
C(12)-C(7)	1·399 (18)	C(20)-N	1·524 (15)
C(12)-C(23)	1·525 (22)	N——C(21)	1·506 (19)
		C(16)-C(22)	1·502 (21)

(b) Selected non-bonded distances (Å)

N⋯O	4·82	N⋯Centre of	
N⋯C(13)	3·88	ring C(1)–(6)	5·62
N⋯C(23)	7·01	N⋯Centre of	
		ring C(7)–(12)	7·52

Table 3 (cont.)

(c) Bond angles (°); mean standard deviation 1·2°

C(1)—C(2)—C(3)	120·2	C(11)-C(12)-C(23)	121·8
C(2)—C(3)—C(4)	119·5	C(1)—C(13)-C(14)	113·7
C(3)—C(4)—C(5)	118·6	O——C(13)-C(14)	101·1
C(4)—C(5)—C(6)	121·2	C(13)-C(14)-C(15)	109·0
C(5)—C(6)—C(1)	120·9	C(14)-C(15)-N	115·4
C(6)—C(1)—C(2)	119·5	C(15)-N——C(20)	107·6
C(7)—C(8)—C(9)	119·5	C(15)-N——C(16)	114·1
C(8)—C(9)—C(10)	119·6	N——C(16)-C(17)	109·6
C(9)—C(10)-C(11)	121·1	C(16)-C(17)-C(18)	114·6
C(10)-C(11)-C(12)	120·8	C(17)-C(18)-C(19)	110·9
C(11)-C(12)-C(7)	118·4	C(18)-C(19)-C(20)	110·8
C(12)-C(7)—C(8)	120·5	C(19)-C(20)-N	111·8
C(2)—C(1)—C(13)	120·3	C(20)-N——C(16)	109·3
C(6)—C(1)—C(13)	120·2	C(15)-N——C(21)	103·8
C(1)—C(13)-O	112·0	C(20)-N——C(21)	109·8
C(13)-O——C(7)	118·1	C(16)-N——C(21)	112·0
C(8)—C(7)—O	125·5	N——C(16)-C(22)	112·4
C(12)-C(7)—O	113·8	C(17)-C(16)-C(22)	111·9
C(7)—C(12)-C(23)	119·8		

(d) Selected torsion angles (°);[*] mean standard deviation 1·6°

C(2)—C(1)—C(13)-O	−43·2
C(6)—C(1)—C(13)-O	136·4
C(2)—C(1)—C(13)-C(14)	70·6
C(6)—C(1)—C(13)-C(14)	−109·8
C(8)—C(7)—O——C(13)	−29·1
C(12)-C(7)—O——C(13)	154·5
C(7)—O——C(13)-C(14)	175·6
C(1)—C(13)-O——C(7)	−63·0
O——C(13)-C(14)-C(15)	−169·0
C(1)—C(13)-C(14)-C(15)	70·8
C(13)-C(14)-C(15)-N	169·3
C(14)-C(15)-N——C(16)	−57·1
C(14)-C(15)-N——C(20)	64·3
C(14)-C(15)-N——C(21)	−179·3
C(15)-N——C(16)-C(17)	174·6
C(15)-N——C(16)-C(22)	−60·2
C(15)-N——C(20)-C(19)	176·7
C(21)-N——C(16)-C(17)	−67·8
C(21)-N——C(16)-C(22)	57·4
C(21)-N——C(20)-C(19)	64·3
N——C(16)-C(17)-C(18)	−53·0
C(16)-C(17)-C(18)-C(19)	53·1
C(17)-C(18)-C(19)-C(20)	−54·5
C(18)-C(19)-C(20)-N	59·2
C(19)-C(20)-N——C(16)	−58·9
C(20)-N——C(16)-C(17)	54·1
C(22)-C(16)-C(17)-C(18)	−178·5

[*] Sign convention as defined by Klyne & Prelog (1960).

In general, molecular dimensions are very similar to those determined for MPP. The mean difference in torsion angle is 2·5°; the maximum difference of 8·3° involves C(8)-C(7)-O-C(13) which is −20·8 in MPP and −29·1° in the present structure. This torsion angle determines the orientation of phenyl ring C(7)–C(12) with respect to the remainder of the molecule. Although it is this ring which carries the extra methyl group linked to C(12), it does not seem possible to rationalize the small difference in orientation with any intramolecular non-bonded interactions of the methyl group. The distances between the N atom and the centres of the phenyl rings are virtually identical in the two structures, as are the dihedral angles between the mean planes of the phenyl rings. The piperidinium

ring, which is in the chair conformation, has ring torsion angles in the range 53·0–58·9°, mean 55·5°. In the piperidinium ring of MPP, corresponding torsion an-

Table 4. *Mean plane calculations*

(*a*) Deviations (Å) of atoms from least-squares planes. In the equations of the planes *x*, *y* and *z* are fractional coordinates relative to the cell axes.

Plane (1) C(1)–(6)
$$8·152x - 6·308y + 6·925z = 2·607$$

C(1)	−0·005	C(2)	0·006	C(3)	0·000	C(4)	−0·007
C(5)	0·007	C(6)	−0·002	C(13)	−0·028		

Plane (2) C(7)–(12)
$$0·625x - 6·692y - 13·709z = 0·636$$

C(7)	−0·001	C(8)	0·010	C(9)	−0·012	C(10)	0·005
C(11)	0·005	C(12)	−0·007	C(13)	0·456	C(23)	0·008
O	−0·081						

Plane (3) C(13)–(15)
$$4·535x - 5·016y - 14·156z = 2·636$$

C(1)	1·302	C(7)	−0·434	N	−0·254	O	−0·268

Plane (4) C(16)–(20), N
$$1·822x + 8·906y - 8·704z = 5·397$$

C(16)	0·221	C(17)	−0·206	C(18)	0·209	C(19)	−0·235
C(20)	0·259	N	−0·248				

(*b*) Dihedral angles (°)

(1)–(2)	81·9		(2)–(3)	21·4
(1)–(3)	74·8		(2)–(4)	79·4
(1)–(4)	52·8		(3)–(4)	88·9
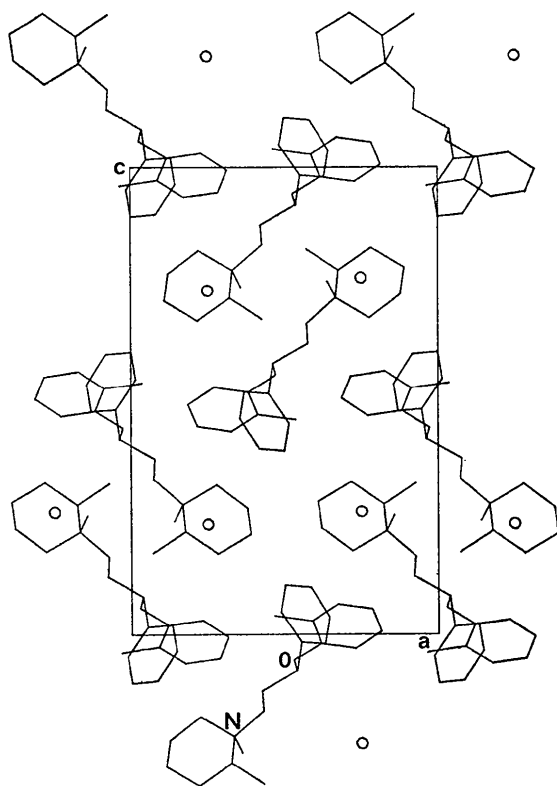
Fig. 2. The crystal structure projected along the *y* axis. Circles denote iodide ions.

gles differ by at most 1·1° and the mean is 55·7°. These angles do not differ significantly from the standard cyclohexane value of 56° (Bucourt, 1974).

C(sp^3)–C(sp^3) lengths range from 1·483 to 1·569 Å, mean 1·512 Å. C(16)–C(22), which in MPP was abnormally short (1·444 Å), is in the present structure 1·502 Å in good agreement with accepted values. The four C(sp^3)–N$^+$ lengths average 1·517 Å in good agreement with previous results (Guy & Hamor, 1975). The angle C(14)–C(15)–N (115·4°) is larger than might be expected at an sp^3-hybridized C atom, but is similar to the corresponding angle in MPP and may indicate a repulsive interaction between C(14) and the positively charged N atom.

In MPP a large bond angle at O of 118·5° was noted and compared with similarly large angles in other aromatic ethers. In the present structure this angle is 118·1° in excellent agreement with the earlier results. C(7)–O and O–C(13) are also similar to those in MPP with the former significantly shorter than a C(sp^2)–O single bond. Not commented upon in the discussion on MPP was a large distortion of the angles at C(7). Thus C(8)–C(7)–O was 125·2° and C(12)–C(7)–O, 114·8°. In the present structure the corresponding angles are similarly distorted, with values of 125·5 and 113·8° respectively. The ring angle C(12)–C(7)–C(8) is normal in both structures. Similar distortions commonly occur in aromatic ethers, *e.g. o*-ethoxybenzoic acid (Gopalakrishna & Cartz, 1972), mescaline hydrobromide (Ernst & Cagle, 1973), *o*-methyl *β*-methylphenylcholine ether bromide (Kneale, Geddes & Sheldrick, 1974) and *β*-methylphenylcholine ether bromide (Hamodrakas, Geddes & Sheldrick, 1974). Hamodrakas *et al.* (1974) have pointed out that the bond linking the ether O atom to the phenyl ring possesses partial double-bond character as indicated by its length (1·372 and 1·386 Å in the two crystallographically independent molecules in the unit cell) and a large bond angle at the O atom (123·9 and 119·0° in the two molecules). There will therefore be a tendency for the Ph–O–C(*x*) system to adopt a near-planar conformation, with C(*x*) oriented synplanar with respect to one of the *ortho*-carbon atoms of the phenyl ring and hence a short contact between these two atoms will occur. The distortion of the C(aromatic)–C(aromatic)–O bond angles from the normal trigonal value can then be attributed to repulsive interactions between these atoms.

In MPT, C(13) lies 0·46 Å from the mean plane of phenyl ring C(7)–(12), torsion angle C(8)–C(7)–O–C(13) −29·1°, so that here the strain is relieved also by a deviation from planarity. The shortest contacts are C(13)···C(8), 2·90, C(13)···H(8), 2·65 and H(13)···H(8), 2·10 Å. The small C(12)–C(7)–O angle (113·8°), however, has the effect of reducing the separation between the methyl C(23) and the O atom [C(23)···O = 2·71 Å]. Bond lengths in the phenyl ring range from 1·343 to 1·404 Å, but the accuracy of the determination is not sufficiently high to warrant any

attempts to explain the variation of bond lengths in terms of electronic effects due to the partial double bond character of C(7)–O.

Table 5. *The shorter intermolecular contacts* (Å) *excluding hydrogen atoms*

Symmetry code

(i)	$\frac{1}{2}-x,\quad -y,\quad \frac{1}{2}+z$
(ii)	$\frac{1}{2}+x,\quad \frac{1}{2}-y,\quad -z$
(iii)	$\frac{1}{2}+x,\ -\frac{1}{2}-y,\quad -z$
(iv)	$1-x,\quad \frac{1}{2}+y,\ -\frac{1}{2}-z$

C(23)···C(17$^{\text{i}}$)	3·50	C(10)···C(23$^{\text{iii}}$)	3·65
C(9)····C(3$^{\text{ii}}$)	3·54	C(8)····C(3$^{\text{ii}}$)	3·66
C(9)····C(2$^{\text{ii}}$)	3·55	C(10)···C(20$^{\text{ii}}$)	3·68
C(3)····C(19$^{\text{ii}}$)	3·57	C(21)···O$^{\text{iv}}$	3·73
C(3)····C(20$^{\text{ii}}$)	3·61	C(3)····C(18$^{\text{ii}}$)	3·74
C(23)···C(18$^{\text{i}}$)	3·64	C(9)····C(20$^{\text{ii}}$)	3·76
C(8)····C(2$^{\text{ii}}$)	3·65		

The crystal packing is shown in Fig. 2, and the shorter intermolecular contact distances, excluding those involving H atoms, are in Table 5. None of these is shorter than the sum of the van der Waals radii. Contact distances involving the I$^-$ ion are all greater than 4 Å.

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The Crystal Structure of an Orthorhombic Form of Adenosine-5'-monophosphate

BY S. NEIDLE, W. KÜHLBRANDT* AND A. ACHARI

Department of Biophysics, King's College, 26–29 Drury Lane, London, WC2B 5RL, England

Adenosine-5'-phosphate monohydrate was crystallized in the orthorhombic space group $P2_12_12_1$, with $a=22·997$ (2), $b=9·406$ (1), $c=6·599$ (1) Å, $Z=4$. The structure was solved by direct methods and refined to a final R_w of 0·0639 for 1320 significant reflexions measured on an automatic diffractometer. The conformation of the molecule differs significantly from that previously reported for the monoclinic monohydrate [Kraut & Jensen, *Acta Cryst.* (1963), 16, 79–88]. The sugar conformation, for example, is here C(2)'-*endo*, and the glycosidic torsion angle has altered by almost 50°.

Introduction

The structure of adenosine-5'-monophosphate (5'-AMP) was first determined by Kraut & Jensen (1963), who crystallized it in the monoclinic space group $P2_1$.

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* Present address: The Free University of Berlin.

The results of this and other nucleotide structure analyses have been instrumental in furthering knowledge of the structures of the nucleic acids (Arnott, 1970). Especially useful and interesting have been the findings that the solid-state conformations of the nucleotides have been found to fall into a small number of discrete classes (Sundaralingam, 1969, 1973). How-