

Crystal and Molecular Structure of 1-Benzyl-1,2,2-trimethyl Azetidinium Bromide

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The structure of the compound, 1-benzyl-1,2,2-trimethyl azetidinium bromide has been determined by a single crystal x-ray diffraction study. The compound crystallizes in the space group Pnam with four formula weights in a unit cell of dimensions $a = 14.36$, $b = 13.73$, $c = 6.90_6$ Å. The compound is partially disordered with the benzyl part ordered and the remainder of the ring disordered about the mirror plane. The azetidinium ring bears a close resemblance in bond distances, bond angles and conformation to the β -lactam ring found in penicillin. The disordering is discussed in detail and a comparison of the effects of fusing a second ring to the azetidinium moiety are explored. A final value of $R = 0.09_4$ for the 432 independent reflections was obtained.

INTRODUCTION

Azetidine (I) and its various derivatives have been known since the nineteenth century (1). Interest in bicyclic



Figure I.

derivatives of these compounds was stimulated by the discovery during World War II that penicillin contains such a ring in the form of a β -lactam (2). Further interest in these compounds was generated by the potential relationship between azetidine and aziridine acting as alkylating agents, which has been considered as one possible criterion in judging effectiveness as an anti-cancer agent (3).

The only structural studies previously completed on azetidine derivatives are those in which it is fused in a bicyclic system, namely the antibiotics, penicillin (4) and cephalosporin C (5). This paper completes our preliminary report (6) on the unfused azetidinium compound, 1-benzyl-1,2,2-trimethyl azetidinium bromide (II). A concurrent study of β -azetidine-2-carboxylic acid (7) has also been reported. Finally, we understand an additional study on *N*-methyl-*N*-*t*-butyl hydroxyazetidinium methylsulfonate is underway (8).

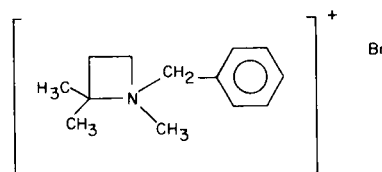


Figure II.

CRYSTAL DATA

A sample of the compound was kindly furnished to us by Professor N. J. Leonard (9). The crystals in the sample were long thin needles and a single crystal suitable for the x-ray determination was selected. Since the crystal was extremely small, no absorption corrections were made.

Intensity data of the zero and first five levels about the [010] axis, the zero and first five levels about the [100] axis and the (h,h,l) zero level were collected using a Buerger precession camera and filtered Mo- K_{α} radiation. Extinctions for $(k + l)$ odd in the $(0k\ l)$ zone and h odd in the $(hk\ 0)$ zone indicated either space group $Pna2_1$ or Pnam.

The cell dimensions of the crystal were $a = 14.36 \pm .02$, $b = 13.73 \pm .02$, and $c = 6.90_6 \pm .006$ Å based on a series of measurements of high order reflections on the $(h0\ l)$ and $(0k\ l)$ zones. The assumption of four molecules per unit cell led to a calculated density of 1.318 grams per c.c. which was in reasonable agreement with a measured density (by flotation methods) of $1.33 \pm .01$ grams per c.c.

Although the structure refined in either space group $Pna2_1$ or Pnam, the resultant positions in Pnam led to a

TABLE I
Coordinates and Temperature Factors (Pnam)

Atom	(Symbol)	x	y	z	B ₁₁	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃
Bromine	Br	.3317	.3326	.2500	.0042	.0039	.0194	.0001	0	0
Methyl-1	M-1	.0666	.9669	.2828	.0029	.0083	.0054	.0030	-.0021	-.0034
Methyl-2	M-2	.1200	.1360	.1564	.0085	.0033	.0434	-.0052	-.0041	.0047
Methyl-3	M-3	.2985	.0638	.0938	.0014	.0118	.0552	-.0039	-.0044	.0155
Ring Carbon-1	C-1	.1401	.0533	.2745	.0021	.0015	.0245	-.0012	-.0053	.0032
Ring Carbon-2	C-2	.1610	.0896	.4771	.0059	.0125	.0320	-.0060	-.0012	-.0125
Ring Carbon-3	C-3	.2635	.0559	.4530	.0052	.0056	.0107	-.0032	.0022	-.0070
Nitrogen	N	.2456	.0162	.2705	.0037	.0023	.0220	-.0005	.0055	.0047
Methylene	Myn	.2557	.9039	.2586	.0006	.0011	.0853	.0006	.0047	.0022
Benzene-1	φ-1	.3575	.8770	.2500	.0011	.0053	.0261	-.0014	0	0
Benzene-2	φ-2	.4032	.8582	.0750	.0045	.0014	.0540	.0012	.0054	-.0041
Benzene-3	φ-3	.4935	.8205	.0750	.0034	.0026	.0866	-.0003	.0009	-.0097
Benzene-4	φ-4	.5380	.8020	.2500	.0008	.0032	.1233	.0005	0	0

chemically reasonable structure, albeit disordered, and it was thus concluded that Pnam was the more probably space group.

The intensities were estimated visually using timed exposures of a selected "typical" reflection from the same crystal. Lorentz-polarization corrections were made in the usual way (10) and then reflections common to more than one zone were utilized in putting all of the intensities on the same relative scale. A rapid dropoff of intensity of higher order reflections, characteristic of disorder in a crystal, severely limited the amount of data collected. A total of 432 independent reflections were thus observed although exposure times up to 72 hours were utilized.

STRUCTURAL DETERMINATION

Patterson maps of the (h0l) and (0kl) projections immediately gave x and y coordinates for the bromide ion. Since the z-coordinate is not fixed in space group Pna2₁, a value of z = 0.25 (compatible with the special position in Pnam) was chosen. Initial refinements in Pna2₁ led to R_r¹¹ values of 0.25, 0.31₂ for the bromide position. A difference Fourier map using the phases from the above refinement and the observed structure factors was calculated. The resulting map, Figure III, contained sixteen

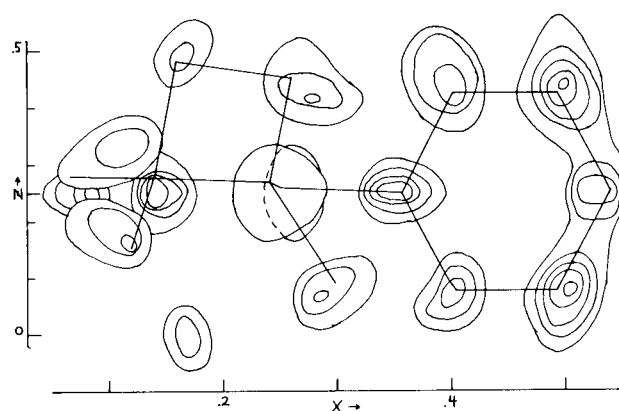


Figure III. Original Fourier Map based on phases of bromine only (in Pna2₁), projected down the b-axis. Contours at arbitrary units beginning with zero contour. Nitrogen and methylene carbon have only one contour shown for reasons of clarity.

peaks of comparable heights and within bond distances of each other rather than the anticipated fourteen peaks corresponding to the number of atoms in the organic moiety. Of the sixteen peaks observed, six conformed rather well to a benzene ring including two with a coordinate z = 0.25. Of the remaining ten, four also had

z -coordinates either on, or near, $z = 0.25$. The remaining six roughly mirrored about $z = 0.25$.

Although the map strongly suggested that the structure belonged to the higher space group (Pnam) with a mirror plane at $z = 0.25$, for the sake of completeness, attempts were made to refine it in the lower space group (Pna₂1). Isotropic refinements, including all of the atoms corresponding to a molecule in the lower space group, with their appropriate scattering factor curves, led to $R, r = 0.107, 0.127$.

At this stage, the determination of the overall structure could be considered essentially complete. Unfortunately, the refinements in Pna₂1 left much to be desired in the final analysis from a chemist's standpoint. The benzene ring was badly distorted with distances ranging from 1.20 to 1.55 Å and angles ranging from 113° to 130°. The four-membered ring contained one distance of 1.72 Å and one methyl group at a distance of 1.40 Å from the four membered ring.

Two paths remained to be pursued at this point. First, refinements could be continued in Pna₂1 but with anisotropic temperature factors, as suggested by the shapes of the peaks on an intermediate Fourier map. Alternatively, the structure could be refined in the centrosymmetric space group (Pnam). Both possibilities were explored in detail.

In Pna₂1, anisotropic refinements led to R, r values of 0.09₆, 0.11₁. However, the phenyl ring remained badly distorted and the other anomalous distances did not improve.

In Pnam, a variety of possibilities existed because six of the atoms in the organic moiety were within 0.20 Å of $z = 0.25$ (Figure IV).

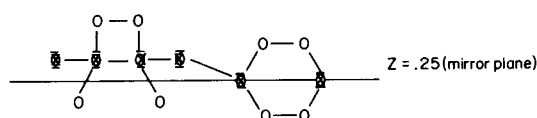


Figure IV. Organic moiety showing one of the two disordered models with six atoms (marked by X) either on or very near the m plane at $Z = 0.25$ in Pnam.

A series of models involving various conformations where one or more of these atoms was simultaneously off the mirror plane was thus possible. The models ranged from a highly ordered one; i.e., all six of the atoms near the mirror plane being fixed on the mirror plane, to a totally disordered model in which all six atoms in question were slightly off the mirror plane. In all such models, the bromide ion coordinate was fixed at $z = 0.25$. Each of the

models was tested in a series of least squares refinements.

The atoms ϕ_1 and ϕ_4 in the benzene ring were ultimately assigned a coordinate $z = 0.25$, and placed on the mirror plane. The phenyl ring itself was ordered and mirrored about $z = 0.25$ in so far as could be determined from our data. Refinements in which such an ordered benzene ring was used refined without anomalous behavior and resulted in chemically reasonable molecular parameters. In those refinements in which a disordered benzene ring was used, the peaks gradually shifted into each other producing both a crystallographically and a chemically unacceptable model.

In the ordered structure for the phenyl ring, all but two of the final coordinates refined to well within one E.S.D. of those for an "ideal" phenyl ring, i.e., a ring having all internal angles at 120° and all bond distances at 1.397Å. The remaining two coordinates were a little more than one E.S.D. from those necessary for an "ideal" phenyl ring. Therefore such an "ideal" ring was used in all subsequent refinements with those temperature factors required by symmetry being held fixed and all others allowed to vary.

For the remaining four peaks near the mirror plane, the disordering about the mirror plane was more pronounced. The methylene carbon peak was so close to the mirror plane (0.06 Å) that even in the final sets of least squares refinements, its z -coordinate oscillated between the space group equivalent positions at $z = 0.2586, 0.2414$. This behavior was exhibited to a lesser degree by the nitrogen peak (0.14 Å from the mirror plane) and the peak for ring carbon-1 (0.17 Å from the mirror plane) and not at all for methyl-1 (0.23 Å from the mirror plane). This anomalous behavior recurred even though refinements were carried through with damping factors as small as 0.1 and weighting factors inversely proportional to the standard errors of the observations. Profiles of the peaks in question (Figure V) show the overlap of the pairs of symmetry related peaks about $Z = 1/4$ for these atoms and strongly suggest that least squares methods are incapable of ultimately refining these peaks. Final positions for these atoms do correspond with the peak centers obtained by fitting a pair of Gaussian peaks within each doublet peak. However, the final molecular parameters involving these atoms undoubtedly have larger errors than those indicated by the E. S. D. values obtained from the last cycle of least squares refinement.

In the remainder of the molecule, the mirrored peaks are sufficiently resolved so that no difficulty exists either in recognizing the separate peaks for each in the Fourier maps, or in the refinement of their positions. Figure VI illustrates the disordered enantiomeric pair.

Using the idealized benzene ring and the remainder of the structure disordered as discussed above, least squares

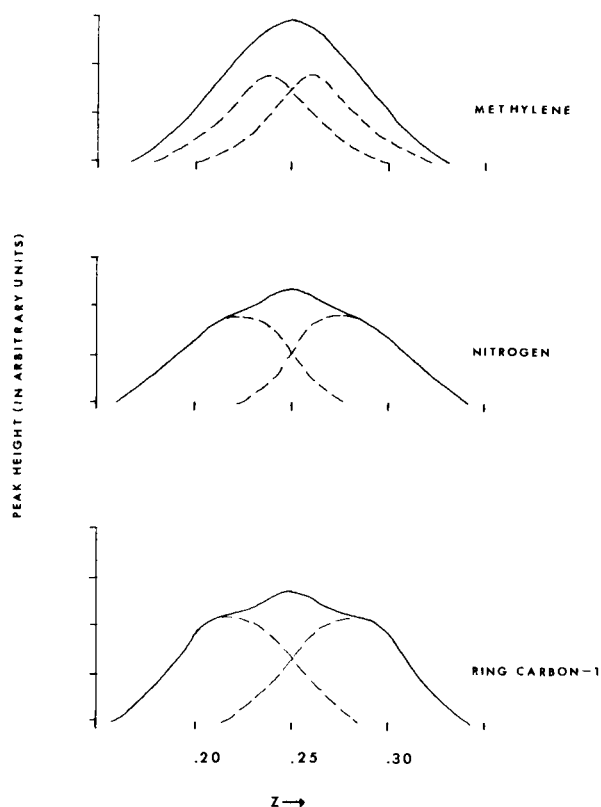


Figure V. Profiles of peaks very near mirror plane in Pnam. Dotted lines show best fit of Gaussian doublet within each peak.

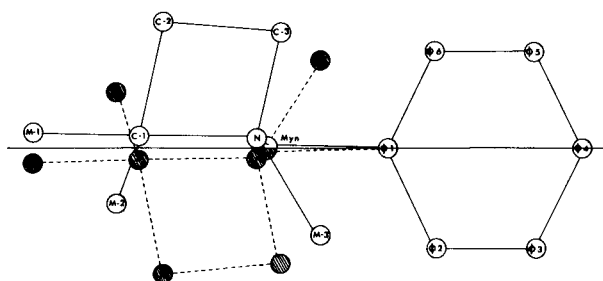


Figure VI. Disordered enantiomorph pairs about $Z = 1/4$ in space group Pnam.

results in space group Pnam led to final R_r values of 0.09₄, 0.11₀ and refinement was terminated.

DISCUSSION

All bond distances and bond angles in the organic moiety have E.S.D. less than or equal to 0.04 Å and 2.5°, respectively. Final values (in Pnam) for the coordinates and anisotropic temperature factors are given in Table I.

The actual distances and angles obtained are indicated on Figure VII which illustrates one of the disordered pair of molecules.

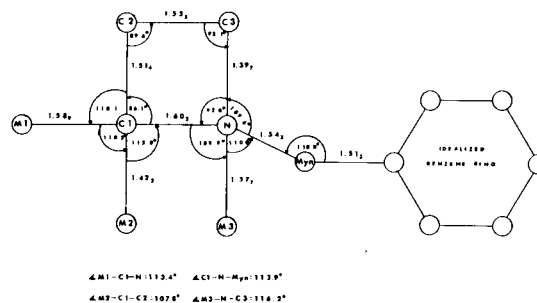


Figure VII. Bond distances and bond angles within the molecule.

The methyl carbon distances and angles conform to the expected values with the exception of the methyl carbon (M-2) which has a very short bond distance of 1.42₅ Å although the angles around it are quite reasonable. On the basis of difference Fourier maps the peak is at a position further along the line connecting the centers of M-2 and ring carbon one (C1) corresponding to a distance of 1.48 Å. The difficulty in the least squares refinement apparently stems from the limited amount of data.

It is of particular interest to compare our results for the azetidinium ring with those obtained in the penicillin studies where the four-membered ring is a β -lactam ring fused to a five-membered ring containing sulfur (see Figure VIII).

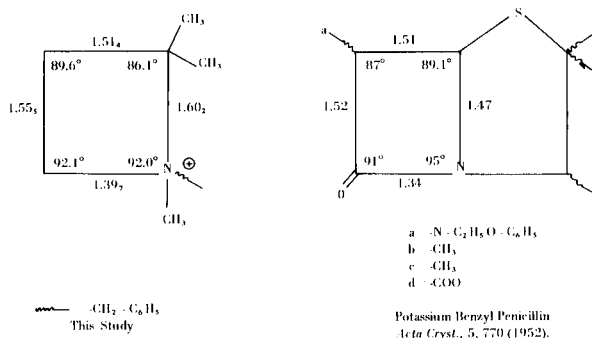


Figure VIII.

The overall correlation of bond distances and bond angles between the two four-membered rings suggests that the geometry of the four-membered ring is not modified as greatly in sodium benzylpenicillin (due to the carbonyl group and the fusion to the other ring) as had been

anticipated. The shortening of the nitrogen-carbonyl bond in penicillin is only from 1.397 to 1.34 Å. The effect of the fusion shortens the other C-N distance only to 1.47 Å. The close similarity in bond angles between the two studies is particularly surprising since it has been our experience in other studies that a ring fusion often changes the angles at the fusion points rather dramatically. To further clarify this point, we have undertaken the study of a compound (Figure IX) in which the azetidinium ring is fused only to a cyclopentane ring where the perturbation due to the β -carbonyl group, and the sulfur atom in the second ring, is not present.

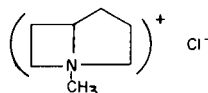


Figure IX.

A comparison of our results with those obtained in the determination of *l*-azetidine-2-carboxylic acid (7) indicate significant differences primarily in those parameters involving nitrogen and C1 (Figure X). A shortening of the

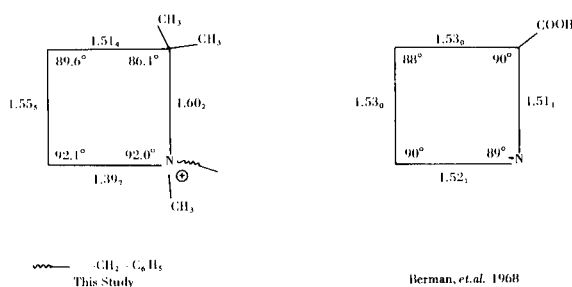


Figure X.

carbon-nitrogen distance in those cases where the nitrogen is a quaternary nitrogen has been previously commented upon in the literature (12) although the magnitude of this effect is insufficient to explain the large difference between the N-C distances (13). The additional studies (Reference 8, Figure IX) may help clarify this point.

The packing in the unit cell is shown in Figure XI (for clarity, only one of the disordered sets of molecules is shown).

Based on geometric considerations (C-H = 1.09 Å, \angle HCH = 109°, all other angles equally split and near 109°), positions were calculated for the hydrogen atoms attached to the azetidine ring. The resultant positions were then

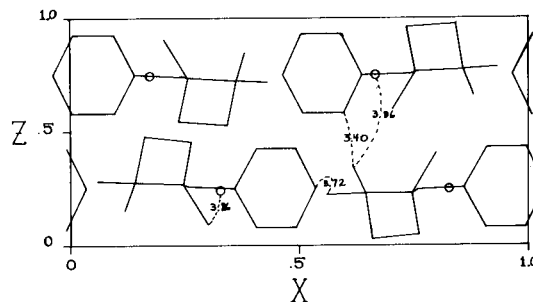


Figure XI. Unit cell contents projected down the b-axis. Only one of the disordered sets is shown. All close contacts less than 3.9 Å are indicated.

compared to the final difference Fourier map and all of the calculated peaks fell in positive regions ranging in height from 0.9-1.9 e/Å³. Figure XII illustrates the molecule with these calculated hydrogen positions shown. No close hydrogen interactions, either inter- or intra-molecular, are evident.

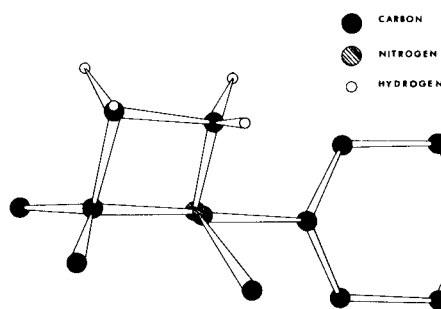


Figure XII. Perspective drawing of one molecule including calculated azetidinium hydrogen positions.

Acknowledgments.

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index and

$$r = \frac{\sum [w(F_o - kF_c)^2]^{1/2}}{\sum [wF_o^2]}$$

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