form (Selman, Wamser & Wilkalis, 1972). Smaller amounts of potassium ion are included.

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The Tricyclic Antidepressants: Iprindole. The Crystal and Molecular Structure of 5-[3-{Dimethylamino}propyl]-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indole Monohydrate

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Iprindole hydrochloride monohydrate is orthorhombic, space group *Pbca*, with $a = 10\cdot812$ (2), $b = 28\cdot585$ (7), $c = 12\cdot422$ (3) Å, $Z = 8$. The structure was solved by tangent formula refinement of diffractometer data collected with Cu radiation. Full-matrix least-squares refinement resulted in a final R of $0\cdot084$ for 2339 reflexions. The indole system is planar. Centrosymmetrically related molecules are linked by a system of hydrogen bonds.

Introduction

Of the classes of psychotropic drugs now in clinical use for the treatment of depressive illness the most widely prescribed are the tricyclic antidepressants such as imipramine, desipramine and amitriptyline. There is considerable evidence that a functional abnormality of one of the brain's biogenic amine (noradrenaline or 5-hydroxytryptamine) systems may be involved in the aetiology of these disorders (Schildkraut & Kety, 1967; Ashcroft *et al.*, 1972). The most significant biochemical effect of the tricyclics is their ability to inhibit the amine recapture or uptake process that trans-

ports the amine back into the presynaptic nerve ending (Shaskan & Snyder, 1970; Horn, Coyle & Snyder, 1971; Iversen 1973). This process is largely responsible for the termination of the synaptic action of the biogenic amines. It has been hypothesized that this inhibition of the uptake process may be responsible for the tricyclic's ameliorative action in the depressive states (Schildkraut & Kety, 1967). It is therefore of interest to investigate what molecular or conformational features the tricyclics have that enable them to act as inhibitors of this uptake process. Valuable information can also be obtained by comparing the structures of tricyclics that, although active clinically, have differing biochemical actions. An excellent example of this is iprindole (1), which, although in clinical use as an antidepressant (El Diery, Forrest & Litt-

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man, 1967), is only a very weak inhibitor of noradren-aline and 5-hydroxytryptamine uptake (Ross, Renyi & Ogren, 1972; Gluckman & Baum, 1969; Lemberger, Sernatinger & Kuntzman, 1970). Iprindole, however, is structurally an atypical 'tricyclic' antidepressant in that one of the rings is not aromatic but consists of a six-membered carbon chain fused to an indole system. Also there are no bridging atoms in the top portion of the molecule between the two outer rings. Although the three-ring system of iprindole is not flat, which is apparently a requirement for activity (Maxwell, Keenan Chaplin, Roth & Eckhardt, 1969; Horn, Coyle & Snyder, 1971), the above two molecular changes may account for its lack of activity as an inhibitor of bio-genic amine uptake.

(I)
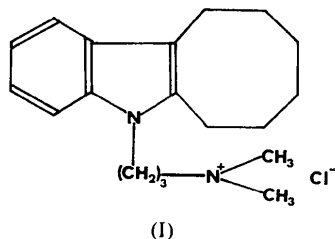
Crystal data

Iprindole hydrochloride monohydrate:
$C_{19}H_{29}N_2^+Cl^-.H_2O$, F.W. 338. Colourless, tabular, elongated **a**, twinning frequent. Orthorhombic. $a=10\cdot812(2), b=28\cdot585(7), c=12\cdot422(3)$ Å, $V=3838\cdot9(7)$ Å^3, $D_x=1\cdot169$ g cm^{-3}, $Z=8$, $\mu=17\cdot03$ cm^{-1} for Cu $K\alpha$ $(\lambda=1\cdot54178$ Å), $F(000)=1472$. Space group $Pbca$ from absences.
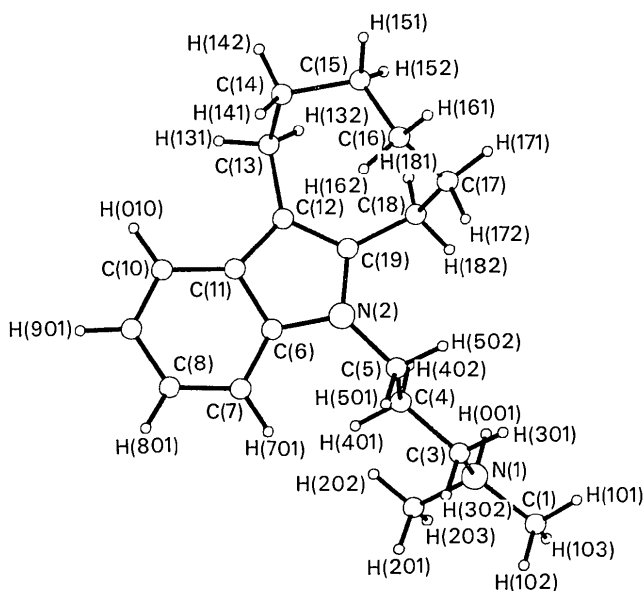

Fig. 1. Conformation of iprindole in the crystal.

Experimental

Most crystals were twinned but a single crystal could be obtained by cleaving along the twin plane. Accurate cell constants were obtained by least-squares refinement of 2θ values for 21 reflexions measured on a Picker four-circle diffractometer, equipped with a graphite monochromator. Intensities were collected from a crystal with dimensions $0\cdot1 \times 0\cdot2 \times 0\cdot2$ mm with the diffractometer operated in the $\theta-2\theta$ scan mode at a speed of 2° (2θ)min^{-1}, scan range $(2\cdot0+0\cdot2601 \tan \theta)^\circ$ and background counts of 20 s. Of 2786 independent reflexions measured, 447 had $I<3\sigma(I)$ and were classified as unobserved. The standard deviations were calculated from the counting statistics with due allowance for instrumental instability as indicated by the fluctuations in the intensity of monitor reflexions. Lorentz and polarization corrections were applied and normalized structure factors derived. No corrections were made for absorption.

Structure determination

The structure was solved by direct methods applied to 483 reflexions with $|E| \geq 1\cdot4$. All programs used were written by Dr G. M. Sheldrick (1973, private communication).

Four symbolic phases were chosen by the program from a list of 17 possible reflexions by a process of pseduo tangent refinement (Germain, Main & Woolfson, 1970). The 16 possible phase sets were refined for eight cycles each, and four sets yielded R_α values (Roberts, Pettersen, Sheldrick, Isaacs & Kennard, 1973) substantially less than 0·30. An E map calculated from the lowest of these $(R_\alpha=0\cdot22)$ indicated the position of the chlorine, two nitrogens and 19 carbon atoms.

Two cycles of full-matrix least-squares refinement with isotropic temperature factors gave $R=0\cdot29$. The function minimized was $\sum_w |F_o - KF_c|^2$ with weights given by:

$$w=\sigma(F_o)\{2F_{min}+F_o+2F_o^2/F_{max}\}^{-1};$$

scattering factors were taken from Cromer & Mann (1968).

The resultant difference map contained an isolated peak of height 6 e Å^{-3}, which was assumed to be the oxygen atom of a water molecule and confirmed by subsequent refinement. Three further cycles with anisotropic temperature factors reduced R to 0·11. At this stage the positions of the hydrogen atoms were calculated and checked against a difference map. The map confirmed the calculated positions and in addition gave the location of one hydrogen atom of the water molecule. The refinement was continued with the hydrogen atoms placed at the calculated positions and treated as rigid groups bonded to a heavy atom at a distance of 1·0 Å. The variables were thus reduced to positional and anisotropic thermal parameters for the

heavy atoms, a single overall parameter for the hydrogen atoms and a scale factor, and positional variables for one of the hydrogen atoms of the water molecule. After two cycles the values of R and R_w* were 0·084

$$* \ R_w = \{\sum w|F_o - F_c|^2/\sum wF\}^{1/2}.$$

and 0·095 for the 2339 observed reflexions.* Final positional and thermal parameters are listed in Tables 1–3. The overall isotropic temperature factor for the hydrogen atoms was 0·048 Å².

Table 1. *Final fractional coordinates for non-hydrogen atoms* ($\times 10^4$)

	x/a	y/b	z/c
Cl(1)	−17 (1)	860	4827 (1)
N(1)	2652 (3)	4544 (1)	6331 (2)
N(2)	4216 (2)	3461 (1)	9121 (2)
O(1)	1277 (4)	−35 (1)	3867 (3)
C(1)	1556 (4)	4650 (1)	5642 (3)
C(2)	3170 (4)	4979 (1)	6807 (3)
C(3)	2329 (3)	4185 (1)	7155 (3)
C(4)	3418 (3)	4047 (1)	7841 (3)
C(5)	3135 (3)	3606 (1)	8503 (3)
C(6)	4535 (3)	3642 (1)	10121 (3)
C(7)	3860 (4)	3925 (1)	10808 (3)
C(8)	4412 (5)	4046 (1)	1770 (4)
C(9)	5591 (5)	3894 (1)	12029 (4)
C(10)	6262 (4)	3613 (1)	11354 (3)
C(11)	5727 (3)	3476 (1)	10361 (3)
C(12)	6132 (3)	3194 (1)	9489 (3)
C(13)	7299 (3)	2915 (1)	9410 (3)
C(14)	7177 (4)	2400 (1)	9734 (4)
C(15)	6509 (5)	2091 (2)	8882 (4)
C(16)	5124 (4)	2154 (1)	8810 (4)
C(17)	4606 (4)	2427 (1)	7887 (3)
C(18)	5143 (3)	2918 (1)	7727 (3)
C(19)	5190 (3)	3193 (1)	8741 (3)

Table 3. *Anisotropic temperature factors* ($Å^2 \times 10^3$)

Coefficients in the temperature factor expression:

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)].$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl(1)	97 (1)	71 (1)	76 (1)	−5 (1)	−20 (1)	−23 (1)
N(1)	50 (2)	41 (2)	54 (2)	1 (1)	−2 (1)	5 (1)
N(2)	40 (2)	43 (2)	46 (2)	4 (1)	−1 (1)	5 (1)
O(1)	99 (3)	120 (3)	88 (3)	12 (2)	28 (2)	10 (2)
C(1)	73 (3)	65 (3)	78 (3)	10 (2)	−21 (2)	6 (2)
C(2)	68 (2)	46 (2)	62 (2)	1 (2)	6 (2)	−4 (2)
C(3)	53 (2)	42 (2)	59 (2)	2 (2)	−4 (2)	−2 (2)
C(4)	51 (2)	53 (2)	58 (2)	7 (2)	−8 (2)	−3 (2)
C(5)	48 (2)	47 (2)	59 (2)	6 (2)	−3 (2)	1 (2)
C(6)	59 (2)	35 (2)	52 (2)	4 (1)	1 (2)	0 (2)
C(7)	83 (3)	47 (2)	67 (2)	−7 (2)	6 (2)	10 (2)
C(8)	117 (4)	64 (3)	62 (3)	−13 (2)	0 (3)	15 (3)
C(9)	124 (4)	59 (3)	62 (3)	−16 (2)	−17 (3)	5 (3)
C(10)	83 (3)	54 (2)	67 (3)	1 (2)	−21 (2)	2 (2)
C(11)	63 (2)	38 (2)	46 (2)	6 (1)	−9 (2)	−6 (2)
C(12)	47 (2)	44 (2)	49 (2)	8 (1)	−2 (2)	0 (1)
C(13)	44 (2)	62 (2)	65 (2)	2 (2)	−9 (2)	2 (2)
C(14)	61 (2)	63 (3)	83 (3)	5 (2)	−18 (2)	10 (2)
C(15)	83 (3)	64 (3)	110 (4)	3 (3)	10 (3)	10 (2)
C(16)	85 (3)	56 (2)	98 (4)	3 (2)	−13 (3)	−10 (2)
C(17)	51 (2)	62 (2)	68 (3)	−20 (2)	−10 (2)	3 (2)
C(18)	55 (2)	66 (2)	46 (2)	−2 (2)	−4 (2)	9 (2)
C(19)	46 (2)	45 (2)	45 (2)	8 (2)	0 (2)	1 (1)

Table 2. *Final positional coordinates for hydrogen atoms* ($\times 10^4$)

	x/a	y/b	z/c
H(001)	3330 (3)	4405 (1)	5888 (2)
H(101)	1270 (4)	4357 (1)	5283 (3)
H(102)	878 (4)	4777 (1)	6106 (3)
H(103)	1779 (4)	4887 (1)	5083 (3)
H(201)	2537 (4)	5125 (1)	7287 (3)
H(202)	3933 (4)	4908 (1)	7232 (3)
H(203)	3379 (4)	5200 (1)	6210 (3)
H(301)	1995 (3)	3901 (1)	6785 (3)
H(302)	1677 (3)	4321 (1)	7632 (3)
H(401)	3631 (3)	4310 (1)	8339 (3)
H(402)	4141 (3)	3979 (1)	7363 (3)
H(501)	2442 (3)	3677 (1)	9011 (3)
H(502)	2883 (3)	3346 (1)	8011 (3)
H(701)	3022 (4)	4045 (1)	10608 (3)
H(801)	3930 (5)	4232 (1)	12306 (4)
H(901)	5976 (5)	4004 (1)	12716 (4)
H(010)	7107 (4)	3502 (1)	11558 (3)
H(131)	7914 (3)	3061 (1)	9909 (3)
H(132)	7616 (3)	2932 (1)	8655 (3)
H(141)	6700 (4)	2382 (1)	10421 (4)
H(142)	8027 (4)	2270 (1)	9850 (4)
H(151)	6688 (5)	1757 (2)	9058 (4)
H(152)	6864 (5)	2169 (2)	8161 (4)
H(161)	4760 (4)	1833 (1)	8776 (4)
H(162)	4845 (4)	2313 (1)	9485 (4)
H(171)	4763 (4)	2243 (1)	7217 (3)
H(172)	3694 (4)	2460 (1)	8000 (3)
H(181)	6003 (3)	2889 (1)	7437 (3)
H(182)	4615 (3)	3089 (1)	7196 (3)
H(OW1)	1024 (47)	217 (17)	4120 (41)

Discussion

The molecular conformation and numbering scheme used are shown in Fig. 1. The bond lengths, bond angles and standard deviations are listed in Table 4 and Table 5.

Table 4. *Bond lengths* (Å) *with e.s.d.'s in parentheses*

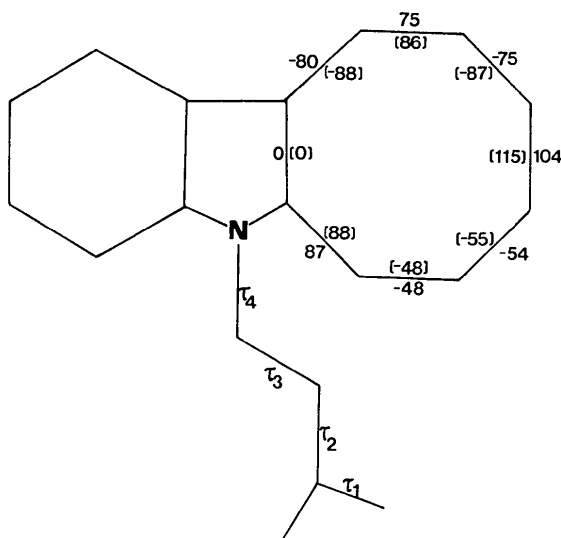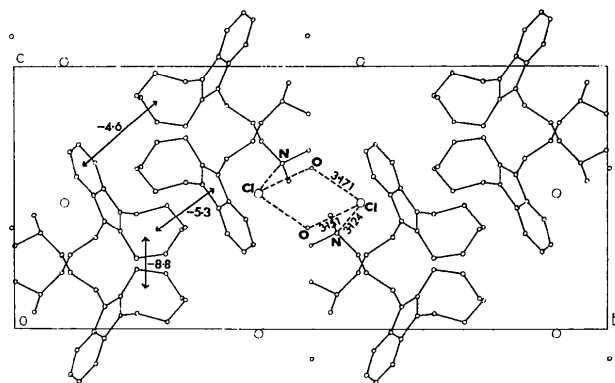| N(2)-C(5)	1·458 (4)	C(8)—C(9)	1·385 (7)
N(2)-C(6)	1·389 (4)	C(9)—C(10)	1·379 (6)
N(2)-C(19)	1·386 (4)	C(10)-C(11)	1·418 (5)
O(1)-H(OW1)	0·833 (49)	C(11)-C(12)	1·418 (5)
C(1)-N(1)	1·493 (5)	C(12)-C(13)	1·496 (5)
C(2)-N(1)	1·487 (4)	C(12)-C(19)	1·379 (4)
C(3)-C(4)	1·505 (5)	C(13)-C(14)	1·531 (5)
C(3)-N(1)	1·491 (4)	C(14)-C(15)	1·557 (6)
C(4)-C(5)	1·536 (5)	C(15)-C(16)	1·510 (7)
C(6)-C(7)	1·386 (5)	C(16)-C(17)	1·497 (6)
C(6)-C(11)	1·405 (5)	C(17)-C(18)	1·531 (5)
C(7)-C(8)	1·379 (6)	C(18)-C(19)	1·485 (5)

The indole system is planar with an r.m.s. deviation of 0·0042 Å from the mean plane (Table 6); the mean C–C and C–N distances are 1·392(2) and 1·387(1) Å,

Table 5. *Valency angles* (°) *with e.s.d.'s in parentheses*

C(6)—N(2)—C(5)	124·3 (3)		C(13)—C(12)—C(11)	127·8 (3)
C(19)—N(2)—C(5)	126·0 (3)		C(19)—C(12)—C(11)	106·7 (3)
C(19)—N(2)—C(6)	108·7 (3)		C(19)—C(12)—C(13)	125·3 (3)
N(1)—C(3)—C(4)	112·6 (3)		C(14)—C(13)—C(12)	115·0 (3)
C(5)—C(4)—C(3)	111·2 (3)		C(15)—C(14)—C(13)	114·0 (3)
C(4)—C(5)—N(2)	110·8 (3)		C(16)—C(15)—C(14)	115·7 (4)
C(7)—C(6)—N(2)	129·6 (3)		C(17)—C(16)—C(15)	118·6 (4)
C(11)—C(6)—N(2)	107·0 (3)		C(18)—C(17)—C(16)	115·8 (3)
C(11)—C(6)—C(7)	123·4 (3)		C(19)—C(18)—C(17)	112·8 (3)
C(8)—C(7)—C(6)	116·9 (4)		C(12)—C(19)—N(2)	109·3 (3)
C(9)—C(8)—C(7)	121·4 (4)		C(18)—C(19)—N(2)	123·7 (3)
C(10)-C(9)—C(8)	121·9 (4)		C(18)—C(19)—C(12)	126·7 (3)
C(11)—C(10)—C(9)	118·6 (4)		C(2)—N(1)—C(1)	110·8 (3)
C(10)-C(11)—C(6)	117·8 (3)		C(3)—N(1)—C(1)	110·4 (3)
C(12)-C(11)—C(6)	108·2 (3)		C(3)—N(1)—C(2)	113·1 (3)
C(12)-C(11)-C(10)	134·0 (4)			

respectively, in good agreement with accepted values. The valency angles are also normal except for the angles at C(19) and C(12) which are respectively 2·6σ larger and smaller than average. The average C(sp^3)–C(sp^2) distance, *i.e.* C(13)–C(12), C(18)–C(19), is 1·491 (1) Å.

Table 6. *Equation of the mean plane through the indole system*

$$4·2501x + 23·1083y - 5·4419z = 4·8277$$

	Deviations from the mean plane (Å)
C(6)	0·0076
C(7)	0·0020
C(8)	−0·0074
C(9)	0·0002
C(10)	0·0046
C(11)	−0·0007
C(12)	−0·0044
C(19)	−0·0003
N(2)	−0·0016

R.m.s. deviation
from plane = 0·0042 Å

Fig. 2. Torsion angles for the cyclooctene system. Experimental results for ipiindole with results of Trefonas & Majeste (1963) for *cis*-9,9-dimethyl-9-azoniabicyclo[6,1,0]nonane ion in parentheses.

There are only a few examples of a cyclooctene system in the crystallographic literature. Dunitz & Ibers (1969) discuss the probable conformation of *cis*-cyclooctene. The conformation found in the present structure is very similar to the most favourable chiral conformation predicted, although the values of the individual torsion angles (Fig. 2) do not compare well with those calculated for the model. Instead, they agree more closely with the torsion angles reported for the *cis*-9,9-dimethyl-9-azoniabicyclo[6,1,0]nonane ion (Trefonas & Majeste, 1963).

The most interesting aspect of the present investigation is the conformation of the side chain since this may well be relevant to the mode of action of this class of psychotropic drugs.

In the crystal structure the side chain is found to be fully extended (Fig.1). To check whether this corresponded to a minimum conformation we calculated potential energy maps varying the four torsion angles, τ_1–τ_4, along the chain (Fig. 2). For all these calculations empirical atom–atom potentials by Giglio (1969) were used. There was close agreement as indicated in Table 7 between the experimental values of the torsion angles found in the crystal studies and the optimized theoretical values for the free molecule. This agreement suggests that the chlorine ion does not influence the conformation of the side chain. It may, however, play a role in the particular energy conformation found in the crystal since our energy calculations indicated the existence of several other minima, including a conformation where the side chain was coiled back towards the cyclooctene ring system. In this orientation, however, the proton attached to the nitrogen points towards the ring system and is thus not available for hydrogen bonding. These calculations will be reported in detail later when the crystal structures of several other tricyclic antidepressants are completed.

Fig. 3. A view along a showing the packing of the molecule. The hydrogen-bonding system is indicated by broken lines (distances in Å). The bold lines indicate the strongest inteiactions in kcal mole^{-1}.

Table 7. *Torsion angles*

	τ_1	τ_2	τ_3	τ_4	E(kcalmole^{-1})
Experimental	$-57\cdot82$	$-167\cdot51$	$176\cdot92$	$-83\cdot24$	$7\cdot77$
Theoretical	$-64\cdot38$	$-166\cdot98$	$181\cdot49$	$-82\cdot01$	$7\cdot43$

Hydrogen bonding and crystal packing

A system of hydrogen bonds, involving the chlorine ion and the water oxygen atom, links the molecules in the crystal structure. Each chlorine ion is coordinated by three hydrogen atoms, two from water molecules and one from the protonated nitrogen as illustrated in Fig. 3. Two of these hydrogen atoms were located from difference maps and included in the refinement. The hydrogen-bonded distances are N–H$\cdots$Cl$^-$ = $3\cdot124$, O–H$\cdots$Cl$^-$ = $3\cdot151$, O–H$'\cdots$Cl$^-$ = $3\cdot171$ Å and the angles N–H$\cdots$Cl$^-$ = $170\cdot1°$, O–H$\cdots$Cl$^-$ = $170\cdot1°$. The system of hydrogen bonds links centrosymmetrically related molecules into columns about the a axis with the side chains interpenetrating between the columns.

Interactions between pairs of molecules were calculated by techniques developed by Motherwell & Isaacs (1972). The strongest interaction of $-8\cdot79$ kcal mole^{-1} is between molecules related by the a glide in Fig. 3.

We thank Dr W.D.S. Motherwell for his interest in the packing problems involved in this work, Dr G.M. Sheldrick for his direct-methods programs, the University of Cambridge Computer Laboratory for computing facilities and the S.R.C. for the provision of the diffractometer.

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The Crystal Structure of 2,2,4,4-Tetramethyl-3-thio-1,3-cyclobutanedione

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The crystal structure of 2,2,4,4-tetramethyl-3-thio-1,3-cyclobutanedione ($C_8H_{12}OS$) has been determined from three-dimensional X-ray diffraction data. The crystals are orthorhombic, space group *Pnma*, $Z = 4$, with cell dimensions $a = 13\cdot545$ (2), $b = 10\cdot055$ (1), and $c = 6\cdot934$ (3) Å. Data were collected manually on a diffractometer using zirconium-filtered Mo $K\alpha$ radiation. 949 independent reflections were observed. The structure was solved by reiterative applications of Sayre's equation and refined by full-matrix least-squares calculation to yield a final R value of $0\cdot071$. The results indicate a slightly disordered structure with a planar cyclobutane ring.

Introduction

The simple derivatives of cyclobutane have been studied extensively in the solid state (Table 3, Shirrell & Williams, 1973*a*). These compounds can exist in either planar or puckered conformations. Although the origin of these conformational differences among cyclobutanes is not very well understood, Bohn & Tai (1970)