Acta Cryst. (1965). **18**, 1039

The Structure of Mitragynine Hydroiodide

By David E. Zacharias, R. D. Rosenstein and G. A. Jeffrey

The Crystallography Laboratory, The University of Pittsburgh, Pittsburgh, Pa. 15213, *U.S.A.*

(*Received* 25 *September* 1964)

Mitragynine, $C_{23}H_{30}N_2O_4$, is an alkaloid containing the indolo[2, 3-*a*] quinolizine ring system substituted with methoxyl, ethyl and methyl β-methoxyacrylyl groups. The structure was unknown at the beginning of this investigation, but was subsequently reported from a chemical study. This X-ray analysis confirms the conclusions of the chemical work and also shows that the methoxycarbonyl and methoxyl groups have a *trans* configuration about the double bond in the acrylyl moiety.

The X-ray analysis was carried out on crystals of the hydroiodide which are orthorhombic with $a = 11{\cdot}51$, $b = 7{\cdot}87$, $c = 26{\cdot}69$ Å, $P2_12_12_1$. The heavy-atom method was used with three-dimensional Fourier syntheses and structure factors computed first on an IBM 1620 and subsequently on an IBM 7070 computer. Two successive refinements with progressive addition of the light atoms gave the complete structure. Subsequent refinement with isotropic temperature factors on all atoms gave an *R* index of 0·12.

Introduction

Mitragynine (Fig. 1, I*a*) is one of two alkaloids reported to occur in the leaves of the tree *Mitragyna speciosa* Korth. (Rubiaceae) which grows in Southeast Asia, the Philippines and New Guinea (Ing & Raison, 1939) and was first isolated about forty years ago (Field, 1921). It is closely related to corynantheidine (I*b*) and dihydrocorynanthine (II), both of which have been isolated from other *Mitragyna* species.

Mitragynine has the molecular composition $C_{23}H_{30}N_2O_4$ and is an indole alkaloid. The indole portion is substituted with a methoxyl group and is fused to a quinolizine ring system which is substituted on adjacent carbon atoms with ethyl and methyl β-methoxyacrylyl groups. Our X-ray crystal structure analysis has confirmed the conclusions drawn by Joshi, Raymond-Hamet & Taylor (1963) regarding the stereochemistry of the ring junction in the quinolizine ring system and its substituent groups. Further, our study discloses a *trans* relationship between the methoxycarbonyl and methoxy portions of the methyl β-methoxyacrylyl substituent of the quinolizine ring system.

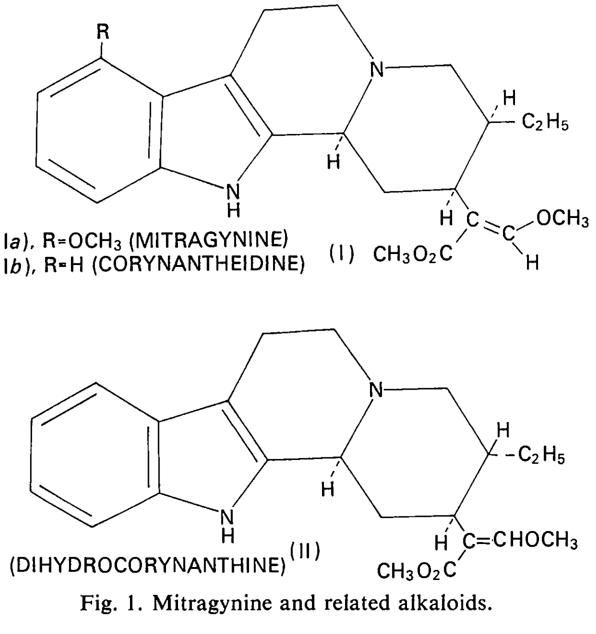


Fig. 1. Mitragynine and related alkaloids.

Crystal data

The crystal data for mitragynine hydrobromide and mitragynine hydroiodide are given in Table 1. All cell dimensions are ±0·05 Å. The hydroiodide salt was selected for analysis after two-dimensional Patterson projections of the hydrobromide along the **a** and **b** directions gave ambiguous results which did not permit location of the heavy atom. The densities were determined by flotation at 26·7 °C.

Intensity data

Three-dimensional data were obtained by visual estimation of multiple-film Weissenberg equi-inclination photographs from nickel-filtered Cu *K* radiation. Six photographs exposed in two groups of three were obtained for seven layers about the *a* axis and five about *b*. The longer exposures in both directions were for twenty hours and the shorter exposures for the *a* and *b* axes were five and three hours, respectively. The structure amplitudes of 1967 independent reflections were evaluated.

The crystal data for the hydrobromide salt were obtained from zero-layer photographs about the *a* and *b* axes.

Table 1. *The crystal data from mitragynine hydrobromide and hydroiodide*

Compound		*a*	*b*	*c*	*U*	*Z*	D_m	D_x
$C_{23}H_{31}BrN_2O_4$	$P2_12_12_1$	11·41 Å	7·48 Å	27·42 Å	2339 Å^3	4	1·368 g.cm^{-3}	1·360 g.cm^{-3}
$C_{23}H_{31}IN_2O_4$	$P2_12_12_1$	11·51	7·87	26·69	2418	4	1·441	1·445

The structure determination

The positional parameters for the iodine atom ($x=0{\cdot}045$, $y=0{\cdot}048$, $z=0{\cdot}040$) were derived from Harker sections of the form $\varrho(\frac{1}{2}, y, z)$, $\varrho(x, \frac{1}{2}, z)$ and $\varrho(x, y, \frac{1}{2})$ and used in the first structure-amplitudes calculation and the related three-dimensional Fourier map. The initial agreement index was $R=0{\cdot}35$. Of the thirty-eight areas of higher electron density which now appeared, eighteen of the highest were selected for use as light-atom positions. One of these subsequently proved to be incorrect. An average isotropic temperature factor $B=2{\cdot}6$ Å^{-2} was derived from a Wilson plot, and carbon scattering factors were assigned to the light atoms. This information was used in a second cycle of calculation which gave an R index of 0·29. Of the eighteen light atom peaks previously selected, seventeen increased in height or remained unchanged on the second three-dimensional Fourier map. The remaining one decreased substantially and was rejected. Fourteen of the higher peaks which appeared on the first Fourier map but which were not used in the second calculation also increased in height. It was decided at this point to try to assign positions to the twelve remaining light atoms

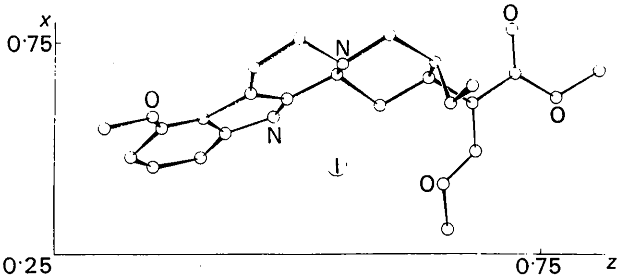


Fig. 2. Configuration of the mitragynine molecule in the hydroiodide as obtained from the three-dimensional Fourier synthesis.

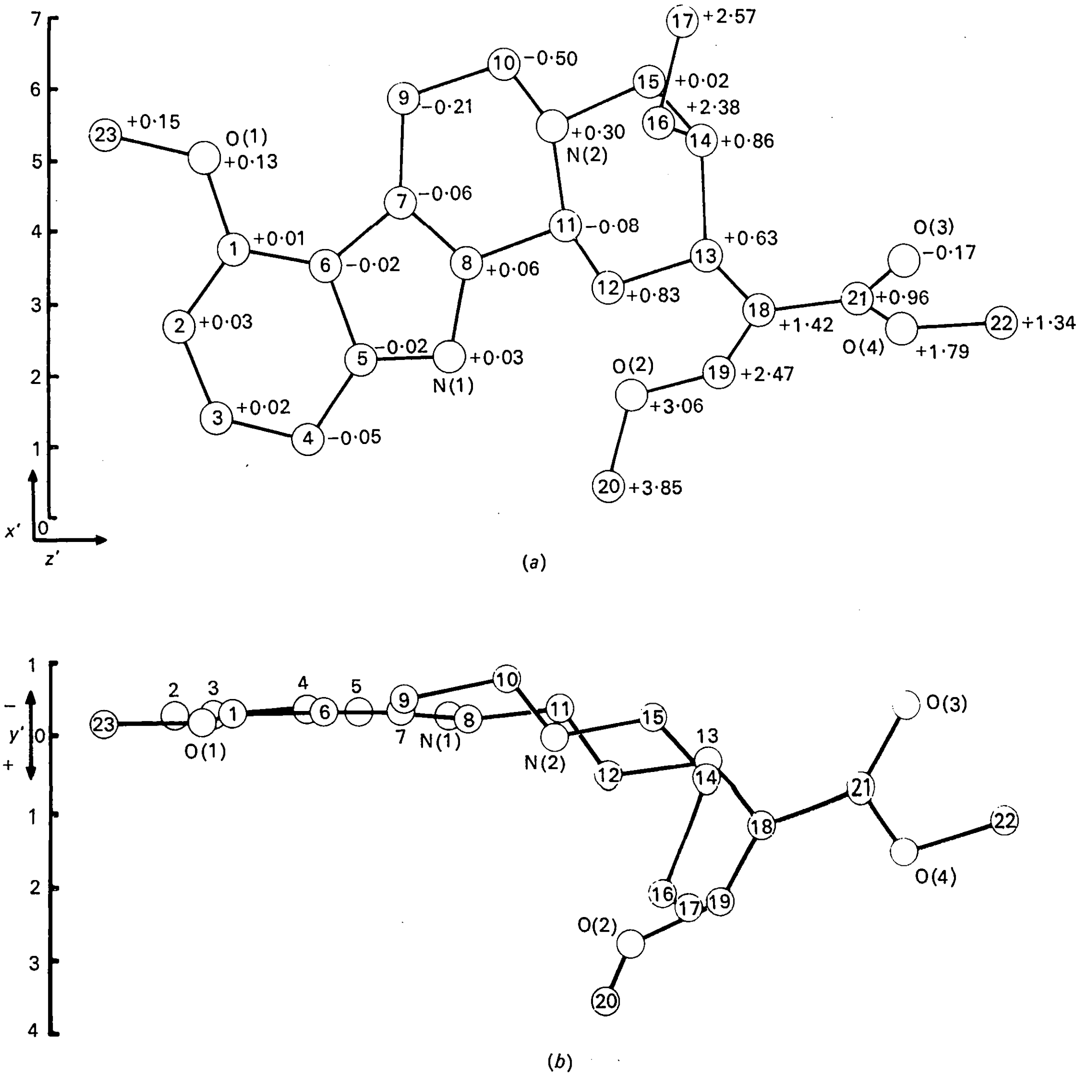


Fig. 3. Configuration of the mitragynine molecule viewed normal and parallel to the plane of the indole ring.

for use in the next structure factor calculation. An arbitrary lower limit of significant electron density relative to the heavy atom was selected and the position parameters of all peaks above this limit including the fourteen previously unused ones were used as input for an intramolecular atomic distance calculation with the IBM 1620 program of Chu (1963*a*). Fifty peaks were evaluated in this manner with rejection of all distances greater than 2·5 Å by the program. The distances of those peaks lying in the range 0·8 to 1·8 Å were considered significant, and on this basis position parameters for the remaining light atoms were selected.

Previous chemical work with mitragynine had indicated the presence of the β-carboline ring system (Saxton, 1960). The appearance at this time of the chemical structure elucidation (Joshi, Raymond-Hamet & Taylor, 1963) gave further encouragement to the construction of a three-dimensional model using the atomic positions selected above. The entire ring system was fairly well defined in the model and although the ethyl and methyl β-methoxyacrylyl groups were indistinguishable, a tentative differentiation among the light atoms was made and these assignments subsequently proved to be correct. The corresponding scattering factors along with the revised isotropic temperature factors of $B=3{\cdot}0$ Å^{-2} for the light atoms and $B=4{\cdot}0$ Å^{-2} for the iodine atom were used in the third set of structure amplitudes calculations. The resulting agreement index was $R=0{\cdot}175$. The ensuing Fourier map was drawn on transparent plastic sheets. The peaks were well resolved and spherical and the structural details of the molecule stood out clearly. The configuration of the molecule as derived from the third three-dimensional Fourier synthesis is shown in Fig. 2. Since the absolute configuration was not directly determined, the handedness in Figs. 2 and 3 has been chosen to be consistent with (I*a*) in Fig. 1, as postulated by Joshi, Raymond-Hamet & Taylor (1963).

Three-dimensional refinement

The structure refinement was accomplished with five cycles of isotropic structure-factor calculation and differential Fourier synthesis with the use of the IBM 7070 programs of Shiono (1962, 1963). In the initial cycle, all coordinate shifts were less than 0·5 Å, most of these being less than 0·1 Å. In the third through fifth cycles, no shift greater than 0·02 Å occurred while the agreement index decreased from $R=0{\cdot}153$ to the final value of $R=0{\cdot}124$.* The final temperature factors were $B=4{\cdot}5$ Å^{-2} for the light atoms and $B=5{\cdot}0$ Å^{-2} for the iodine. Table 2 lists the final fractional atomic coordinates and their average standard deviations.

Discussion of the structure

The general stereochemistry of the molecule is shown in Fig. 3, in which the atomic positions are plotted both (*a*) perpendicular and (*b*) parallel to the plane. The equation of this plane, referred to the crystallographic axes is

$$0{\cdot}390x-0{\cdot}159y-0{\cdot}131z=1\ .$$

It makes angles of 28°, 68·5° and 73° with (100), (010), and (001) respectively. The perpendicular distance to the plane from the crystallographic origin is 2·3 Å.

In the quinolizine ring system of the molecule, the ring fused to the indole portion has a half-chair form while the other ring is in a nearly normal chair configuration. With reference to Fig. 3(*b*), the methyl β-methoxyacrylyl group is attached equatorially to C(13) and the ethyl group axially to C(14). The angles of the bonds from C(11) at the junction of the two rings of the quinolizine system indicate that the hydrogen atom attached to C(11) is axially oriented. Thus, although the three hydrogen atoms attached to C(11), C(13), and C(14) were not directly located, they are inferred to lie on the same side of the general plane of

Table 2. *Final fractional atomic coordinates and their average standard deviations for one asymmetric molecule*

Atom	x	y	z	σ(Å)	Atom	x	y	z	σ(Å)
C(1)	0·546	0·152	0·360	0·017	C(16)	0·602	0·352	0·658	0·020
C(2)	0·489	0·046	0·328	0·017	C(17)	0·648	0·520	0·680	0·027
C(3)	0·457	−0·116	0·344	0·021	C(18)	0·607	−0·028	0·681	0·018
C(4)	0·482	−0·182	0·392	0·020	C(19)	0·494	−0·066	0·683	0·018
C(5)	0·537	−0·066	0·424	0·017	C(20)	0·311	−0·149	0·653	0·024
C(6)	0·572	0·098	0·409	0·017	C(21)	0·676	−0·060	0·723	0·019
C(7)	0·631	0·177	0·451	0·015	C(22)	0·690	−0·122	0·811	0·025
C(8)	0·617	0·066	0·488	0·018	C(23)	0·549	0·380	0·298	0·023
C(9)	0·693	0·337	0·453	0·021	N(1)	0·567	−0·083	0·474	0·016
C(10)	0·763	0·348	0·502	0·021	N(2)	0·698	0·275	0·546	0·015
C(11)	0·678	0·089	0·540	0·021	O(1)	0·573	0·315	0·350	0·016
C(12)	0·604	0·024	0·584	0·019	O(2)	0·415	−0·047	0·649	0·013
C(13)	0·666	0·036	0·634	0·017	O(3)	0·783	−0·069	0·721	0·014
C(14)	0·706	0·234	0·642	0·017	O(4)	0·623	−0·080	0·767	0·015
C(15)	0·771	0·303	0·594	0·020	I	0·456	−0·451	0·541	0·001

---

* The table of observed and calculated structure factors was submitted with the manuscript and has been deposited as document 8126 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A copy may be secured by citing the document number and remitting $ 5·00 for photoprints or $ 2·25 for 35 mm microfilm. Advance payment by check or moneyorder, payable to Chief, Photoduplication Service, Library of Congress, is required.

the molecule, in agreement with the formula (I*a*) proposed by Joshi, Raymond-Hamet & Taylor (1963), from the chemical and proton magnetic spectral data. The methoxy and methoxycarbonyl groups are attached *trans* to the C(18)–C(19) double bond.

The bond lengths and valence angles are shown in Fig. 4. With mean estimated standard deviations of 0·025 Å and 2° respectively, they do not differ significantly from accepted values. The mean C–C length in the indole system is 1·40 Å with a spread of ±0·05 Å. The average C–C length of the aliphatic bonds in the remainder of the molecule is 1·54 Å with a spread of ±0·10 Å. These bond lengths conform to those usually found in indole rings and saturated alicyclic hydrocarbon structures respectively. In the aromatic portion of the molecule, the average bond angle is 120° in the benzene ring and 108° in the pyrrole ring. The aliphatic carbon bond angle mean is 111°.

The position of the iodine ion is unusual in that it is closely associated with one molecule only. It is 3·64 Å from the indole nitrogen and 3·53 Å from the quinolizine nitrogen in the same molecule. The shorter $I^- \cdots {}^+N$ distance is in keeping with the expected greater basicity of the non-aromatic nitrogen. All other intermolecular iodine distances are greater than 4 Å. All intermolecular distances less than 4 Å are given in Table 3.

All stereochemical calculations referred to in this section were computed on the IBM 1620 with the programs of Chu (1963*b*).

References

Chu, S. C. (1963*a*). *Intramolecular and Intermolecular Distance Program for IBM* 1620 *Computer*. Tech. Rep. 43, Crystallography Laboratory, Univ. of Pittsburgh.

Table 3. *Intermolecular distances under* 4 Å.

I x, y, z	II $\frac{1}{2}-x, \bar{y}, \frac{1}{2}+z$	III $\frac{1}{2}+x, \frac{1}{2}-y, \bar{z}$	IV $\bar{x}, \frac{1}{2}+y, \frac{1}{2}-z$
C(1)I–C(15)III	3·41 Å	C(9) I–C(20)III	3·98 Å
–C(22)II	3·32	C(15)I–O(1)III	3·90
C(2)I–C(14)III	3·78	C(16)I–C(22)IV	3·47
–C(15)III	3·47	–O(4)IV	3·32
–C(17)III	3·97	C(17)I–O(4)IV	3·51
–C(22)II	3·77	C(20)I–C(22)IV	3·84
–C(23)IV	3·63	–C(23)III	3·91
–O(3)II	3·88	–O(1)III	3·80
C(3)I–C(15)III	3·66	C(22)I–C(23)II	3·64
–C(17)III	3·69	O(1)II	3·29
–C(23)IV	3·79	O(2)IV	3·71
–O(3)III	3·63	C(23)I–O(3)II	3·74
C(4)I–C(15)III	3·87	O(3)III	3·44
C(5)I–C(15)III	3·73		
C(6)I–C(15)III	3·55		
–C(22)II	3·79		

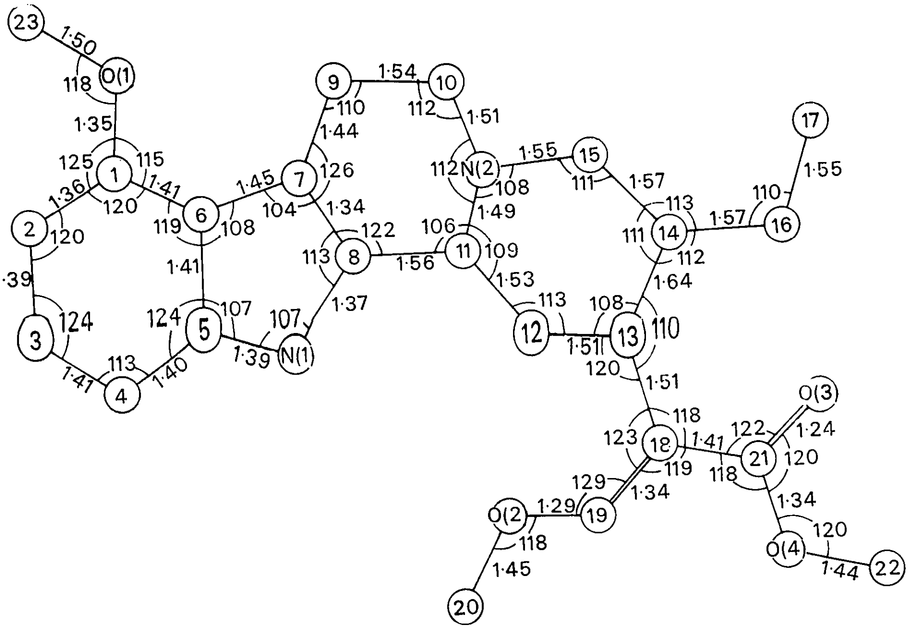


Fig. 4. Bond lengths and angles in the mitragynine molecule.

CHU, S. C. (1963*b*). *Interatomic Distance and Bond Angle Program; Least Squares Plane Program; A Program for Calculating Standard Deviation of Bond Lengths and Bond Angles, all for IBM* 1620 *Computer*. Tech. Rep. 45, Crystallography Laboratory, Univ. of Pittsburgh.
FIELD, E. (1921). *J. Chem. Soc.*, p. 887.
ING, H. R. & RAISON, C. G. (1939). *J. Chem. Soc.* p. 986.
JOSHI, B. S., RAYMOND-HAMET & TAYLOR, W. I. (1963). *Chem. and Ind.* p. 573.
SAXTON, J. E. (1960). *The Alkaloids*. Vol. VII, p. 162. New York: Academic Press.
SHIONO, R. (1962). *IBM* 7070 *Programs for Isotropic and Anisotropic Structure Factor Calculations*. Tech. Rep. 29, Univ. of Pittsburgh Computation and Data Processing Center.
SHIONO, R. (1963). *Three Dimensional Differential Fourier Synthesis Program for IBM* 7070 *Computer*. Tech. Rep. 42, Univ. of Pittsburgh Computation and Data Processing Center.

Acta Cryst. (1965). **18**, 1043

The Structure of the Methylene Dibromide Adduct of Sporidesmin at —150°C

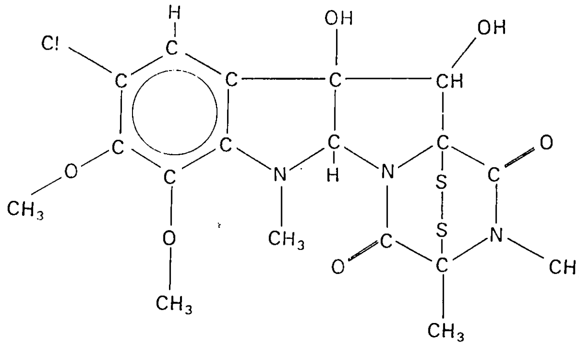
BY J. FRIDRICHSONS AND A. MCL. MATHIESON

Division of Chemical Physics, Chemical Research Laboratories, Commonwealth Scientific and Industrial Research Organization, Melbourne, Australia

(*Received* 21 *September* 1964)

The structure of sporidesmin, the causative agent of facial eczema in sheep, isolated by Synge & White from cultures of the fungus *Pithomyces chartarum* (previously *Sporidesmium bakerii* Syd.) has been determined from its CH_2Br_2 adduct.

The compound crystallizes in the orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 9{\cdot}681$, $b = 10{\cdot}629$, $c = 23{\cdot}358$ Å at − 150 °C. Data were collected for 0–7 layers about *a* and the 0-layer about *b*. The positions of the Br atoms (occupied only 0·65) and also the S atoms were determined from normal and generalized Patterson projections and Harker sections. Two three-dimensional electron-density distributions with two-dimensional ϱ_0 and $\Delta\varrho$ distributions led to the structure (I), corresponding to the formula $C_{18}H_{20}O_6N_3S_2Cl\,.\,0{\cdot}65\ CH_2Br_2$.



(I)

The structure was refined by several cycles of full-matrix least-squares calculations, the final *R* being 0·144.

Introduction

The serious disease in sheep, known as 'facial eczema', which causes extensive liver damage and ultimate death is widely spread in New Zealand and outbreaks have occurred also in Australia (Janes, 1959). Extensive research (Thornton & Percival, 1958, 1959) has established the disease as due to the ingestion of spores of the fungus *Pithomyces chartarum* (previously known as *Sporidesmium bakeri* Syd.), found frequently on pasture grass in the tropics and subtropics (Ellis, 1960), but detected also in Britain in one case (Lacey & Gregory, (1962).

Synge & White (1959) were able to isolate from cultures of this fungus the main metabolic toxic agent which they named sporidesmin and which could be obtained in crystalline form as a CCl_4 adduct, the chemical analysis of which indicated the composition $C_{19}H_{21}O_6N_3S_2Cl\,.\,CCl_4$. Preliminary cell parameter measurements, carried out by Mrs M. M. Harding,