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STRUCTURE AND REACTIVITY OF ILLUDINS

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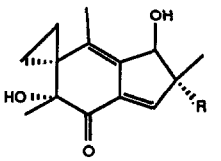
Abstract – An X-ray crystallographic analysis of illudin S, an antitumor sesquiterpene from *Omphalotus illudens*, has been carried out. Crystal data: $C_{15}H_{20}O_4$, orthorhombic, space group $P2_12_12$, a = 15.103(5), b = 10.574(5), c = 8.917(3) Å, Z = 4, F(000) = 568, λ (Cu) = 1.54184 Å. Final residual index R = 0.037. Interatomic distances indicate nonbonded repulsive interactions between the methylenes of the cyclopropane ring and the adjacent tertiary hydroxyl and methyl groups. Relief of this interaction may explain the ready isomerization of illudins to isoilludins. Molecular mechanics calculations show isoilludin M to be ~5 kcal/mol more stable than illudin M in agreement with this postulate. Reaction of illudin M with dilute HCl gives two chloroindantriols by nucleophilic attack of chloride on the cyclopropane ring leading to a quinoid intermediate which is trapped by solvent. Illudins can thus act as bifunctional alkylating agents.

Illudin S and M (1 and 2) are sesquiterpenes produced by the mushroom *Omphalotus illudens* (formerly *Clitocybe illudens*) when grown in culture.[1,2] Illudin S has been isolated from fruit bodies of the yellow-orange mushroom, and is believed to be one of the main toxins of *O. olivascens* [3] and the closely related *Lampteromyces japonicus*.[4,5] Recent studies have shown that illudin S and M are cytotoxic to human leukemia cells (HL 60) at concentrations of 6-100 nM.[6] Cytokinetic experiments showed that illudin S caused a complete block at the G_1-S phase of the cell cycle. Kinetics of inhibition of radiolabeled thymidine, uridine and leucine incorporation suggested a primary effect on DNA synthesis. In colony and liquid culture assays, cell killing was time dependent but near maximal with a 2-h exposure. Myeloid and T-lymphocyte leukemia cells were most sensitive (50% inhibitory concentration, 6-11 nM), but B-cell leukemia/lymphoma, melanoma and ovarian carcinoma cells were at least 10 times more resistant. Multiple drug-resistant leukemia cells remained susceptible to illudins.[6]

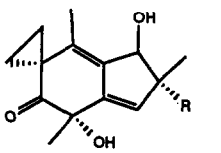
In order to determine the reasons for the extreme cytotoxicity of illudins (which approaches that of ricin, one of the most potent toxins known), we have undertaken a detailed study of structure and reactivity of these compounds and their derivatives. Clarification of the mechanism of toxicity will enable us to modify the structure so as to produce a compound with even greater selectivity in its toxicity toward leukemia cells than normal cells.

It seemed desirable to begin this study by carrying out an X-ray crystallographic analysis of illudin S. Such an analysis has never been reported for illudin S, although X-ray analyses of an iodobenzoate of isoilludin S[4] and also its triacetate[7] have been published. Isoilludin S(3) is formed in an unambiguous way by acyloin rearrangement of illudin S so that the absolute configuration of the latter could be inferred from that determined for isoilludin S.



1 Illudin S (R = CH_2OH)

2 Illudin M (R = CH_3)



3 Isoilludin S (R = CH_2OH)

4 Isoilludin M (R = CH_3)

Crystals of illudin S obtained from ethyl acetate were orthorhombic with space group $P2_12_12$. There were four molecules in a unit cell of dimensions a = 15.103(5), b = 10.574(5), c = 8.917(3) Å. The structure was solved by direct methods using the SHELXTL software and a computer-generated drawing of the molecule is shown in Figure 1, while crystallographic data are given in Table 1.

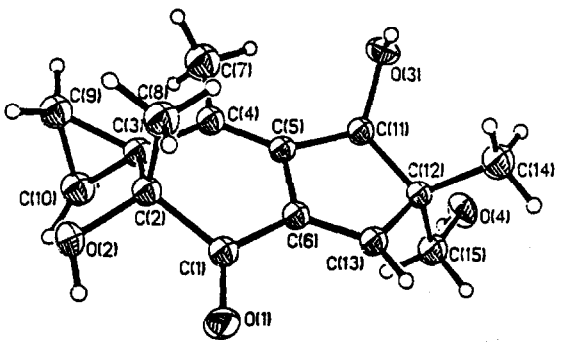


Figure 1. Crystal structure of the Illudin S molecule, illustrating the atom numbering scheme. All atoms except hydrogen are shown as ellipsoids of 30% probability.

The six-membered ring is seen to be in an envelope conformation with C3 C4 C5 C6 and C1 almost coplanar with C11 C12 and C13 of the five-membered ring. Thus, the following torsion angles were obtained: C3 C4 C5 C6, 2.8°, C4 C5 C6 C1, –6.4°, C4 C5 C6 C13 172.0°, C4 C5 C11 C12, –168.6°, C1 C6 C13 C12, 176.5°, C5 C6 C13 C12, –1.8°, C6 C5 C11 C12, 5.8°, C11 C5 C6 C13, –2.8°. On the other hand, C2 is appreciably above the plane defined by C3 C4 C5 C6 C1 as indicated by the torsion angles C2 C3 C4 C5, 24.6° and C2 C1 C6 C5, –17.9°. Perhaps one of the most notable features of the structure which may have a bearing on its reactivity is the location of the tertiary hydroxyl (O2) and the adjacent methyl (C8) with respect to the cyclopropane ring (C9 and C10). The interatomic distances O2-C9 and O2-C10 are 2.885 and 2.825 Å respectively. These distances are well within the sum of the van der Waals radii of oxygen and methylene (3.4 Å).[8] Similarly, the C8-C9 distance is 3.221 Å, which is less than the sum of the van der Waals radii for methyl and methylene (4 Å). These values indicate repulsive nonbonded interactions between the methylenes of the cyclopropane ring and the adjacent hydroxyl (O2) and methyl (C8) groups and may explain the tendency for the methyl to migrate to C1, giving isoilludin S. The axial configuration of this methyl is also favorable for overlap of its orbital with the π orbital of the carbonyl leading to sigma bond formation between C1 and C8.

The rearrangement of illudin to isoilludin can be brought about in several ways. For example, if an aqueous solution of illudin M is made alkaline (to pH 13), the compound is gradually converted to the isomer (4). Alternatively, a solution of illudin M in ethyl acetate is heated under reflux in the presence of alumina (Brockmann activity I, neutral) for several hours.[9] Isoilludin S is obtained in a similar manner. It is also reported to be formed by heating on a hot stage at 200° or by repeatedly passing its solution in ethyl acetate through a column of Brockmann's alumina.[4]

Confirmation that isomerization of illudin is a thermodynamically favorable reaction was obtained by molecular mechanics calculations carried out on illudin M (2) and isoilludin M (4).[10] The computer-generated drawing of the energy-minimized structure of illudin M (Fig. 2) is very similar to that determined for illudin S by X-ray analysis. The structure obtained for isoilludin M shows that unfavorable nonbonded interactions involving the cyclopropane ring are not present and this appears to be reflected in the energy found for this structure (25.13 kcal/mol) compared to that found for illudin M (30.42 kcal/mol).

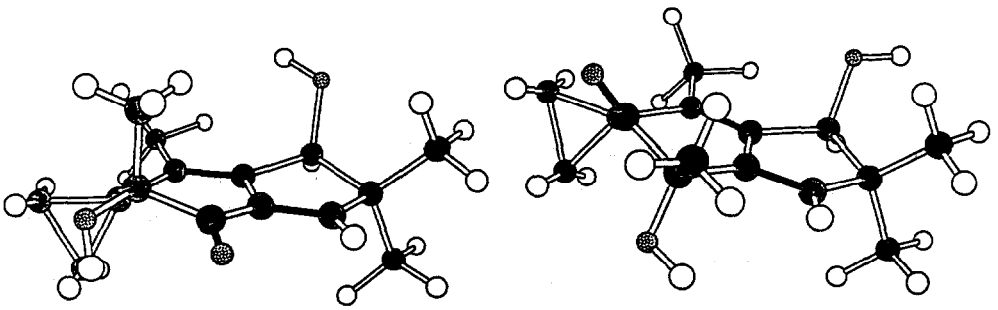
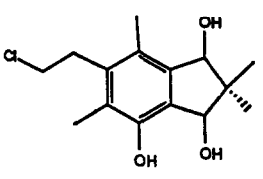


Fig. 2. Energy minimized structures of Illudin M and Isoilludin M

The stability of illudins at low pH has also been examined. When illudin M was dissolved in dilute HCl at room temperature, it was converted in several hours to two chloroindantriols (5 and 6). The diastereomers were separated by chromatography. They had almost identical mass spectra, and these indicated the location of the chlorine. The NMR spectra of the diastereomers, and their triacetates confirmed the assigned structures. In particular, the signals for the two methine protons in the five-membered ring of 5 (δ 4.60, 5.22) and also of 6 (δ 4.07, 4.48) moved downfield on acetylation to δ 6.16, 6.21 and 5.83, 5.95, respectively. The signals for the chloroethyl group in 5 and 6 were essentially unchanged in the corresponding acetates. This evidence ruled out structures with a chlorine substituent on the



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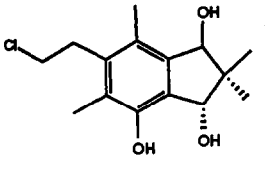

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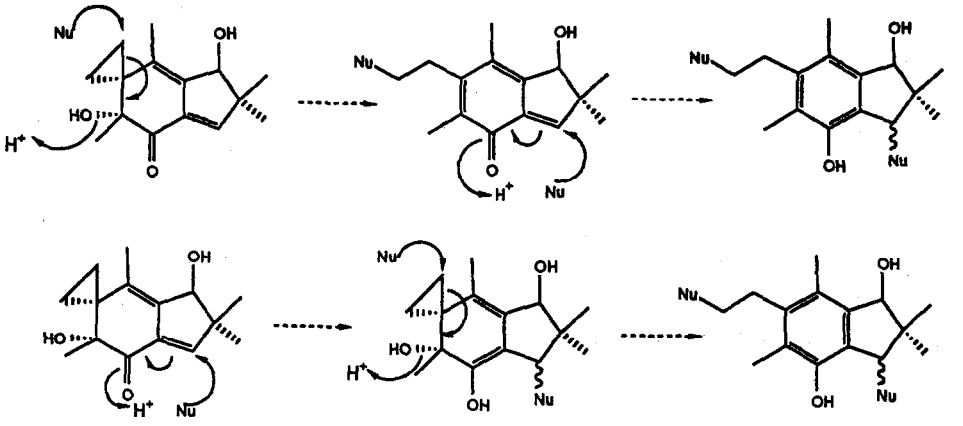


Scheme 1

five-membered ring and a hydroxyethyl group on the benzene ring. Formation of the chloroindantriols can be envisaged as proceeding *via* opening of the cyclopropane ring and extrusion of the tertiary hydroxyl leading to a quinoid intermediate which undergoes Michael type reaction with water giving the final product. Alternatively, Michael type reaction may occur first, followed by cyclopropane ring opening as illustrated in Scheme 1.

Evidence for a quinoid intermediate has been obtained by NMR spectroscopic analysis of the reaction of illudin M with DCl in D_2O (0.6 N). Of particular significance was the vinyl proton region of the spectrum (Fig. 3). Initially, the solution gave a sharp singlet at δ 6.47 expected for the vinyl proton in illudin M. After 17 min (at room temperature),

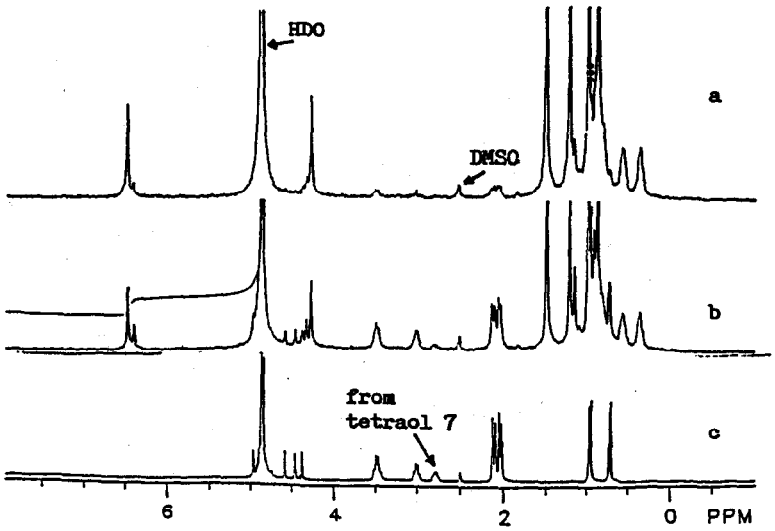
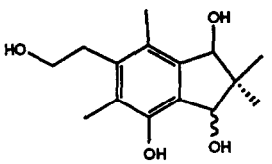


Figure 3. NMR spectra of reaction of Illudin M with DCl in D_2O: a, 17 min b, 41 min c, 180 min after adding DCl to the solution of illudin M.

this peak had decreased about 15%, while a new singlet appeared at δ 6.39 with an intensity about 16% that of the δ 6.47 peak. The latter peak decreased steadily, and had completely disappeared in 180 min., while the new peak increased slightly, then gradually disappeared as well (180 min). These results clearly show that the intermediate in the reaction has the cyclopropane ring-opened quinoid structure. It is very reactive so its concentration is always small compared to the changes in concentration of the reactant (2) and products (5, 6) during the reaction. It cannot be detected by U.V. spectroscopy. There is of course the possibility that under different conditions, e.g. higher pH, and with a more powerful nucleophile, Michael type reaction may occur first followed by cyclopropane ring opening.

Evidence that cyclopropane ring opening is the rate determining step comes from a study of the kinetics of decomposition of illudin M in dilute acid. In dilute aqueous HCl at pH 0, illudin M was found to undergo a pseudo first-order reaction ($k = 4.7 \times 10^{-3}$ min^{-1}) with a half life ($t_{1/2}$) of 147 min. With a more dilute HCl solution, the rate of reaction decreased. This was not merely a result of change of pH, since in dilute H_2SO_4 at pH 0 a much slower first-order reaction was observed ($k = 6.5 \times 10^{-4}$ min^{-1}, $t_{1/2} = 1073$ min), indicating that the reaction rate depends on the nature of the nucleophile, i.e. Cl^- versus H_2O. The product of the dilute H_2SO_4 reaction was the tetraol 7. Some of this compound was also formed when illudin M was treated with very dilute HCl.



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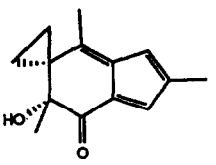

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The reaction of illudin S with dilute HCl is complicated by the presence of the primary hydroxyl. If an aqueous solution of illudin S is treated with dilute HCl, the solution soon becomes yellow and an orange-yellow precipitate forms within 30 min. This precipitate has been identified as the acylfulvene 8 which results from reverse Prins reaction with loss of formaldehyde. The structure of 8 was determined previously.[11] In acetone-water solution, 8 reacts further with acid, but the product appears to be polymeric and has not been characterized.

The above reactions show that illudins are prone to nucleophilic substitution (S_N2') on the cyclopropane ring, the kinetics of which depend on the nature of the nucleophile and the pH of the medium. Intrinsic factors favoring the reaction are both relief of ring strain as well as repulsive van der Waals interactions, by opening of the cyclopropane ring. The highly reactive quinoid intermediate is then trapped by solvent giving a stable phenolic end product. Thus, illudins can behave as bifunctional alkylating agents.

Not surprisingly, the toxicity of illudins is much greater than that of its derivatives. When tested against human leukemia (HL) 60 cells, illudin S and M had IC50 values of about 10 nM. Isoilludin M was far less toxic (IC50, 3.8×10^3 nM) as were the chloroindantriols 5 and 6 (4.8×10^3, 6.5×10^3 nM, respectively). Cytotoxicity of illudins may thus be related to their ability to act as alkylating agents in the cell. It was previously found[6] that the toxicity of illudin M was three orders of magnitude greater than that of the dihydro derivative, obtained by reduction of the ketone with sodium borohydride. This result is consistent with the idea that the compound is an alkylating agent as indicated in Scheme 1. We

are now examining reactions of these compounds with "biological" nucleophiles (e.g. glutathione) to gain further insight into the mechanism of toxicity of the illudins.

Experimental Section

M.p.s. were determined with a Kofler hot-stage apparatus. Spectra were obtained on the following instruments: General Electric QE-300 console with an Oxford magnet and a Nicolet computer system (^{1}H NMR 300 MHz; ^{13}C NMR 75.48 MHz); Perkin-Elmer 1330 IR spectrophotometer; UVikon 819 Kontron UV spectrophotometer. ^{1}H NMR spectra were taken for solutions in $CDCl_3$ with Me_4Si as internal standard. High resolution mass spectra were determined at the University of Minnesota Mass Spectrometry Service Laboratory. Column chromatography was carried out with silica gel 60 (70-230 mesh or finer than 230 mesh; EM Laboratories, Elmsford, NY). Analytical t.l.c. was carried out on Merck 60 F-254 silica gel plates. Reactions were routinely monitored by t.l.c.

Illudin S and Illudin M — These compounds were isolated from cultures of *Omphalotus illudens* (formerly *Clitocybe illudens*) as described previously.[1] Illudin S was recrystallized from ethyl acetate (m.p. 137-138°); NMR (^{1}H) δ 0.41-0.44 (m,1), 0.81-0.87 (m,1), 0.97-0.99 (m,1), 1.11-1.14 (m,1), 1.20 (s,3), 1.37 (s,3), 1.69 (s,3), 3.50 (AB quartet, J_{AB} 10.5 Hz, δ_{AB} 0.08, 2), 3.56 (s,OH), 4.72 (s,1), 6.45 (s, 1) ppm.
Illudin M was recrystallized from hexanes-ethyl acetate (m.p. 134-135°); NMR (^{1}H) δ 0.38-0.45 (m,1), 0.80-0.87 (m,1), 0.93-0.99 (m,1) 1.10 (s,3), 1.12-1.17 (m,1), 1.21 (s,3), 1.36 (s,3), 1.69 (s,3), 3.57 (br.s, OH), 4.40 (s,1), 6.54 (s,1) ppm.

Isoilludins – These were prepared as described previously.[4,5,9] Isoilludin M was also obtained by dissolving illudin M in water and adjusting the pH of the solution to 13 with dilute NaOH solution. The solution was kept for three days, then extracted with ethyl acetate. Chromatography of the extract gave isoilludin M with properties identical to those of the compound obtained by heating a solution of illudin M in ethyl acetate in the presence of alumina[9]; NMR (^{1}H) δ 1.02 (s,3), 1.05-1.17 (m,1), 1.17 (s,3), 1.23-1.32 (m,2), 1.48 (s,3), 1.65 (s,3), 1.72-1.80 (m,1), 3.58 (br.s,OH), 4.28 (s,1), 5.80 (s,1) ppm.

Reaction of Illudin M with dilute HCl.– Illudin M (50 mg) was dissolved in water (20 ml) and to the solution was added dropwise conc. HCl solution (2 ml). The resulting solution was kept overnight at room temperature, then extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and the solvent removed leaving a semi-solid residue which on chromatography (ethyl acetate-hexane 1:3) gave chloroindantriol **5** m.p. 60 °C; NMR (^{1}H) δ 0.86 (s,3), 1.26 (s,3), 1.64 (br s, OH), 2.19 (s,3), 2.26 (s,3), 3.10 (t, J = 7.8 Hz, 2), 3.49 (t, J = 7.8 Hz, 2), 4.60 (s,1), 5.22 (d, J = 5 Hz, 1), 7.04 (s, OH) ppm. MS m/z 286 (M^++2, 4), 284.1167, $C_{15}H_{21}O_3Cl$ (M^+, 12), 266.1067 (M^+–H_2O, 63), 251 (M^+–H_2O–CH_3, 100), 231 (M^+–Cl–H_2O, 41), 217.1229 (M^+–CH_2Cl–H_2O, 46). The other major product was the isomer **6**, m.p. 149-150 °C; NMR (^{1}H) δ 0.85 (s,3), 1.03 (s,3), 1.19 (m, OH), 2.20 (s,3), 2.31 (s,3), 2.49 (s, OH), 3.09 (t, J = 7.8 Hz, 2), 3.45 (t, J = 7.8 Hz, 2), 4.07 (br, s, 1), 4.48 (s, 1), 6.54 (s, OH) ppm. MS m/z 284.1179, $C_{15}H_{21}O_3Cl$ (M^+, 12), 266.1062, $C_{15}H_{19}O_2Cl$ (M^+–H_2O), 251 (M^+, 100), 231,$C_{15}H_{19}O_2$ (M^+–Cl–H_2O, 38), 217.1242 $C_{14}H_{17}O_2$ (M^+–CH_2Cl–H_2O, 46).

Acetylation of **5** (acetic anhydride-pyridine, 24h) afforded a triacetate isolated as an oil; NMR (^{1}H) δ 1.07 (s,3), 1.08 (s,3), 2.10 (s,3), 2.11 (s,3), 2.13 (s,3), 2.20 (s,3), 2.26 (s,3), 3.15 (t, J = 8 Hz, 2), 3.52 (t, J = 8 Hz, 2), 6.16 (s, 1), 6.21 (s, 1) ppm. This spectrum indicates that the methine protons in the five-membered ring of **5** have shifted downfield on acetylation which confirms the presence of two hydroxyls in the ring. The triplets from the two-carbon side chain are unaffected by acetylation, consistent with the presence of a chloroethyl rather than hydroxyethyl group. Likewise, acetylation of **6** gave an oil with the following NMR spectrum: δ 1.03 (s,3), 1.11 (s,3), 2.60 (s,3), 2.11 (s,3), 2.15 (s,3), 2.23 (s,3), 2.30 (s,3), 3.16 (t, J = 8.7 Hz, 2), 3.53 (t, J = 8.7 Hz, 2), 5.83 (s, 1), 5.95 (s, 1) ppm.

Reaction of Illudin M with dilute H_2SO_4 solution – To a solution of illudin (10 mg) in H_2O (10 ml) was added dilute H_2SO_4 (10 ml, 2N) and the resulting solution was kept for 4 days at room temperature. The solution was then extracted with ethyl acetate and the extract on thin layer chromatography showed two closely running polar spots, the isomers **7**, which was confirmed by NMR spectroscopy.

Kinetics of the Reaction of Illudin M with acid – To a solution of illudin M [UV λ_{max}228 nm (ε13,900) 318 nm (ε3600)] in water (1 mg/20 ml) was added dil HCl (5N), giving a solution with pH 0. The progress of the reaction at room temperature (25°C), was followed by measuring at appropriate intervals the intensity of the 318 nm band which is

proportional to the concentration of illudin M present [The chloroindantriol products 5 and 6 have λ_{max} 284 nm (ε2000)]. The reaction gave a good first order plot with rate constant $k = 4.7 \times 10^{-3}$ min^{-1} and half-life $t_{1/2}$ = 147 min. A similar reaction with dil H_2SO_4 at pH 0 instead of dil HCl (with the same concentration of illudin M) also showed first-order kinetics ($k = 6.5 \times 10^{-4}$ min^{-1}, $t_{1/2}$ = 1073 min.)

Reaction of Illudin S with dilute HCl – To a solution of illudin S (40 mg) in H_2O (2 ml) was added dil HCl (2 ml, 2N). After about 30 min, the yellow solution had become cloudy and an orange-yellow precipitate formed. The mixture was kept in the refrigerator overnight; then it was extracted with chloroform. The extract yielded one major product, an orange-yellow solid whose NMR and UV spectral properties were identical to those reported for the fulvene 8: UV λ_{max}233, 325 nm; NMR (^{1}H) δ 0.6-1.6 (m,4), 1.40 (s,3), 2.05 (s,3), 2.15 (br,s,3), 6.46 (q, J = 1.5 Hz, 1), 7.20 (br,s, 1) ppm.

Crystallographic analysis of Illudin S – A pale-yellow transparent crystal was mounted along its longest dimension on a Nicolet R3m/V diffractometer, and data was collected at room temperature. Intensities of three check reflections were monitored after every 60 reflections; no significant decay was observed during the time required for data collection. The cell parameters were measured and refined from data from 15 strong high angle (20<2θ<40°) reflections. Data used in structure determination were corrected for Lorentz and polarization effect, but no absorption correction was applied because of low value of μ. The unit cell dimensions and other pertinent data are given in Table 1.

The systematic absences (0k0, k = 2n+1; 00l, l = 2n+1) were consistent with $P22_12_1$. The data was therefore transformed to the standard setting of $P2_12_12$ (No.18) using the matrix 001 010 –100. The structure was solved by direct methods using the program SHELXTL plus on a Digital Computer Micro VAX II. The structure was refined using full-matrix least squares. Due to insufficient data, only oxygen atoms were refined anisotropically. Hydrogen atoms were included at the ideal positions. Unit weights were used in the initial stages, while in the final cycles the weighting scheme used was of the form $w^{-1} = \sigma^2(F) + 0.0004\ F^2$. The refinement minimizing the function $(|F_o| - |F_c|)^2$ converged at R = 0.037 and R_w = 0.042. A few low-angle reflections were found to be affected by secondary extinction. An empirical isotropic extinction parameter, x, was used employing the equation $F_c = F[1 + 0.002 \times (F^2 / \sin 2\theta)]^{-1/4}$ and refined to a value of 0.026(3).

TABLE 1. Summary of crystal data, intensity collection, and structural refinement for Illudin S.

cell constants	15.103 (5), 10.574 (5), 8.917 (3) Å
cell volume (Å^3)	1424 (1)
crystal system	orthorhombic
space group	$P2_12_12$
molecular weight	264
Z, F (000)	4, 568
ρ_c, ρ_o (g cm^{-3})	1.23, 1.25
cryst dimens (mm)	0.19 x 0.25 x 0.35
abs coeff, μ (mm^{-1})	0.69
radiation	Cu, 1.54184 Å
monochromator	highly oriented graphite
temp (°C)	21 ± 1
2θ angle (°)	2–110
scan type	coupled θ (crystal / 2θ (counter)
scan width	$K\alpha_1$ – 1° to $K\alpha_2$ + 1°
scan speed (°min^{-1})	variable, 2.02 – 4.88
background time/scan time	0.5
total reflections measured	1142, (+h, +k, +l)
unique data used	1022
no. of parameters (NP)	173
$R = (\Sigma \| \|F_o\| - \|F_c\| \| / \Sigma \| F_o \|)$	0.037
$R_w = [\Sigma_w(\|F_o\| - \|F_c\|)^2 / \Sigma_w \| F_o \|^2]^{1/2}$	0.042
$\Delta\rho_{max}$ (e Å^{-3})	0.34
shift : error (max)	0.012
g.o.f.	2.24

Supplementary Material Available: Atomic coordinates and equivalent isotropic displacement parameters, anisotropic thermal parameters for oxygen atoms, final fractional coordinates and thermal parameters for H atoms and observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.

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