Formation of Oxadiazolo[4,5-*a*]indolines *via* Addition Reactions of Cycloalkano[*b*]indoles with Nitrile Oxides. Crystal Structure of an Adduct

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Reactions of stable nitrile oxides with cycloalkano[*b*]indoles gave as main product adducts **3** containing the oxadiazolo[4,5-*a*]indoline ring system. The structure elucidation of the isolated adducts was based on their spectral data, chemical behaviour and in one case the structure was confirmed by crystallographic X-ray analysis. The mechanism of the reaction is also discussed.

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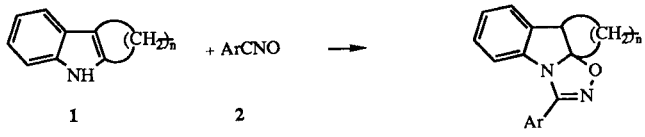
The continuing interest in the chemistry of indoles comes largely from the potent biological activity of many indole derivatives [1]. In connection with our previous work on the synthesis of heterocyclic propellanes *via* 1,3-dipolar cycloaddition reaction [2], we studied the reactions of nitrile oxides with cycloalkano[*b*]indoles in an attempt to prepare new propellane-type indole derivatives. The reactions of nitrile oxides with several indoles, already studied [3-5], yielded cycloadducts to the 2,3-double bond and not nucleophilic addition products from the indole nitrogen. The reactivity of cycloalkano[*b*]indoles as dipolarophiles is expected to be lower than that of the unsubstituted at the 2,3 positions indoles because of steric factors. Reactions of cycloalkano[*b*]indoles with substituted *o*-benzoquinones were shown to give propellanes [6,7] but there is strong evidence that these additions proceed through an ionic rather than a concerted pathway [6]. Also, reactions of cycloalkano[*b*]indoles with tosyl azide, studied to a great extent, lead to several products depending on the size of the cycloalkane fused ring [8-10].

Results and Discussion.

The reactions of cycloalkano[*b*]indoles **1** with the stable nitrile oxides **2** were carried out in chloroform at room temperature using cycloalkano[*b*]indole in excess (3:1). The reactions afforded as main products oxidized one to one adducts of **1** and **2**, as it was shown by their spectral and analytical data. Thus, in the ir spectra, the isolated products give absorptions in the range 3370-3500 indicative for O-H bond and 1600-1615 cm^{-1} for C=N bond, whereas in the mass spectra they give besides the molecular ion characteristic peaks at m/z [M -OH]$^+$, [M -$C_{n+1}H_{2n+1}N$]$^+$ and a peak at m/z 146 corresponding to the common fragment $[C_8H_4NO_2]^+$. The proton nmr spectra are also consistent with an one to one adduct of **1** and **2**. A characteristic feature of all the nmr spectra is that one of the aromatic protons is strongly shielded to δ 5.75-6.33.

We also tried to have some chemical evidence for the structure of the isolated adducts. Thus no reactions were observed with deoxygenating reagents (triphenyl phosphine, sodium dithionite) characteristic for possible *N*-oxide isomers and with nucleophiles (dimethylamine) characteristic for possible epoxide isomers, whereas reaction of the adduct of **1a** with **2a** with acetic anhydride gave an acetyl derivative having in the ir spectrum the carbonyl group absorption at 1725 cm^{-1} consistent with an ester carbonyl group rather than an acetyl-oxime carbonyl group. All these findings led us to accept structure **3** for the isolated products and subsequently, structure **4** for the acetylation product.



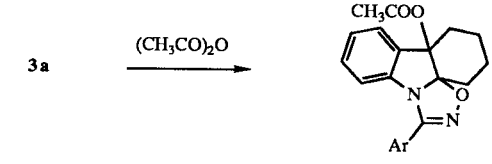
1 2 3

1a, n = 4
1b, n = 5
1c, n = 6

2a, Ar = 2,6-$Cl_2C_6H_3$-
2b, Ar = 2,4,6-$(CH_3)_3C_6H_2$-

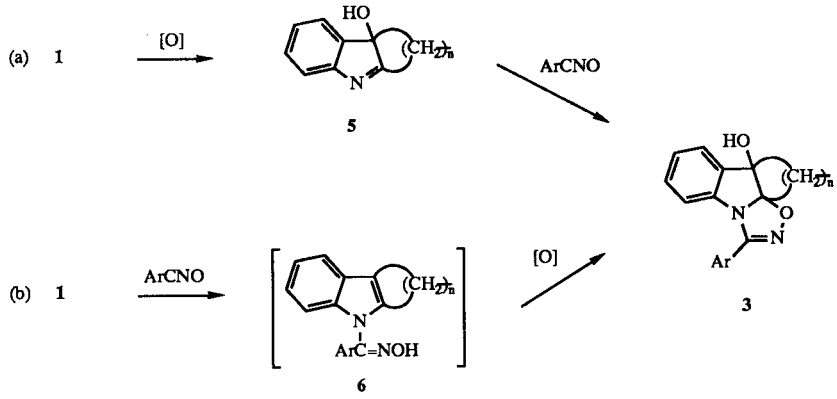
3a, n = 4 Ar = 2,6-$Cl_2C_6H_3$-
3b, n = 5 Ar = 2,6-$Cl_2C_6H_3$-
3c, n = 6 Ar = 2,6-$Cl_2C_6H_3$-
3d, n = 4 Ar = 2,4,6-$(CH_3)_3C_6H_2$-
3e, n = 5 Ar = 2,4,6-$(CH_3)_3C_6H_2$-
3f, n = 6 Ar = 2,4,6-$(CH_3)_3C_6H_2$-

Structure **3** was completely confirmed from the X-ray crystallographic analysis carried out on **3a**. An ORTEP drawing for **3a** is given in Figure 1. From X-ray data comes out that H(10) is in the shielding region of the dichlorophenyl ring, rationalizing the high field observed chemical shifts for one aromatic proton of cycloadducts **3**.



4

Scheme I



Concerning the reaction mechanism for the formation of the adducts **3** two general routes are possible (Scheme I): a) oxidation of **1** to the 3-hydroxy derivatives **5** and subsequent cycloaddition of the nitrile oxide to the carbon nitrogen double bond of **5** or b) nucleophilic addition of the indole nitrogen on the nitrile oxide and subsequent oxidation of the intermediate oxime **6** with synchronous ring closure.

It is known that 2,3-disubstituted indoles and especially tetrahydrocarbazoles show a tendency to autoxidation and give through the generally accepted initial formation of the relative reactive 3-hydroxyperoxyindolenines several products [11]. The kind and the yield of these subsequent products depend largely on the substituents and in the case of cycloalkano[*b*]indoles vary with the size of the cycloalkane fused ring [12]. Taking in account this property of indoles pathway (a) seems to be the more probable. In our reactions the yields of products **3** depend on the size of the cycloalkane ring and decrease in the order cyclohexane > cyclooctane > cycloheptane. We have also to mention that in the reactions with **1b** and **1c** the formation of some other not fully characterized byproducts was detected. Pathway (a) is also supported by the fact that **5** (n = 4) which was synthesized by hyperoxide catalysed oxidation of **1a** to the corresponding hydroxyperoxy derivative and subsequent reduction [13], reacts readily (two

Table I

Analytical and Spectral Data of **3**

Compound	Mp °C	Yield %	IR (Nujol), cm^{-1}) ν OH	ν C = N	^1H NMR ($CDCl_3$, δ)	MS, m/z (%)	Molecular Formula (MW)	Analysis % Calcd./Found C	H	N
3a	143-145	67	3430	1615	0.80-2.59 (m, 8H), 3.01 (s, 1H), 6.02-6.33 (m, 1H), 6.75-7.53 (m, 6H)	378/376/374 (10) $M^{+\bullet}$, 361/359/357 (1), 295/293/291 (82), 267/265/263 (8), 146 (100)	$C_{19}H_{16}Cl_2N_2O_2$ (375.26)	60.81 60.59	4.30 4.59	7.47 7.39
3b	206-209	35	3500	1615	0.80-2.55 (m, 10H), 3.67 (s, 1H), 5.95-6.28 (m, 1H) 6.65-7.55 (m, 6H)	392/390/388 (7) $M^{+\bullet}$, 375/373/371 (4), 295/293/291 (100), 267/265/263 (8), 146 (39)	$C_{20}H_{18}Cl_2N_2O_2$ (389.28)	61.71 61.89	4.66 4.83	7.20 7.11
3c	197-200	74	3420	1605	0.85-2.60 (m, 12H), 3.40 (s, 1H), 6.09-6.30 (m, 1H) 6.59-7.65 (m, 6H)	406/404/402 (12) $M^{+\bullet}$, 389/387/385 (3), 295/293/291 (100), 267/265/263 (9), 146 (52)	$C_{21}H_{20}Cl_2N_2O_2$ (403.31)	62.54 62.66	5.00 5.08	6.95 6.84
3d	152-155	95	3480	1600	0.70-2.75 (m, 17H), 3.38 (s, 1H), 5.90-6.19 (m, 1H), 6.56-7.40 (m, 5H)	348 (28) $M^{+\bullet}$, 331 (0.5), 265 237 (5), 146 (59), 120 (76)	$C_{22}H_{24}N_2O_2$ (348.44)	75.84 76.02	6.94 7.15	8.04 7.93
3e	209-212	20	3370	1600	0.70-2.90 (m, 19H), 3.65 (s, 1H), 5.85-6.10 (m, 1H) 6.62-7.50 (m, 5H)	362 (22) $M^{+\bullet}$, 345 (2), 265 (100), 237 (5), 146 (59), 120 (76)	$C_{23}H_{26}N_2O_2$ (362.47)	76.21 76.31	7.23 7.37	7.73 7.62
3f	172-175	52	3490	1600	0.70-2.70 (m, 21H), 3.45 (s, 1H), 5.75-6.15 (m, 1H), 6.58-7.50 (m, 5H)	376 (24) $M^{+\bullet}$, 359 (2), 265 (37) 237 (8), 146 (69), 120 (100)	$C_{24}H_{28}N_2O_2$ (376.49)	76.56 76.89	7.50 7.62	7.44 7.39

days, room temperature) with **2a** resulting **3a** in 90% yield. Since this catalysed oxidation of **1** is not a common procedure for the synthesis of **5** and the other unknown, to the best of our knowledge, omologous hydroxyindolenines **5** (n = 5,6) have not been isolated as oxidation products of the corresponding cycloalkano[*b*]indoles, this route for the synthesis of **3** can not be applied in all cases. Furthermore when the reaction of **1a** with **2a** was repeated in a nitrogen atmosphere the yield of **3a** was decreased from 67% to 11% without formation of other products. On the other hand in all the reactions which carried out using excess of cycloalkano[*b*]indole **1**, the greater amount of **1** was isolated unreacted after the end of the reaction, whereas from a blank experiment (keeping a chloroform solution of **1a** at room temperature for seven days) no **5** was isolated. All these findings lead us to accept that the oxidation of the cycloalkano[*b*]indole is initiated by the presence of the nitrile oxide which is added to the oxidized reactive intermediate in a rather synchronous stage.

Although the reactions of cycloalkano[*b*]indoles with nitrile oxides did not give the expected propellane-type derivatives, the obtained adducts **3** which contain the oxadiazolo[4,5-*a*]indoline ring system are considered to be a rather interesting class of compounds and the whole subject is under further study with other dipoles and other indole derivatives.

Table II
Positional Parameters ($x10^4$) of the Non-H Atoms, E.s.d.'s in Parentheses

Atom	X	Y	Z
CL(1)	6588.2(8)	531.6(5)	1126.5(3)
CL(2)	1147.7(9)	1970.1(5)	1278.2(6)
C(1)	3882(3)	1278(1)	1137(2)
C(2)	2793(3)	1791(2)	717(2)
C(3)	3011(1)	2171(2)	-147(2)
C(4)	4288(1)	2023(2)	-610(2)
C(5)	5363(4)	1501(2)	-236(2)
C(6)	5157(3)	1141(2)	633(2)
C(7)	150(3)	-989(2)	2857(2)
C(8)	-620(3)	-1039(2)	1997(2)
C(9)	-10(3)	-709(2)	1197(2)
C(10)	1366(3)	-323(2)	1231(2)
C(11)	2109(3)	-271(1)	2103(2)
C(12)	1530(3)	-607(1)	2905(2)
C(13)	2619(3)	-530(2)	3731(2)
C(14)	3295(4)	-1373(2)	4013(2)
C(15)	4352(4)	-1678(2)	3284(3)
C(16)	5721(4)	-1123(2)	3234(3)
C(17)	5436(3)	-233(2)	3574(2)
C(18)	3854(3)	45(2)	3330(2)
C(19)	3745(3)	940(1)	2101(2)
N(1)	3555(2)	83(1)	2300(1)
N(2)	3852(3)	1411(1)	2818(2)
O(18)	3666(2)	901(1)	3627(1)
O(13)	2003(2)	-196(1)	4557(1)
C(30)	-1620(8)	1968(5)	3458(6)
C(31)	-512(7)	1369(5)	3506(4)
O(31)	44(3)	1113(2)	4409(2)

EXPERIMENTAL [a]

Preparation of Starting Materials.

Cycloalkano[*b*]indoles were prepared by the Fisher method [12,14]. 2,6-Dichlorobenzonitrile oxide **2a** and mesitonitrile oxide **2b** were prepared according to known procedures [15] from the corresponding aldoximes with *N*-bromosuccinimide and triethylamine.

General Procedure for the Reactions.

The reactions were carried out by keeping a chloroform solution (10 ml) of cycloalkano[*b*]indole **1** (3 mmoles) and nitrile oxide **2** (1 mmole) at room temperature until the disappearance of the starting nitrile oxide as it was checked by tlc (10-30 days). Then after evaporation of the solvent the residue was chromatographed on a silica gel column with a mixture of hexane-ethyl acetate 5:1 as eluant. Products **3** were further purified by recrystallization with dichloromethane:hexane mixtures. Analytical and spectral data of compounds **3** are summarized in Table 1.

Reaction of **3a** with Acetic Anhydride.

A solution of **3a** (1 mmole) and acetic anhydride (1 ml) in toluene (5 ml) was refluxed for 30 hours. After the removal of the solvent the residue was refluxed with water and extracted with ether. The ether extract was dried and after evaporation of the ether **4** was isolated in 30% yield by column chromatography (silica gel, eluant hexane-ethyl acetate 5:1), mp 164-166°; ir (Nujol): 1725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.55-3.30 (m, 8H), 2.00

Table III
Anisotropic Thermal Parameters ($x10^3$) of the Non-H Atoms; E.s.d's in Parentheses

Atom	U11	U22	U33	U12	U13	U23
CL(1)	67.3(5)	83.5(5)	58.3(4)	15.1(4)	16.3(3)	17.5(4)
CL(2)	69.2(5)	68.7(5)	78.6(5)	22.4(4)	16.3(4)	12.8(4)
C(1)	51(1)	27(1)	33(1)	-9(1)	3(1)	1(1)
C(2)	57(2)	34(1)	46(1)	-3(1)	0(1)	1(1)
C(3)	80(2)	41(2)	49(2)	3(2)	-10(2)	11(1)
C(4)	95(2)	49(2)	37(1)	-6(2)	11(2)	11(1)
C(5)	79(2)	53(2)	46(2)	-3(2)	20(1)	6(1)
C(6)	57(2)	38(1)	38(1)	-4(1)	8(1)	3(1)
C(7)	41(2)	51(2)	51(2)	-9(1)	11(1)	4(1)
C(8)	36(2)	66(2)	67(2)	-12(1)	-4(1)	-6(2)
C(9)	48(2)	57(2)	48(2)	0(1)	-13(1)	-5(1)
C(10)	48(2)	39(1)	35(1)	2(1)	-3(1)	1(1)
C(11)	35(1)	28(1)	32(1)	3(1)	1(1)	-4(1)
C(12)	32(1)	34(1)	36(1)	1(1)	6(1)	1(1)
C(13)	36(1)	41(1)	29(1)	3(1)	7(1)	4(1)
C(14)	50(2)	47(2)	54(2)	3(1)	9(2)	16(1)
C(15)	65(2)	50(2)	67(2)	22(2)	7(2)	10(2)
C(16)	49(2)	82(2)	64(2)	22(2)	9(2)	19(2)
C(17)	41(2)	82(2)	36(2)	-8(2)	-3(1)	6(2)
C(18)	39(1)	42(1)	26(1)	-3(1)	1(1)	-2(1)
C(19)	41(1)	33(1)	34(1)	-2(1)	6(1)	-1(1)
N(1)	33(1)	32(1)	25(1)	-2.7(9)	3.4(8)	0.6(8)
N(2)	75(2)	37(1)	38(1)	-12(1)	12(1)	-3(1)
O(18)	75(1)	43(1)	28.7(9)	-9(1)	9.4(9)	-6.1(8)
O(13)	50(1)	59(1)	27.9(9)	7(1)	11.2(8)	5.1(9)
C(30)	83(5)	171(6)	185(7)	28(4)	27(4)	96(5)
C(31)	94(4)	203(7)	116(4)	55(4)	52(3)	97(4)
O(31)	62(1)	77(2)	70(1)	13(1)	22(1)	19(1)

Table V

Bond Lenths and Angles

Bond lengths or angles		Bond lengths or angles	
C1-C2	1.392(2)	C9-C8	1.383(4)
C2-C3	1.390(4)	C8-C7	1.383(4)
C3-C4	1.363(5)	C7-C12	1.380(4)
C4-C5	1.369(4)	C12-C13	1.503(3)
C5-C6	1.380(4)	C13-C18	1.565(3)
C6-C1	1.389(4)	C18-O18	1.499(3)
C6-C11	1.739(3)	O18-N2	1.424(3)
C2-C12	1.727(3)	N2-C19	1.269(3)
C1-C19	1.481(3)	C18-C17	1.514(4)
C19-N1	1.416(3)	C17-C16	1.532(5)
N1-C18	1.476(3)	C16-C15	1.521(5)
N1-C11	1.433(3)	C13-O13	1.419(3)
C11-C12	1.379(3)	C13-C14	1.529(4)
C11-C10	1.386(3)	C14-C15	1.510(5)
C10-C9	1.380(4)		
C6-C1-C2	116.8(2)	C9-C8-C7	120.1(3)
C1-C2-C3	121.1(3)	C6-C7-C12	119.1(3)
C2-C3-C4	119.9(3)	C7-C12-C11	119.9(3)
C3-C4-C5	120.7(3)	C7-C12-C13	129.0(2)
C4-C5-C6	119.2(3)	C11-C12-C13	111.0(2)
C5-C6-C1	122.3(2)	C12-C13-C18	102.3(2)
C1-C6-C11	119.4(2)	C12-C13-C14	111.8(2)
C5-C6-C11	118.3(2)	C12-C13-O13	114.4(2)
C1-C2-C12	119.2(2)	C18-C13-O13	112.4(2)
C3-C2-C12	119.0(2)	C18-C13-C14	109.7(2)
C2-C1-C19	122.0(2)	O13-C13-C14	106.3(2)
C6-C1-C19	121.1(2)	C13-C14-C15	111.1(2)
C1-C19-N1	123.7(2)	C14-C15-C16	111.7(3)
C1-C19-N2	121.2(2)	C15-C16-C17	112.8(3)
N1-C19-N2	115.0(2)	C16-C17-C18	111.6(2)
C19-N1-C11	117.4(2)	C17-C18-C13	114.4(2)
C19-N1-C18	102.7(2)	C17-C18-N1	111.8(2)
C18-N1-C11	107.8(2)	C17-C18-O18	109.3(2)
N1-C11-C10	126.9(2)	C13-C18-N1	106.3(2)
N1-C11-C12	111.1(2)	C13-C18-O18	111.2(2)
C10-C11-C12	122.0(2)	N1-C18-O18	103.3(2)
C11-C10-C9	117.2(2)	C18-O18-N2	106.9(2)
C10-C9-C8	121.6(3)	O18-N2-C19	107.3(2)

Table IV

Positional and Isotropic Thermal Parameters ($x10^4$) of the H-Atoms; E.s.d.'s in Parenthese

Atom	X	Y	Z	U
H(3)	229(3)	246(2)	-38(2)	49(8)
H(4)	446(3)	228(2)	-121(2)	64(8)
H(5)	630(4)	140(2)	-54(2)	9(10)
H(7)	-27(3)	-123(2)	339(2)	65(9)
H(8)	-157(3)	-133(2)	195(2)	59(8)
H(9)	-51(3)	-75(2)	61(2)	57(8)
H(10)	179(3)	-10(2)	67(2)	41(7)
H(14A)	251(3)	-176(2)	407(2)	43(7)
H(14B)	392(3)	-131(2)	463(2)	61(9)
H(15A)	465(3)	-224(2)	342(2)	55(8)
H(15B)	378(4)	-169(2)	260(2)	71(9)
H(16A)	655(4)	-136(2)	359(2)	9(10)
H(16B)	602(4)	-107(2)	259(3)	9(10)
H(17A)	616(3)	15(2)	329(2)	54(8)
H(17B)	557(3)	-21(2)	421(2)	58(8)
H(O13)	158(4)	25(2)	449(3)	9(10)
H(30A)	-180(9)	221(5)	282(6)	26(40)
H(30B)	-219(3)	187(2)	355(2)	21(8)
H(31A)	9(4)	147(2)	329(3)	7(10)
H(031)	-73(5)	86(3)	467(3)	11(20)

(s, 3H), 6.12-6.45 (m, 1H), 6.90-7.78 (m, 6H); ms: m/z 420/418/416 ($M^{+\cdot}$).

Anal. Calcd. for $C_{21}H_{18}Cl_2N_2O_3$: C, 60.44; H, 4.35; N, 6.71. Found: C, 60.14; H, 4.19; N, 6.88.

Synthesis of **3a** from 11-Hydroxytetrahydrocarbazolenine **5** (n = 4) and **2a**.

A solution of **2a** (0.5 mmole) and **5** (n = 4) (1.5 mmoles) prepared according to the literature [13], in chloroform (10 ml) was stored at room temperature for 2 days. After evaporation of the solvent **3a** was isolated in 90% yield by column chromatography (silica gel, hexane-ethyl acetate 5:1).

Crystallographic Analysis.

Suitable crystals of **3a** for X-ray diffraction studies were formed from ethanol. Preliminary oscillation and Weissenberg

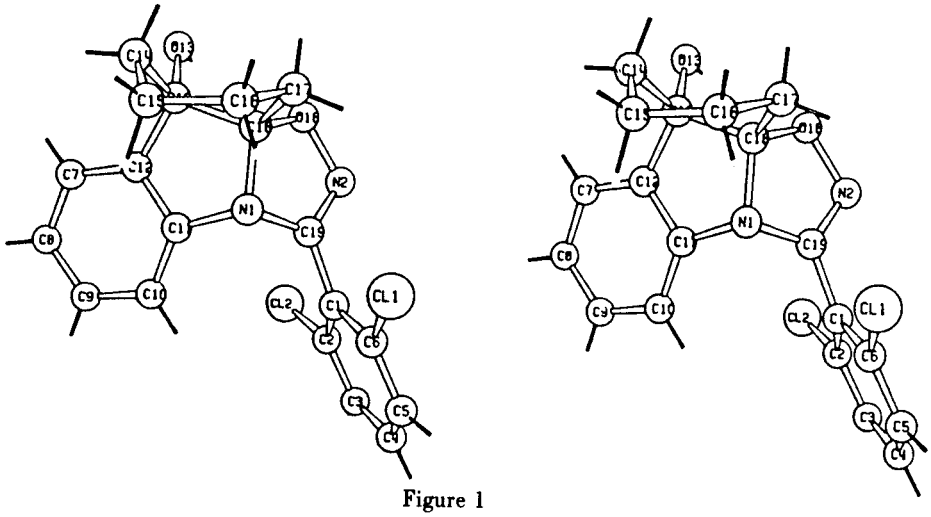


Figure 1

photographs indicated the space group $P2_1/c$. Unit cell dimensions and diffraction intensities were measured with Nb-filtered Mo radiation (λ = 0.71069 Å) on a Syntex $P2_1$ diffractometer. Unit cell dimension, a = 8.967(1), b = 16.043(2), c = 14.192(2)Å, β = 92.17°(1)Å, V = 2040.1(5)Å^3 were determined by a least-squares fit of 2θ angles for 15 reflections ($18 < 2\theta < 25°$); Z = 4 D (calcd.) = 1.371 g cm^{-3}. The θ-2θ technique was employed for the intensity recording, with scan speed variable 2.5-20.0 deg. min^{-1}, scan range 1.8 deg plus a_1-a_2 separation and background counting 0.5 of scan time. The limit of 2θ was 48°. The intensities of three standards monitored after every 67 reflections showed less than 3% fluctuation. Lp but no absorption correction was performed. The structure was solved by direct methods and was refined by blocked full matrix least-squares, in which $\Sigma w\Delta^2$ was minimized using the SHELX 76 program [16]. The weighting scheme was $1/w = \sigma^2(F_o) + 0.0008\ F_o^2$. A difference Fourier map showed the existence of a solvent molecule (ethanol) hydrogen bonded to O(13). The final refinement gave R = 0.0397 and R_w = 0.0511 for 2369 observed reflections with $F_o \geq 5.0\sigma(F_o)$. The number of refined parameters was 333 and S = 1.66. An ORTEP view of the structure is presented in Figure 1.

Lists of the positional and of anisotropic thermal parameters of the non-H atoms, of the positional parameters of the hydrogen atoms and bond lengths and angles are given in Tables II, III, IV and V.

REFERENCES AND NOTES

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