STUDIES ON NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS. NOVEL SYNTHESIS OF NAPHTHO[1,2-*b* AND 2,1-*b*][1,8]NAPHTHYRIDINES AND OXIDATION REACTIONS WITH PEROXY ACIDS

Isao Takeuchi,[a] Koosuke Asai,[a] Yoshiki Hamada,*[a] Katsuyoshi Masuda,[a] Hiroko Suezawa,[b] Minoru Hirota,[b] Yukihisa Kurono,[c] and Keiichiro Hatano[c]

[a] Faculty of Pharmacy, Meijo University, 150 Yagotoyama Tempaku-ku, Nagoya 468, Japan, [b] Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University, 156 Tokiwadai Hodogaya-ku, Yokohama 240, Japan, and [c] Faculty of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Abstract - A modified Friedländer condensation of 2-aminonicotinaldehyde with α– and β–naphthols lead successfully to two new naphtho[1,2-*b* and 2,1-*b*][1,8]-naphthyridines in a single synthetic procedure. The oxidation of the naphthonaphthyridines with peroxy acids afforded novel products such as a seven-membered oxazepine moiety. Structures were characterized by standard spectroscopy. The crystal and molecular structures (**3**) and (**4**) were determined by X-ray analyses.

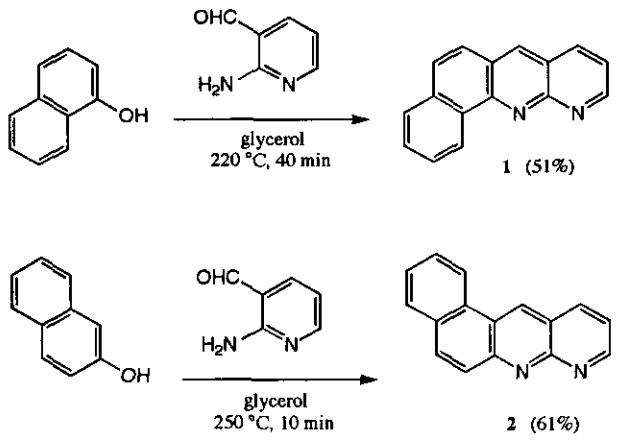
Many mutagens and carcinogens are present in polycyclic aromatic hydrocarbons and/or nitrogen-containing heterocycles. It is well-known that the metabolic redox reactions *in vivo* are essential to the formation of these compounds, such as benz[*a*]anthracene,[1] benz[*a*]pyrene,[2] and 4-nitroquinoline *N*-oxide (4-NQO), all possessing carcinogenic activity. The chemical derivatives of these polyheterocyclic compounds, *e.g.*, amsacrin[3] of acridine analogues, express the anticancer activity, the extent depending on the very potent inhibitor of DNA nicking-closing enzyme topoisomerase II.[4] This reflects the variation in and complexity of biological metabolic reactions of the aromatic and heterocyclic compounds.

Naphthonaphthyridine is a tetracyclic aromatic hydrocarbon containing two nitrogens in its ring. Four naphthonaphthyridine isomers as potential sources of biological bifunctional activity were synthesized in our previous study.[5] Seven of 36 possible naphthonaphthyridine isomers have been prepared by us and others.[6] The chemical reactions of naphthonaphthyridine compounds are little understood. An important reaction in the metabolism of non-biomaterials and/or drugs is oxidation catalyzed by oxygenase such as P450. Peroxygenase and catalase have partial metabolic roles. Two new isomers were thus synthesized by a convenient modification of the Friedländer condensation and their biomimetic oxidation was examined using peroxy compounds for elucidation of basic reactions and functions. Novel oxidation products including a seven-membered oxazepine moiety have been produced and their structures characterized by standard ir, uv-vis, nmr, and X-ray analysis. The synthesis and oxidation of two naphthonaphthyridine isomers and their crystal and molecular structures are discussed in the following.

RESULTS AND DISCUSSION

The naphthonaphthyridine isomer was previously synthesized by the Skraup reaction using amino-benzoquinolines as starting materials. The difficulty in preparing aminobenzoquinolines in adequate amounts and low yields of target compounds demonstrated the need for improved synthetic methods. A modified Friedländer condensation reaction of 2-aminonicotinaldehyde[7] with naphthols provided naphtho-naphthyridines in a single procedure. Naphtho[1,2-*b*][1,8]naphthyridine (**1**) from α-naphthol and naphtho[2,1-*b*][1,8]naphthyridine (**2**) from β-naphthol were obtained as shown in Scheme 1 under conditions essentially the same as for the Ullmann-Fetvadjian reaction.[8] The reaction conditions for **1** are summarized in Table 1. Decrease in reaction temperature lessened yield. The addition of glycerol as solvent improved yield by 1.7 times as much. PPA and diphenyl ether as solvents and $ZnCl_2$ as catalyst caused no significant increase in yield. The best yield for **1** was 51% by condensation at 220°C for 40 min in glycerol without $ZnCl_2$ (Entry 13). The best yield for the angularly closed product (**2**) was 61% at 250°C for 10 min in glycerol. No side reaction products (linear cyclic products) could be detected in the synthesis of **2**. The chemical properties of **1** were the same as those of an authentic sample obtained by the dehydrogenation of 5,6-tetrahydronaphtho[1,2-*b*][1,8]naphthyridine[9] with palladium on carbon in *p*-cymene. The structures of **1** and **2** were confirmed by ^{1}H-nmr data in Tables 2 and 3 and nOe measurements.

The oxidation of naphthonaphthyridines with hydrogen peroxide and *m*-chloroperbenzoic acid (*m*-CPBA) in acetic acid and chloroform, respectively, afforded products such as *N*-oxide (Scheme 2). Each product could be separated by a routine chemical method, purified, and in some cases recrystallized. The structures



Scheme 1

Table 1. Reaction Conditions of the Cyclization of **1**

Entry No.	α-Naphthol (m mol)	Aldehyde[a] (m mol)	Temp (°C)	Time (min)	Solvent or catalyst	Yield (**1**) (%)	Recovery of Aldehyde[a] (%)
1	5.0	5	240	10		26	
2	7.5	5	240	10		31	
3	7.5	5	220	10		30	
4	7.5	5	150	30		11	15
5	7.5	5	160	30	PPA	25	
6	7.5	5	180	30	diphenyl ether	26	17
7	7.5	5	170	7	$ZnCl_2$	13	
8	7.5	5	180	4	$ZnCl_2$	21	
9	7.5	5	190	30	$ZnCl_2$, DMA	25	
10	7.5	5	180	30	$ZnCl_2$, glycerol	12	
11	7.5	5	180	30	glycerol	30	15
12	7.5	5	180	60	glycerol	36	
13	7.5	5	220	40	glycerol	51	
14	7.5	5	240	10	glycerol	47	10
15	7.5	5	240	20	glycerol	47	

a) 2-Aminonicotinaldehyde

in Scheme 2 were determined by spectroscopy.

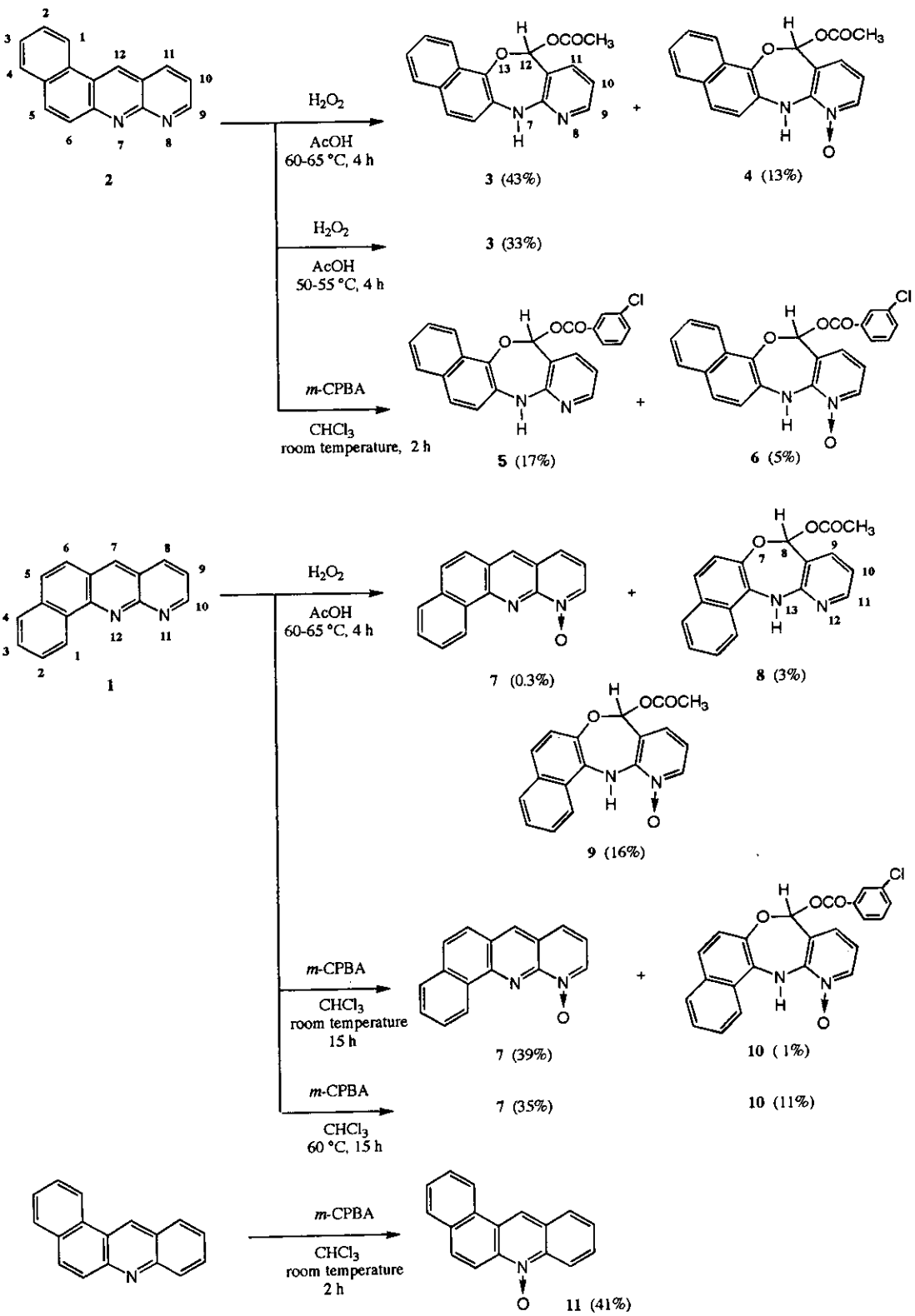
Reactions of **2** with 30% H_2O_2 in acetic acid at 60-65°C for 4 h afforded **3** and **4**. The overall ^{1}H-nmr spectrum of **3** was essentially the same as that of **4**. Proton signals due to positions 9, 10, and 11 of the pyridine ring showed double doublets and signals at positions 10 and 11 of compound (**4**) shifted to the higher magnetic field than that of **3**, indicating an *N*-oxide at position 8 of compound (**4**). Ir NH bands at 3260 and 3180 cm^{-1} (KBr) for **3** and **4** and blue shifts of uv λ max due to tetracyclic aromatic nuclei suggest the addition of peracetic acid at positions 12. To elucidate the structure of **4**, nOe and HMBC spectroscopy was carried out. NOe of proton at position 1 (*peri-* to position 12) (0.6%) was, unexpectedly, less than that at position 11 (9.6%), indicating the distance between protons at positions 1 and 12 to be larger than between positions 11 and 12. HMBC measurements for **4** (Figure 1), suggested seven-membered ring enlargement of the middle pyridine ring. To confirm the above structures, X-ray crystallography was conducted (Figure 2). X-ray molecular models demonstrated the formation of a seven-membered 1,4-oxazepine ring moiety for **3** and **4**. Reaction of **2** with peracetic acid failed to afford an *N*-oxide at position 7.

The structures of **5** and **6**, from reaction of **2** with *m*-CPBA, were determined by elemental analysis, mass and ^{1}H-nmr spectroscopy and nOe and HMBC data.

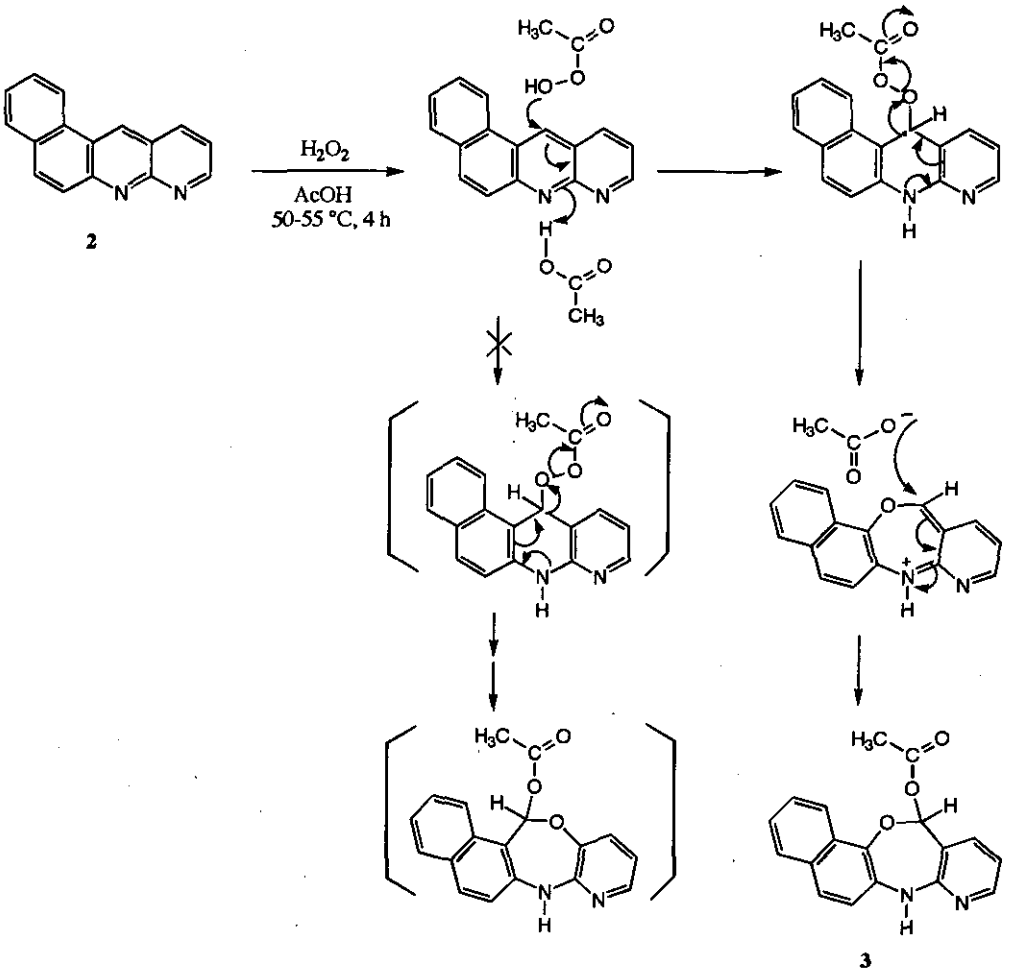
Reaction of **1** with 30% hydrogen peroxide in acetic acid at 60-65°C for 4 h gave **7**, **8**, and **9** in 0.3%, 3%, and 16% yields, respectively. The structure of **7** was found to be an *N*-oxide at position 11 based on a comparison of proton signals at positions 8, 9, and 10 of compound (**1**) with those of compound (**7**). From nOe and HMBC, **8** and **9** were found to be seven-membered 1,4-oxazepines similar to those of **3** and **4**.

Reaction of **1** with *m*-CPBA in chloroform at room temperature for 15 h afforded **7** (ordinary *N*-oxide at position 11) and **10** (seven-membered 1,4-oxazepine) in 39% and 1% yields, respectively. Increase in temperature to 60°C in this reaction caused the yield of **10** to be 11%.

The formation of a seven-membered 1,4-oxazepine by peroxy acid addition and the oxidation of **1** and **2** is reported here for the first time, since no such a product is found in similar reactions of dicyclic 1,8-naphthyridine[10] and tricyclic acridine.[11] In the reaction of acridine with peroxybenzoic acid, 2-(2-hydroxyanilino)benzaldehyde was formed as a side product.[11] Reaction of tetracyclic 7-azabenz[*a*]anthracene (containing one nitrogen in its ring system) with *m*-CPBA afforded only the ordinary 7-azabenz[*a*]anthracene 7-oxide (bottom in Scheme 2), but no seven-membered 1,4-oxazepine, indicating strongly a nitrogen at position 8 to be required for 1,4-oxazepine formation.


2
H_2O_2
AcOH
60-65 °C, 4 h
3 (43%)
4 (13%)
H_2O_2
AcOH
50-55 °C, 4 h
3 (33%)
m-CPBA
$CHCl_3$
room temperature, 2 h
5 (17%)
6 (5%)
1
H_2O_2
AcOH
60-65 °C, 4 h
7 (0.3%)
8 (3%)
9 (16%)
m-CPBA
$CHCl_3$
room temperature
15 h
7 (39%)
10 (1%)
m-CPBA
$CHCl_3$
60 °C, 15 h
7 (35%)
10 (11%)
m-CPBA
$CHCl_3$
room temperature
2 h
11 (41%)

Scheme 2



Scheme 3

The photolysis of acridine 10-oxide[12] and its methyl derivatives[13] in methanol gives 1,4-oxazepine due to solvent addition. Ring expansion in this study may thus be considered as a novel reaction that occurs through routes differing from photochemical synthesis. For 1,4-oxazepine formation from **1** and **2** with peroxy acids, the reaction mechanism shown in Scheme 3 is proposed.

ACKNOWLEDGMENT

The authors are grateful to the members of the Analysis Center of Meijo University for conducting the elemental analysis.

EXPERIMENTAL

^{1}H-Nmr spectra were recorded with a JEOL JNM GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the δ scale (ppm). The following abbreviations are used: s=singlet, d=doublet, dd=double doublet, and m=multiplet. Ms was taken with a Hitachi GC-MS M-80

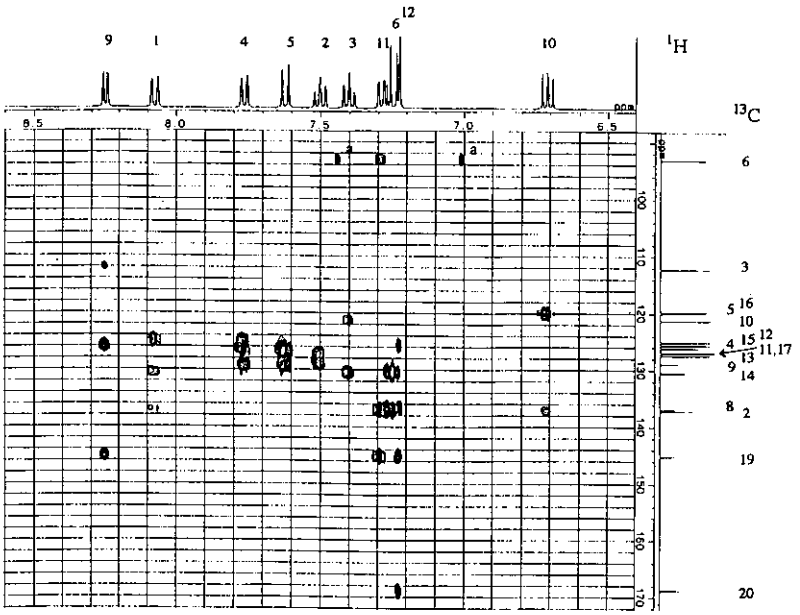
Table 2. ^{1}H-Nmr Spectral Data for Compounds (2-6, 11)

Compd No.	Solvent	Chemical Shifts (δ)												
		H-1	H-2	H-3	H-4	H-5	H-6	H-8	H-9	H-10	H-11	H-12	-NH	-COR
2	$CDCl_3$	8.71 m	7.73 m	7.68 m	7.91 m	8.00 d ($J_{5,6}$=9.4)	8.12 d		9.26 dd ($J_{10,11}$=8.4, $J_{9,10}$=4.0, $J_{9,11}$=2.0)	7.52 dd	8.42 dd	9.39 s		
	DMSO-d_6	9.01	7.86	7.82	8.10	8.23	8.02		9.29	7.74	8.74	10.04		
														Acetyl
3	$CDCl_3$	8.09 m	7.48 m	7.35 m	7.73 m	7.56 d ($J_{5,6}$=8.7)	7.05 d		8.22 dd ($J_{10,11}$=7.4, $J_{9,10}$=4.7, $J_{9,11}$=1.7)	6.79 dd	7.62 dd	7.23 s	7.50 s	1.97 s
4	$CDCl_3$	8.08 m	7.51 m	7.41 m	7.78 m	7.64 d ($J_{5,6}$=8.7)	7.25 d		8.26 dd ($J_{10,11}$=7.7, $J_{9,10}$=6.4, $J_{9,11}$=1.0)	6.73 dd	7.30 dd	7.24 s	9.83 s	1.98 s
														Benzoyl
5	$CDCl_3$	8.08 *m*	7.39 *m*	7.25 *m*	7.69 *m*	7.56 d ($J_{5,6}$=8.7)	7.08 d		8.24 dd ($J_{10,11}$=7.4, $J_{9,10}$=4.7, $J_{9,11}$=1.7)	7.79 dd	7.72 dd	7.46 s	7.34 s	7.22-7.70
	DMSO-d_6	7.95	7.39	7.39	7.75	7.64	7.56		8.29	6.88	7.92	7.48	9.89	7.43-7.66
6	$CDCl_3$	8.09 m	7.39 m	7.36 m	7.74 m	7.65 d ($J_{5,6}$=8.7)	7.30 d		8.30 dd ($J_{10,11}$=7.7, $J_{9,10}$=6.7, $J_{9,11}$=1.0)	6.77 dd	7.40 dd	7.47 s	9.90 s	7.28-7.75
	DMSO-d_6	7.98	7.45	7.35	7.81	7.71	7.82		8.46	6.94	7.65	7.59	10.23	7.46-7.69
ABA[a]	$CDCl_3$	8.75 m	(7.57 - 7.86)		7.89 m	7.95 d ($J_{5,6}$=9.3)	8.02	8.28 m	(7.57-7.86)		8.09 m	9.41 s		
11	$CDCl_3$	8.72 m	(7.64 - 7.88)		7.92 m	7.99 d ($J_{5,6}$=9.4)	8.79	8.93 m	(7.64-7.88)		8.10 m	8.95 s		

a) 7-Azabenzo[*a*]anthracene

Table 3. ^{1}H-Nmr Spectral Data for Compounds (1, 7-10)

Compd No.	Solvent	Chemical Shifts (δ)												
		H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	-NH	-COR
1	$CDCl_3$	9.68 m	(7.77-7.82)		7.91 m	(7.78, 7.79) d ($J_{5,6}$=9.4)	d	8.71 s	8.43 dd ($J_{8,9}$=8.4, $J_{9,10}$=4.0, $J_{8,10}$=2.0)	7.55 dd	9.30 dd			
	DMSO-d_6	9.40	(7.83-7.89)		8.07	7.94	8.01	9.35	8.70	7.72	9.29			
7	$CDCl_3$	9.67 m	(7.78-7.83)		7.88 m	7.71 d ($J_{5,6}$=9.1)	7.81 d	8.71 s	7.85 dd ($J_{8,9}$=8.4, $J_{9,10}$=6.1, $J_{8,10}$=1.0)	7.33 dd	8.85 dd			
														Acetyl
8	$CDCl_3$	8.03 m	(7.44 -7.60)		7.85 m	7.21 d ($J_{5,6}$=8.7)	7.45 d		7.01 s	7.61 dd ($J_{9,10}$=7.4, $J_{10,11}$=4.7, $J_{9,11}$=1.7)	6.80 dd	8.24 dd	7.72 s	2.08 s
9	$CDCl_3$	8.19 m	7.63 m	7.52 m	7.87 m	7.23 d ($J_{5,6}$=8.7)	7.55 d		7.03 s	7.31 dd ($J_{9,10}$=8.1, $J_{10,11}$=6.4, $J_{9,11}$=1.3)	6.74 dd	8.32 dd	10.61 s	2.10 s
														Benzoyl
10	$CDCl_3$	8.22 m	7.64 m	7.52 m	7.85 m	7.24 d ($J_{5,6}$=8.7)	7.52 d		7.26 s	7.40 dd ($J_{9,10}$=7.7, $J_{10,11}$=6.4, $J_{9,11}$=1.3)	6.78 dd	8.35 dd	10.66 s	7.32-7.89

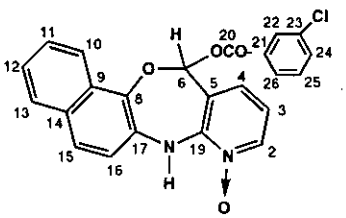


a) Noise

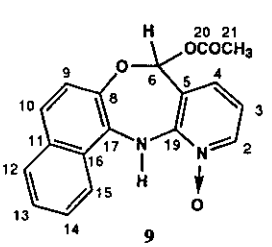
Figure 1. HMBC spectrum of compound **4** in $CDCl_3$

Table 4. ^{13}C-Nmr Spectral Data for Compounds (**4-6** and **9**) in $CDCl_3$

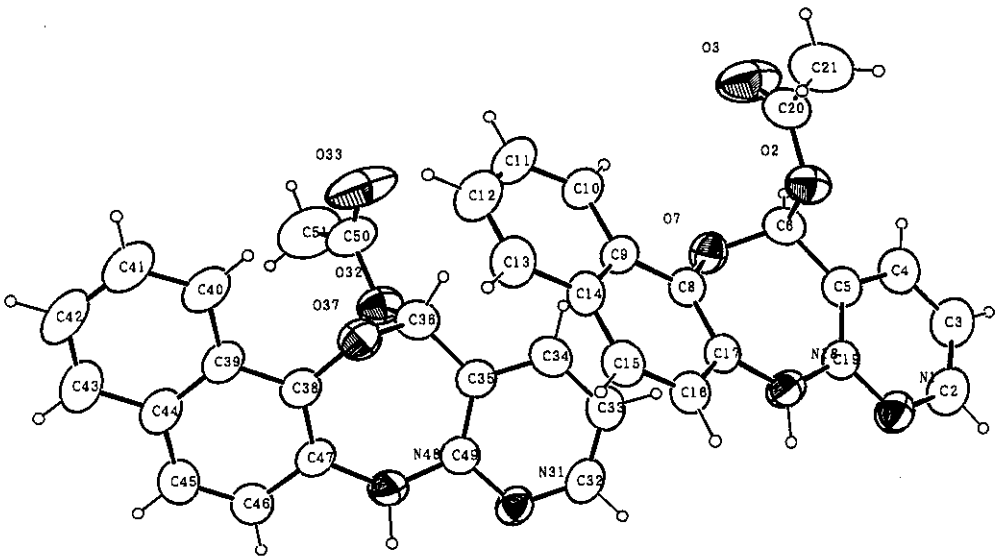
	Compounds (No.)			
C (No.)	**4**	**5**	**6**	**9**
2	137.17	149.47	137.41	137.06
3	112.25	114.48	112.43	112.20
4	126.15	136.82	126.25	125.76
5	119.96	117.70	119.94	120.02
6	93.13	95.47	93.89	93.40
8	136.94	134.75	134.73	140.93
9	128.93	129.43	128.95	122.38
10	121.28	121.31	121.31	124.05
11	126.96	126.90	127.10	131.68
12	125.07	124.51	125.21	128.63
13	127.41	127.35	127.46	125.23
14	130.10	130.13	130.10	126.96
15	125.60	125.40	125.87	120.21
16	119.77	119.41	119.76	125.47
17	126.96	129.02	126.97	125.90
19	145.18	153.17	145.33	145.27
20	168.77	163.70	163.30	168.60
21	20.54	130.82	130.60	20.67
22		129.94	129.86	
23		136.37	137.05	
24		133.60	133.96	
25		129.72	129.90	
26		127.92	127.94	



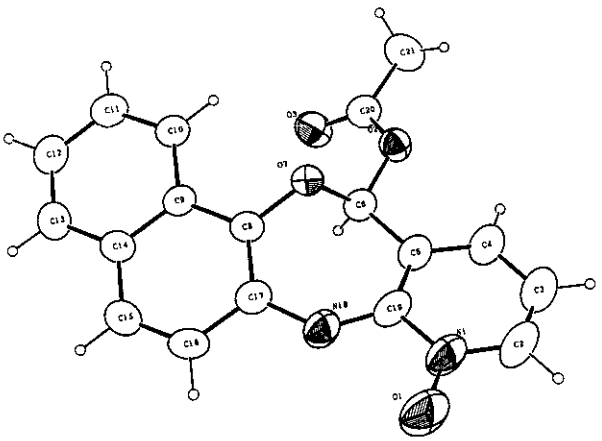
6



9



Compound (**3**)



Compound (**4**)

Figure 2. Perspective views of **3** and **4** with atomic labels and thermal ellipsoids at 50% probability for non-hydrogen atom. Hydrogens are shown as arbitrary circles. Octant shaded ellipsoids are nitrogen and oxygen atoms.

spectrometer. Ir and uv-vis spectra were recorded on a JASCO IRA-1 and a Shimadzu UV-240 spectrophotometer, respectively.

Naphtho[1,2-*b*][1,8]naphthyridine (1)

A mixture of α-naphthol (1.08 g, 7.5 mmol) and 2-aminonicotinaldehyde (0.61 g, 5 mmol) was heated for 40 min at 220°C in glycerol (5 ml). The cooled reaction mixture was dissolved in $CHCl_3$ and washed with 5% NaOH. The $CHCl_3$ solution was extracted with 18% HCl, the aqueous solution was neutralized with

Table 5. Summary of Crystal Data and Intensity Collection Parameters for **3** and **4**

	3	**4**
Formula	$C_{18}H_{14}N_2O_3$	$C_{18}H_{14}N_2O_4$
F.W., amu	306.3	322.1
Crystal dimensions (mm^3)	0.15 x 0.24 x 0.42	0.12 x 0.36 x 0.42
Space group	$P2_1/n$	$P2_1/c$
Temperature	293 K	293 K
a, Å	9.515 (1)	18.905 (1)
b, Å	21.681 (1)	10.976 (1)
c, Å	14.825 (1)	7.470 (2)
β, °	103.09 (1)	100.90 (1)
V, $Å^3$	2978.4 (8)	1521.8 (6)
Z	8*	4
F (000)	1280	672
Calcd density (*Dc*) (g/cm^3)	1.366	1.407
Radiation	graphite monochromated Mo *K*α	
μ (cm^{-1})	0.88	0.94
2θ range (°)	4 - 50	
Scan technique	$\omega - 2\theta$	
Scan range (ω, °)	$0.42 + 0.52 \tan\theta$	$0.82 + 0.55 \tan\theta$
Criterion for observation	$Fo > 3\sigma(Fo)$	
Measured data	5732	3042
Unique obsd data	3223	1840
*R***	0.053	0.056
*Rw***	0.052	0.058
No. of Variables	415	217

* Two independent molecules in an asymmetric unit.

** $R = \Sigma \| Fo| - |Fc| \| / \Sigma |Fo|$, $Rw = [\Sigma w(|Fo| - |Fc|)^2 / \Sigma wFo^2]^{1/2}$ with unit weight.

28% NH_4OH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was recrystallized from MeOH to give 0.59 g (51%) of **1** as yellow needles, mp 213-215°C. Ms *m/z* : 230 (M^+). Ir (KBr): 3050, 1595, 1523, 1465 cm^{-1}. Uv (cyclohexane) λmax (log ε)=217 (4.11), 231 (4.19), 249 (4.12), 275 (4.27), 286 (4.34), 336 (3.42), 352 (3.51), 371 (3.69), 391 (3.78). NOe: irradiation (DMSO-d_6) at δ 9.15 (H-7)--17.7% and 18.0% enhancement at δ 8.01 (H-6) and δ 8.71 (H-8); irradiation (DMSO-d_6) at δ 8.08 (H-4)-- 11.6% and 13.1% enhancement at δ 7.88 (H-3) and δ 7.94 (H-5). *Anal.* Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.72; H, 4.20; N, 12.36.

Naphtho[2,1-*b*][1,8]naphthyridine (2)

A mixture of β-naphthylamine (10.8 g, 7.5 mmol) and 2-aminonicotinaldehyde (6.1 g, 0.05 mol) was

heated for 10 min at 250°C. The cooled reaction mixture was treated in the same manner as in the reaction of **1**. The residue was recrystallized from MeOH to give 7.0 g (61%) of **2** as yellow needles, mp 216-218°C. Ms *m/z* : 230 (M^+). Ir (KBr): 3040, 1600, 1500, 1433, 1408 cm^{-1}. Uv (cyclohexane) λmax (log ε)=219 (3.73), 244 (3.68), 275 (3.70), 282 (3.74), 286 (3.74), 295 (3.41), 348 (2.99), 366 (3.21), 385 (3.30). NOe: irradiation (DMSO-d_6) at δ 10.04 (H-12)--32.8% and 17.5% enhancement at δ 9.01 (H-1) and δ 8.74 (H-11); irradiation (DMSO-d_6) at δ 8.10 (H-4)-- 14.6% and 17.6% enhancement at δ 7.82 (H-3) and δ 8.23 (H-5). *Anal.* Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.56; H, 4.62; N, 12.04.

Oxidation of 2 with Peracetic Acid (Method 1)

A solution of **2** (1.38 g, 6 mmol) and 30% H_2O_2 (2.0 ml, 18 mmol) in AcOH (60 ml) was stirred at 60-65°C for 4 h and then poured into 10 ml of water. The powdered MnO_2 (1 g) was added and the MnO_2 was filtered off after decomposition of H_2O_2. The filtrate was neutralized with aqueous 10% Na_2CO_3 and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on sillica gel and eluted with $CHCl_3$. The first elution gave 0.83 g (43%) of **3** as pale yellow needles, mp 191-193°C (from CH_3CN). Ms *m/z*: 306 (M^+), 263 (M^+-$COCH_3$), 247 (M^+-$OCOCH_3$). Ir ($CHCl_3$): 3400 (NH), 1754 (C=O). Uv (cyclohexane) λmax (log ε)=218 (4.51), 271 (4.44), 312 (4.06). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.25; H, 4.83; N, 9.26.

The second elution gave 0.24 g (13%) of **4** as pale brown plates, mp 211-213° C (from CH_3CN). Ms *m/z*: 322 (M^+), 306 (M^+-O), 289 (M^+-$COCH_3$), 263 (M^+-$OCOCH_3$), 247 (306 -$OCOCH_3$). High-resolution ms *m/z* : Calcd for $C_{18}H_{14}N_2O_4$ (M^+): 322.0951. Found: 322.0950. Calcd for $C_{18}H_{14}N_2O_3$ (M^+-O): 306.1002. Found: 306.0980. Ir ($CHCl_3$): 3220 (hydrogen bonding in NH---ON), 1763 (C=O). Uv (cyclohexane) λmax (log ε)=216 (4.65), 259 (4.62), 284 (4.23), 319 (4.29). NOe: irradiation $CDCl_3$) at δ 8.08 (H-1)--5.3% and 1.3% enhancement at δ 7.51 (H-2) and δ 7.25 (H-12); irradiation ($CDCl_3$) at δ 7.25 (H-12)-- 9.6% and 0.6% enhancement at δ 7.29 (H-11) and δ 8.08 (H-1).

Oxidation of 2 with *m*-CPBA (Method 2)

A solution of **2** (1.15 g, 5 mmol) and *m*-CPBA (1.73 g, 12 mmol) in $CHCl_3$ (50 ml) was stirred at room temperature for 4 h. A solution of 5% Na_2CO_3 (100 ml) was added to the reaction mixture and the whole was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was treated in the same manner as Method 1. The first elution gave 0.18 g (17%) of **5** as colorless needles, mp 205-207 ° C (from CCl_4). Ms *m/z*: 402 (M^+), 263 (M^+-CO-*m*-Cl-C_6H_5), 247

(M^+-OCO-*m*-Cl-C_6H_5). Ir ($CHCl_3$): 3400 (NH), 1735 (C=O). Uv (cyclohexane) λmax (log ε)=209 (4.97), 218 (4.95), 271 (4.83), 311 (4.44). NOe: irradiation (DMSO-d_6) at δ 7.56 (H-6)--18.0% and 9.0% enhancement at δ 9.89 (NH) and δ 7.64 (H-5); irradiation ($CDCl_3$) at δ 7.46 (H-12)-- 16.8% and 7.8% enhancement at δ 7.72 (H-11) and δ 8.08 (H-1). *Anal.* Calcd for $C_{23}H_{15}N_2O_3Cl$: C, 68.58; H, 3.75; N, 6.95. Found: C, 68.10; H, 3.78; N, 6.97.

The second elution gave 0.03 g (5%) of **6** as colorless needles, mp 225-227°C (from CCl_4). Ms *m/z*: 418 (M^+), 402 (M^+-O), 279 (M^+-CO-*m*-Cl-C_6H_5), 263 (M^+-OCO-*m*-Cl-C_6H_5). Ir ($CHCl_3$): 3220 (hydrogen bonding in NH---ON), 1740 (C=O). Uv (cyclohexane) λmax (log ε)=318 (4.33), 284 (4.30), 259 (4.66), 241 (4.33), 210 (4.82). NOe: irradiation (DMSO-d_6) at δ 7.82(H-6)--21.6% and 12.3% enhancement at δ 10.23 (NH) and δ 7.71 (H-5); irradiation ($CDCl_3$) at δ 7.59 (H-12)-- 7.8% and 6.0% enhancement at δ 7.65 (H-11) and δ 7.98 (H-1). *Anal.* Calcd for $C_{23}H_{15}N_2O_4Cl$: C, 65.96; H, 3.61; N, 6.69. Found: C, 65.48; H, 3.57; N, 6.69.

Oxidation of 1 with Peracetic Acid

A solution of **1** (0.46 g, 2 mmol) and 30% H_2O_2 (0.67 ml, 6 mmol) in AcOH (20 ml) was stirred at 60-65°C for 4 h. The reaction mixture was treated in the same manner as Method 1. The first elution gave 6 mg (0.3%) of **7** as the yellow needles, mp 232-234°C (from Me_2CO). Ms *m/z*: 246 (M^+), 230 (M^+-O), 229 (M^+-OH). Uv (cyclohexane) λmax (log ε)=213 (4.16), 229 (4.20), 272 (4.33), 286 (4.33), 314 (3.88), 328 (3.95), 364 (3.49), 383 (3.69), 405 (3.69). *Anal.* Calcd for $C_{16}H_{10}N_2O$: C, 78.04; H, 4.10; N, 11.38. Found: C, 77.78; H, 4.22; N, 11.20.

The second elution gave 0.02 g (3%) of **8** as yellow needles, mp 144-146°C (from CCl_4). Ms *m/z*: 306 (M^+), 263 (M^+-$COCH_3$), 247 (M^+-$OCOCH_3$). Ir ($CHCl_3$): 3420 (NH), 1752 (C=O). Uv (cyclohexane) λmax (log ε)=217 (4.57), 251 (4.38), 272 (4.07), 292 (3.84), 327 (4.05). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.16; H, 4.62; N, 9.04. The third elution gave 0.1 g (16%) of **9** as colorless needles, mp 88-89°C (from AcOEt). High-resolution ms *m/z*: Calcd for $C_{18}H_{14}N_2O_4$ (M^+): 322.0952. Found: 322.0950. Calcd for $C_{18}H_{14}N_2O_3$ (M^+-O): 306.1004. Found: 306.1008. Ir ($CHCl_3$): 3210 (hydrogen bonding in NH---ON), 1760 (C=O). Uv (cyclohexane) λmax (log ε)=219 (4.53), 252 (4.44), 339 (4.10). NOe: irradiation ($CDCl_3$) at δ 7.23 (H-6)--8.2% and 0.5% enhancement at δ 7.54 (H-5) and δ 7.03 (H-8); irradiation ($CDCl_3$) at δ 7.03 (H-8)--0.7% and 5.9% enhancement at δ 7.23 (H-6) and δ 7.30 (H-9).

Oxidation of 1 with *m*-CPBA

A solution of **1** (1.38 g , 6 mmol) and *m*-CPBA (2.07 g, 12 mmol) in $CHCl_3$ (50 ml) was stirred at room temperature for 15 h. The reaction mixture was treated in the same manner as Method 2. The first elution gave 0.57 g (39%) of **7**. The product was identical with **7** synthesized by means of the *N*-oxidation of **1** with peracetic acid.

The second elution gave 0.03 g (1%) of **10** as colorless needles, mp 178-180°C (from hexane). Ms *m/z*: 418 (M^+), 402 (M^+-O), 279 (M^+-CO-*m*-Cl-C_6H_5), 263 (M^+-OCO-*m*-Cl-C_6H_5). Ir ($CHCl_3$): 3210 (hydrogen bonding in NH---ON), 1736 (C=O). Uv (cyclohexane) λmax (log ε)=205 (4.19), 208 (4.19), 219 (4.10), 252 (3.94), 341 (3.61). NOe: irradiation ($CDCl_3$) at δ 7.30 (H-8)--5.5% and 1.9% enhancement at δ 7.40 (H-9) and δ 7.53 (H-6); irradiation ($CDCl_3$) at δ 7.40 (H-9)--8.4% and 9.2% enhancement at δ 6.78 (H-10) and δ 7.30 (H-8). *Anal.* Calcd for $C_{23}H_{15}N_2O_4Cl$: C, 65.96; H, 3.61; N, 6.69. Found: C, 65.53; H, 3.64; N, 6.44.

Oxidation of 7-Azabenzo[*a*]anthracene with *m*-CPBA

A solution of 7-azabenzo[*a*]anthracene (0.46 g , 2 mmol) and *m*-CPBA (1.38 g, 8 mmol) in $CHCl_3$ (50 ml) was stirred at room temperature for 2 h. The reaction mixture was treated in the same manner as Method 2. The elution gave 0.2 g (41%) of **11** as yellow prisms, mp 215-217°C (from AcOEt). Ms *m/z*: 245 (M^+), 229 (M^+-O), 228 (M^+-OH). *Anal.* Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71. Found: C, 82.91; H, 4.47; N, 5.66.

Crystal Structure Determination and Refinement

Crystals of both **3** and **4** suitable for X-ray analysis were obtained by slow evaporation of the MeCN or MeOH solution. A preliminary examination of the crystals on Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo *Kα* radiation (λ=0.71073 Å) indicated a monoclinic unit cell for both compounds. The space groups, $P2_1/n$ for **3** and $P2_1/c$ for **4**, were suggested from the systematic absence of each reflection. Least-squares refinements of the setting angles of 25 reflections, collected in the range of 18° $< 2\theta <$ 22° for the both, led to the crystal data summarized in Table 5. Net intensities were reduced to a set of relative structure factors by the application of the standard Lorentz and polarization factors. No absorption correction was made. The both structures were solved by the direct method and refined by difference Fourier and least-squares techniques.[14] Most non-hydrogen atoms of each molecule in an assymetric unit were found in each initial E-map. Subsequent difference Fourier syntheses revealed all non-hydrogen atomic positions. The non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms bound to carbon were included in calculated positions as fixed parameters. Final cycles

of full-matrix least-squares refinement were carried to convergence at R= 0.053 and Rw= 0.052 for **3** and R= 0.056 and Rw= 0.058 for **4**.[15] The final difference Fouriers for both were judged to be essentially featureless. The atomic coordinates for non-hydrogen atoms of **3** and **4** with the isotropic equivalent thermal factors are given in supplementary Tables.[16]

REFERENCES

1. A.W. Wood, R.L. Chang, W. Levin, R.E. Lehr, N, S-Ridder, J.M. Karle, D.M. Jerina, and A.H. Conney, *Proc. Natl. Acad. Sci. USA.*, 1977, **74**, 2746.
2. S.K. Yang, D.W. McCourt, J.C. Leutz , and H.V. Gelboin, *Science*, 1977, **196**, 1199.
3. a) W.A. Denny, B.C. Baguley, B.F. Cain, and M.J. Waring, "Mechanism of Action of Anticancer Drugs", eds. by S. Neidle and J. Waring, Macmillian, London, 1983; b) G.J. Atwell, B.C. Baguley, G.J. Finlay, G.W. Rewcastle, and W.A. Denny, *J. Med. Chem.*, 1986, **29**, 1769.
4. L. Yang, T.C. Rowe, E.M. Nelson, and L.F. Liu, *Cell*, 1985, **41**, 127.
5. I. Takeuchi, Y. Hamada, and M. Hirota, *Chem. Pharm. Bull.*, 1993, **41**, 747.
6. a) S.V. Kesser, Y.P. Gupta, P. Singh, S.K. Gupta, and P.S. Pahwa, *Indian Acad. Sci., Sect. A*, 1979, **88A**, 191 [*Chem. Abstr.*, 1979, **91**, 140743y]; b) Y.P. Gupta, P. Singh, S.K. Sharma, and P.S. Pahwa, *Indian J. Chem., Sect. B*, 1980, **19B**,400 [*Chem. Abstr.*, 1980, **93**, 239281z].
7. T.G. Majewicz and P. Caluwe, *J. Org. Chem.*, 1974, **39**, 720.
8. N.P. BuuHoi, *J. Chem. Soc.* (C), 1967, 213.
9. R.P. Thummel, Y. Decloitre, and F. Lefoulon, *J. Heterocycl. Chem.*, 1986, **23**, 689.
10. W.W. Paudler, D.J. Pokorny, and S.J. Cornrich, *J. Heterocycl. Chem.*, 1970, **7**, 291.
11. R.M. Acheson and B. Adcock, *J. Chem. Soc.* (C), 1968, 1045.
12. H. Mantsch, V. Zanker, W. Seiffert, and G. Prell, *Liebigs Ann. Chem.*, 1969, **723**, 95.
13. S. Yamada, M. Ishikawa, and C. Kaneko, *Tetrahedron Lett.*, 1972, 971.
14. The programs used include the modified versions of Busing and Levy's ORFLS, and ORFFE, and Johnson's ORTEP II.
15. The atomic scattering factors were taken from "International Tables for X-ray Crystallography," Vol IV, Kynoch Press, Birmingham (1974).
    $R= \Sigma \| Fo | - | Fc \| / \Sigma | Fo |$, $Rw= [\Sigma w (| Fo | - | Fc |)^2 / \Sigma w Fo^2]^{1/2}$ with unit weight.
16. Tables of the anisotropic temperature factors for non-hydrogen atoms and the idealized atomic coordinates for hydrogen atoms are also available from one of the authors (K. H.).

Received, 22nd May, 1996