

SYNTHESIS OF 2,3,5,6-TETRAHYDROIMIDAZO[2,1-*b*]THIAZOLESGirts Kaugars^{**}, Scott E. Martin^a, Stephen J. Nelson^a, and William Watt^b^aAnimal Health Discovery Research and ^bPhysical and Analytical

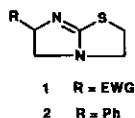
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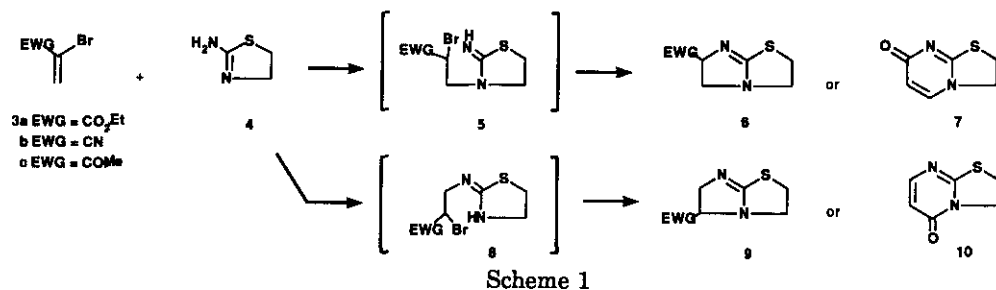
Abstract - The reactions of 2-amino-2-thiazoline with alkylating and acylating agents give initial reaction on the endocyclic nitrogen. Acyl groups, however, readily rearrange to the exocyclic nitrogen to give the products usually observed in these reactions. These observations clear up a considerable amount of confusion in the literature and lead to the efficient synthesis of 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles.

INTRODUCTION

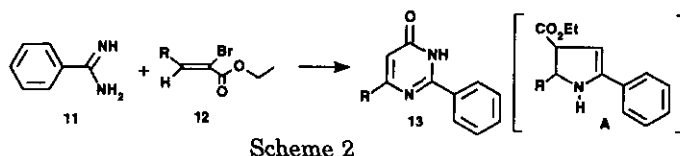
We were interested in synthesizing the bicyclic system (1), which would be readily convertible to analogs



of the immunomodulator and anthelmintic Levamisole (2), or its racemic form Tetramisole, should R be a functionality suitable for further modification. Our synthesis is shown in Scheme 1. Reaction of an α -bromo Michael acceptor (3) with the ring nitrogen of 2-amino-2-thiazoline (4), followed by dehydrobromination, would give the desired ring system (6). However, reaction of α -bromo Michael acceptors (12) with benzamidine (11) (Scheme 2)¹ gives the pyrimidone (13) rather than the 5-membered



ring compound (A), which is our desired type. Furthermore, in our starting material (4) the two nucleophilic sites are different and therefore can lead to 6 or 9 as well as the pyrimidone compounds (7) or (10) from 3a (Scheme 1) or the corresponding products from 3b and 3c.



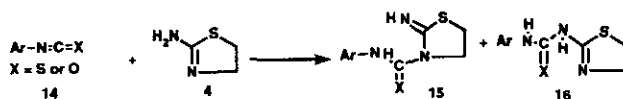
The problem, which has plagued chemists for several decades, and which we faced in this instance, is the question of regioselectivity in cases where two nucleophilic centers are present. The problem in a related system - endo- and exo-carbamoylation of 2-aminobenzimidazoles - has been investigated² and acylation of C-aminoazoles with amidine or guanidine structure has been recently reviewed.³

We examined the published literature for reactions of 4 and our own results for this system and concluded that the endocyclic nitrogen is always the more nucleophilic, the more reactive center, but that rearrangement reactions have often led to confusing results and incorrect structure assignments.

A review of the literature⁴⁻¹⁵ revealed that incorrect structure assignments were quite prevalent both in acylation-type⁴⁻¹² and alkylation¹³⁻¹⁵ reactions; many were later corrected. Most of the previous work⁴⁻¹⁵ implied that alkylation occurs on the ring nitrogen, but acylation on the exocyclic nitrogen. However, there is no general agreement on this point, possibly because intuitively a tertiary imino nitrogen would seem to be less nucleophilic than an amino, even though in the present instance both are a part of an

isothiourea functionality.

The earliest report of the reaction of **4** with acylating type agents seems to be in 1928,⁴ when **4** was reacted with aryl isothiocyanates (**14**) (Scheme 3). At <50°C the reaction was reported to go on the ring nitrogen (**15**), but at higher temperatures on the exocyclic one (**16**). Structure proof at that time was essentially nil,



Scheme 3

but the structures indeed were correct as verified by Rasmussen⁵ with an X-ray structure determination of the phenyl isothiocyanate analog (**15**). Isomerization of **15** to **16** (X = O) occurred on heating; dissociation and apparent rearrangement of the less stable sulfur analog occurred in DMF at -30°C.

Careful work by Yamamoto⁶ established analogous behavior for methyl isothiocyanate and corrected some earlier structure misassignments.⁷ This work then allowed Karady⁸ to assign the correct structures from the methyl isocyanate reaction.

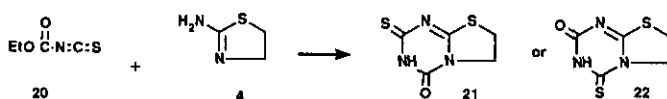
The structure of the product from the reaction of **4** with benzoyl isothiocyanate was established correctly by Klayman.⁹ The cyclic product (**18**) arises from initial reaction of the aminothiazoline endocyclic nitrogen of **4** with the isothiocyanate functionality of **17**, then cyclization and dehydration (Scheme 4). In this case the reaction product from exocyclic nitrogen reaction was also obtained, but was inert to cyclization.



Scheme 4

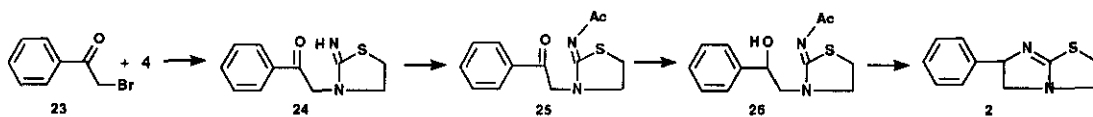
However, very recently Rahman,¹⁰ without citing the Klayman paper, assigned the alternate structure (**19**) to the product from the same reaction. The melting points are very similar, but unfortunately the ¹H nmr data were reported in grossly different solvents (CDCl₃ and trifluoroacetic acid) and thus make comparisons useless.

The reaction of **4** with ethoxycarbonyl isothiocyanate (**20**) presents the same type of a problem. The original assignment as **21** by Capuano¹¹ is incorrect. Klayman¹² determined the structure to be **22** by X-ray. Again, the initial reaction is on the endocyclic nitrogen and the isothiocyanate, then cyclization (Scheme 5).



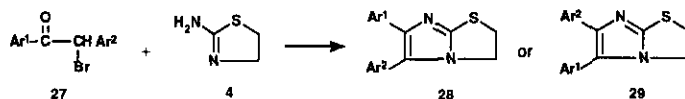
Scheme 5

Alkylation reactions of **4** appear to have received less attention, even though Levamisole (**2**) and Tetramisole are made by such a process (Scheme 6).¹³ However, there is a recent example of incorrect



Scheme 6

structure assignment as **29**,¹⁴ which was later corrected to **28** (Scheme 7).¹⁵ As before, the initial reaction is between the endocyclic nitrogen of **4** and the phenacyl bromide (**27**).



Scheme 7

The general problem then is that alkylation and acylation reactions of ambident nucleophiles, especially the ones in which the nucleophilic sites are similar, often result in nagging problems of uncertain regiochemistry, whose final resolution may well require an X-ray structure determination. When the original structure assignments have been correct, the result has been a matter of luck more than anything else.

RESULTS AND DISCUSSION

A. Alkylation OF 4 with α -Bromo Michael Acceptors (3a-c)

We examined several compounds of type 3, some of which are commercially available, but can also be conveniently prepared *in situ* by a bromination/dehydrobromination sequence starting with the α,β -

Table 1. Spectral data for 6a-c.

EWG	^{13}C nmr [δ (ppm)]			^1H nmr [δ (ppm)]	
	C ₅	C ₆	C ₈	CO ₂ Et	C ₆ -H
a CO ₂ Et	52.0	74.8	175.4	4.75	
b CN	53.6	61.0	178.6	4.87	
c CO Me	50.4	81.9	174.4	4.88	

unsaturated compounds. The ^1H and ^{13}C nmr data of the products are shown in the Table 1. These data show that all compounds are of the same type, are not pyrimidones, but do not distinguish between 6 and 9. However, one product (6c or 9c) was easily air oxidized to what turned out to be 30. This compound gave crystals suitable for single crystal X-ray structure determination, which showed that the structure was indeed of type (6) (Figure 1). Therefore the reaction sequence for our synthesis is alkylation (1,4-addition) on the ring nitrogen to give 5, which then cyclizes to 6.

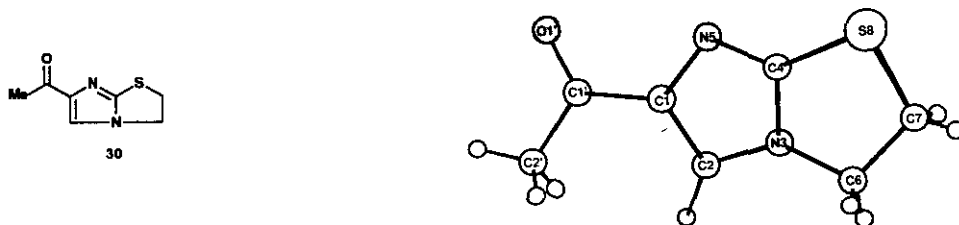
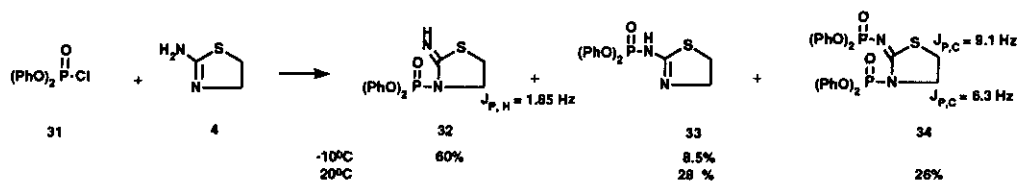


Figure 1. ORTEP drawing of 30.

B. Phosphorylation of 4 with Diphenyl Chlorophosphate (31).

The second aspect of this problem is the acylation type reaction, which, as described in the introduction, is reported to give both exocyclic and endocyclic nitrogen acylation. Our result indicates that exocyclic acylation results from a rearrangement as shown by the following phosphorylation reactions (Scheme 8).

We chose the phosphorylation reaction as a model for acylation because the possible products should be readily differentiated by long-range C-P coupling in the ^{13}C nmr. At -10°C compounds **(32)** (60%) and **(33)**



Scheme 8

(8.5%) were obtained, but at ambient temperature (20°C) **(33)** (28%) and **(34)** (26%). In addition, recrystallization of **(32)** from boiling ethyl acetate gave **(33)**, which demonstrates the ready rearrangement of an acyl type group from the ring nitrogen to the exocyclic nitrogen.

Compounds **(32)** and **(33)** could be differentiated on the basis of ^1H and ^{13}C nmr spectra. Compound **(32)** showed P-N-CH₂ coupling (1.85 Hz) in the ^1H nmr spectrum; compound **(34)** showed similar coupling. The ^{13}C nmr spectrum of **(34)** showed P-N-C coupling to N-CH₂ (6.3 Hz) and P-N-C-C coupling to S-CH₂ (9.1 Hz); compound **(32)** gave broadened peaks for which the couplings could not be measured; compound **(33)** gave very sharp singlets as expected for that structure. The same types of measurements have been used to determine the structures of the related 2-methylamino analogs.¹⁶ The results are in full agreement with ours.

CONCLUSIONS

An analysis of the reactions described in the literature and our own studies show that nucleophilic reactions, both alkylation and acylation, of 2-amino-2-thiazoline (**(4)**) proceed by initial reaction on the more nucleophilic endocyclic nitrogen. However, the products from acylation type reactions are prone to 1,3-rearrangement and are then observed as acylated on the exocyclic nitrogen. Whether the unrearranged product can be isolated depends primarily on the reaction conditions, especially the temperature.

EXPERIMENTAL

General: Melting points were determined on a Mettler FP61 melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AM 300 spectrometer at 300 and 75 MHz, respectively, with tetramethylsilane as the internal standard. Elemental analyses were performed by the Physical and Analytical Chemistry unit of The Upjohn Company.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole-6-carboxylic acid ethyl ester (6a). Triethylamine (1.90 ml, 13.7 mmol) and 20 mg of hydroquinone was added to a solution of (3a) (1.89 g, 10.5 mmol) in 5 ml of MeOH at 5°C. 2-Amino-2-thiazoline (4) (1.10 g, 10.5 mmol) was then added. The solution was stirred for 15 min, the resultant white precipitate was filtered, and the filtrate was concentrated to a yellow oil. Chromatography over 75 g of silica gel with EtOAc gave 6a (1.45 g, 69%) as a colorless oil. ^1H Nmr (300 MHz, CDCl_3) δ 1.11 (t, $J = 7.2$ Hz, 3H), 3.00 (dt, $J = 6.6$ and 8.2 Hz, 1H), 3.15-3.22 (m, 2H), 3.30-3.50 (m, 3H), 3.95-4.10 (m, 2H), 4.75 (t, $J = 9.1$ Hz, 1H); ^{13}C nmr (75 MHz, CDCl_3) δ 13.9, 34.1, 48.3, 52.0, 60.9, 74.8, 171.1, 175.4; HRms for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ calcd 200.0619, found 200.0631.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole-6-carbonitrile (6b). Bromine (1.60 g, 10.0 mmol) in 5 ml of CH_2Cl_2 was added to a solution of acrylonitrile (530 mg, 10.0 mmol) in 20 ml of CH_2Cl_2 . The solution was heated to reflux, cooled to room temperature, and then triethylamine (3.50 ml, 25.0 mmol) followed by 2-amino-2-thiazoline (4) (1.02 g, 10.0 mmol) was added. The reaction mixture was stirred for 16 h at room temperature and then refluxed for 4 h. The reaction mixture was filtered and the filtrate concentrated to an orange oil. Chromatography over 50 g of silica gel with EtOAc gave 6b (978 mg, 64%) as a yellow oil. ^1H Nmr (300 MHz, CDCl_3) δ 3.04-3.52 (m, 6H), 4.87 (t, $J = 7.9$ Hz, 1H); ^{13}C nmr (75 MHz, CDCl_3) δ 34.7, 48.3, 53.6, 61.0, 118.9, 178.6. The hydrochloride was prepared in 95% yield with HCl gas in THF. Recrystallization from MeOH/ether gave the analytical sample, mp 204.6°C. ^1H Nmr (300 MHz, DMSO) δ 3.67-3.87 (m, 2H), 3.91-4.04 (m, 2H), 4.09-4.16 (m, 2H), 5.80 (dd, $J = 7.1$ and 9.4 Hz, 1H); ^{13}C nmr (75 MHz, DMSO) δ 37.3, 47.6, 51.5, 52.5, 117.2, 179.0. Anal. Calcd for $\text{C}_8\text{H}_8\text{N}_3\text{ClS}$: C, 37.80; H, 4.76; N, 22.04. Found: C, 37.47; H, 4.38; N, 21.50.

1-(2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-6-yl)ethanone (6c) and 1-(2,3-Dihydroimidazo[2,1-*b*]thiazol-6-yl)ethanone (30). Bromine (1.60 g, 10.0 mmol) in 5 ml of CH_2Cl_2 was added to a solution of

methyl vinyl ketone (0.70 g, 10.0 mmol) in 20 ml of CH_2Cl_2 at 0°C . A solution of triethylamine (3.5 ml, 25 mmol) in 5 ml of CH_2Cl_2 followed by 2-amino-2-thiazoline (4) (1.02 g, 10.0 mmol) in 15 ml of CHCl_3 was added to the reaction mixture. The reaction mixture was stirred for 72 h and concentrated to dryness. Chromatography over 150 g of silica gel with 96:2:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{Et}_3\text{N}$ gave **6c** (1.42 g, 84%) as an oil. ^1H Nmr (300 MHz, CDCl_3) δ 2.34 (s, 3H), 3.20-3.63 (m, 6H), 4.88 (dd, $J = 7.9$ and 9.4 Hz, 1H); ^{13}C nmr (75 MHz, CDCl_3) δ 27.5, 34.1, 48.4, 50.4, 81.9, 174.4, 207.5; both spectra show that **30** is also present in a detectable amount. After 4 weeks **6c** was rechromatographed over 500 g of silica gel with 5:95 $\text{MeOH}/\text{CHCl}_3$ to yield **30** as a crystalline solid, mp 159.6°C . ^1H nmr (300 MHz, CDCl_3) δ 2.49 (s, 3H), 3.86 (t, $J = 7.3$ Hz, 2H), 4.24 (t, $J = 7.3$ Hz, 2H), 7.61 (s, 1H), ^{13}C nmr (75 MHz, CDCl_3) δ 26.5, 34.8, 46.0, 121.0, 147.3, 151.0, 193.3. Anal. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{OS}$: C, 49.98; H, 4.79; N, 16.65; S, 19.06. Found: C, 49.81; H, 4.58; N, 16.57; S, 18.84.

(4,5-Dihydro-2-thiazolyl)phosphoramidic acid diphenylester (33) and [3-(Diphenoxyphosphinyl)-2-thiazolidinylidene]phosphoramidic acid diphenyl ester (34). Diphenyl chlorophosphate (0.52 ml, 2.50 mmol) was added to a solution of 2-amino-2-thiazoline (4) (255 mg, 2.50 mmol) and triethylamine (0.35 ml, 2.50 mmol) in 5 ml of CH_2Cl_2 . The reaction mixture was stirred for 16 h, diluted with water, and extracted twice with CHCl_3 . Chromatography on silica gel with 2:1 $\text{EtOAc}/\text{hexane}$ gave **34** (367 mg, 26%) as a colorless oil and **33** (232 mg, 28%) as a white solid, mp 150.5°C after recrystallization from EtOAc . **34**: ^1H Nmr (300 MHz, CDCl_3) δ : 3.15 (t, $J = 7.1$ Hz, 2H), 3.99 (t, $J = 7.1$ Hz 2H), 7.05-7.30 (m, 20H); ^{13}C nmr (75 MHz, CDCl_3) δ : 29.8, 29.9, 50.9, 51.0, 120.3, 120.4, 124.7, 125.8, 129.4, 129.8, 149.5, 149.6, 150.8, 150.9, 171.9.

33: ^1H Nmr (300 MHz, CDCl_3) δ : 3.31 (t, $J = 7.5$ Hz, 2H), 3.69 (t, $J = 7.5$ Hz, 2H), 7.11-7.33 (m, 10H), 7.95 (brs, 1H); ^{13}C nmr (75 MHz, CDCl_3) δ : 29.6, 46.3, 120.4, 120.4, 124.5, 129.4, 151.7, 175.8. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_3\text{PS}$: C, 53.89; H, 4.52; N, 8.38; S, 9.59. Found: C, 53.84; H, 4.69; N, 8.49; S, 9.61.

3-Diphenoxyphosphinyl-2-thiazolidineimine (32) and (4,5-Dihydro-2-thiazolyl)phosphoramidic acid diphenyl ester (33). A solution of 2-amino-2-thiazoline (4) (255 mg, 2.50 mmol) and triethylamine (0.35 ml, 2.50 mmol) in 5 ml of CH_2Cl_2 was cooled to -10°C and diphenyl chlorophosphate (0.52 ml, 2.50 mmol) in 2 ml of CH_2Cl_2 was added. The reaction mixture was stirred for 30 min at -10°C , then it was

diluted with water and extracted twice with CH_2Cl_2 , and concentrated to a colorless oil. Chromatography over silica gel with 2:1 EtOAc/hexane gave **32** (500 mg, 60%) as a white solid and **33** (120 mg, 8.5%).

32: ^1H Nmr (300 MHz, CDCl_3) δ : 3.03 (t, $J = 6.5$ Hz, 2H), 3.95 (dt, $J = 6.5$ and 1.85 Hz, 2H), 7.20-7.40 (m, 10H); ^{13}C nmr (75 MHz, CDCl_3) δ : 30.7, 52.5, 120.5, 125.6, 129.7, 150.0, 162.3.

Crystallography

Crystal data for 30 at 25 °C: $\text{C}_6\text{H}_8\text{N}_2\text{OS}$, $M_r = 156.15$, monoclinic, space group $\text{P}2_1/c$, $a = 4.956(2)$, $b = 10.059(1)$, $c = 16.889(6)\text{Å}$, $\beta = 114.85(3)$, $V = 764.1(4)\text{Å}^3$, $F(000) = 328$, $Z = 4$, $D_c = 1.36\text{gm/cm}^3$, $\mu(\text{Cu K}\alpha) = 30.87\text{ cm}^{-1}$, $0.16 \times 0.22 \times 0.48\text{mm}$, $\theta/2\theta$ scans, $2\theta_{\text{max}} = 136^\circ$, $N = 1091$, 91 parameters, $S = 2.88$, $wR(F^2) = 0.173$, $R = 0.071$ for 903 reflections with $F_o^2 > 3\sigma$.

Intensity measurements were collected at 25 °C with a Siemens $\text{P}2_1$ diffractometer controlled by a Harris computer. Monochromatized Cu $\text{K}\alpha$ ($\lambda = 1.5402$) radiation and a graphite monochromator were used for intensity measurement. The step-scan technique was used with a scan rate of $4^\circ/\text{min}$ and a scan width of 3.4° . Ten reflections periodically monitored showed no loss of intensity during the data collection. Of the 1091 unique reflections measured, 903 had intensities $>3\sigma$. Standard deviations in the intensities were approximated by the equation:

$$\sigma^2(\mathbf{I}) = \sigma^2(\mathbf{I})_{\text{counting statistics}} + 0.0136\mathbf{I}^2$$

where the coefficient of \mathbf{I} was calculated from the variations in intensities of the monitored reflections. Unit cell parameters were determined accurately by least squares fit of Cu $\text{K}\alpha_1$ 2θ values ($\lambda(\text{Cu K}\alpha_1) = 1.5402$) for 25 high 2θ reflections.¹⁷ Polarization corrections appropriate for a monochromator with 50% perfect character were applied. An absorption correction¹⁸ was applied: minimum transmission was 0.367 and the maximum transmission was 0.633. The structure was solved by direct methods, using RANTAN.¹⁹ Hydrogen atoms were clearly found in a difference map. The structure was refined by least squares with the coordinates and anisotropic thermal parameters for nonhydrogen atoms included in the refinement. Isotropic thermal parameters for hydrogen atoms were set 1/2 unit higher than the isotropic equivalent of the thermal parameter of the attached heavier atom. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle & Turner,²⁰ except, for hydrogens which were from Stewart, Davidson & Simpson.²¹ In the final refinement cycle, all shifts were

$<0.04\sigma$. A final difference map showed no peaks $>0.43e\text{\AA}^{-3}$. The CRYM system of computer programs was used²². A ball & stick drawing with atom numbering is shown in Figure 1. The final coordinates, bond lengths and angles are shown in Tables 2 & 3. Tables of hydrogen atom coordinates, anisotropic thermal parameters, structure factors are available from the author W.W.

Table 2. Fractional coordinates ($\times 10^4$) and $B_{eq}(\text{\AA}^2)$ for 30. Estimated standard deviations are in parentheses.

$$B_{eq} = 4/3(a^2B_{11} + b^2B_{22} + c^2B_{33} + abc\cos\alpha B_{12} + accos\beta B_{13} + bccos\gamma B_{23})$$

	x	y	z	B_{eq}
C(1)	9034(11)	2689(4)	2843(3)	3.1(2)
C(2)	7881(11)	3861(5)	2398(3)	3.4(2)
N(3)	5189(9)	3526(4)	1764(2)	3.0(2)
C(4)	4838(11)	2181(5)	1836(3)	3.3(2)
N(5)	7068(9)	1642(4)	2478(3)	3.8(2)
C(6)	2891(12)	4220(5)	1029(3)	3.9(2)
C(7)	287(12)	3275(6)	669(4)	3.8(2)
S(8)	1558(3)	1590(1)	1017(1)	5.02(6)
C(1')	11858(12)	2519(5)	3605(3)	3.4(2)
O(1')	12567(8)	1435(4)	3969(2)	4.7(2)
C(2')	13866(12)	3693(6)	3924(4)	4.3(2)

Table 3. Bond lengths (\AA) and angles ($^\circ$) for 30.

A. Bond lengths(\AA)

C(1)-C(2)	1.385(7)	C(4)-N(5)	1.298(6)
C(1)-N(5)	1.391(6)	C(4)-S(8)	1.737(5)
C(1)-C(1')	1.460(6)	C(6)-C(7)	1.510(7)
C(2)-N(3)	1.357(5)	C(7)-S(8)	1.817(6)
N(3)-C(4)	1.375(6)	C(1')-O(1')	1.228(6)
N(3)-C(6)	1.462(6)	C(1')-C(2')	1.491(7)

B. Bond angles($^\circ$)

C(2)-C(1)-N(5)	110.6(4)	N(5)-C(4)-S(8)	134.9(4)
C(2)-C(1)-C(1')	127.0(4)	C(1)-N(5)-C(4)	104.2(4)
N(5)-C(1)-C(1')	122.4(4)	N(3)-C(6)-C(7)	105.7(4)
C(1)-C(2)-N(3)	105.1(4)	C(6)-C(7)-S(8)	109.6(3)
C(2)-N(3)-C(4)	107.1(4)	C(4)-S(8)-C(7)	91.1(2)
C(2)-N(3)-C(6)	135.1(4)	C(1)-C(1')-O(1')	120.8(4)
C(4)-N(3)-C(6)	117.5(4)	C(1)-C(1')-C(2')	18.2(4)
N(3)-C(4)-N(5)	113.0(4)	O(1')-C(1')-C(2')	121.0(4)
N(3)-C(4)-S(8)	112.1(3)		

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Received, 17th June, 1994