

STUDIES OF SCHMIDT-TYPE REARRANGEMENTS OF PENTACYCLO-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]UNDECAN-8-ONE. UNEXPECTED INCURSION OF THE HUISGEN REARRANGEMENT†

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Abstract—Reaction of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**1**) with H₂NOSO₃H·HCO₂H affords two pentacyclic lactams (**2a**) (15%) and (**2b**) (30%). Reaction of **1** with HN₃·Tf₂O results in the formation of a pentacyclic urea (**3**) (16%) and a tricyclic azidonitrile (**4**) (18%). The unusual "double Schmidt rearrangement" that results in the formation of **3** is rationalized via formation of an intermediate tetrazole (**5**) which undergoes subsequent acylation with concomitant Huisgen rearrangement.

INTRODUCTION

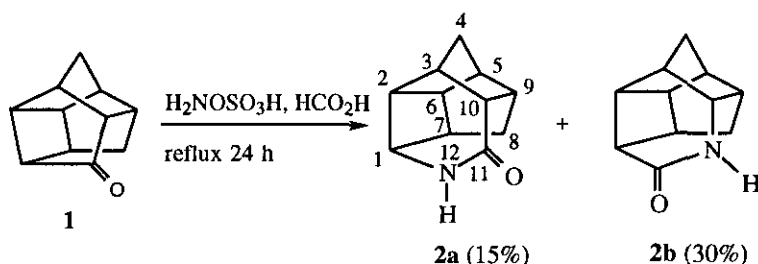
The synthesis and chemistry of novel, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (PCUs) have been studied extensively in recent years.^{1,2} Compounds of this type are of interest as intermediates in the synthesis of unusual polycyclic cage systems² and of triquinane natural products.³ In particular, ring expansion processes, when performed on PCU-8-one and/or PCU-8,11-dione, provide a convenient entry into a wide variety of unusual pentacyclic C₁₂ and C₁₃ cage systems. Methods that have been employed for this purpose include: (i) reactions of PCU-ones with N₂CHCO₂Et performed in the presence of F₃B·OEt₂,⁴ (ii) Tieffenau-Demjanov ring expansions,⁵ and (iii) Baeyer-Villiger reactions.⁶ As part of a continuing study of ring expansion reactions of PCU-ones,^{4,5} we have examined Schmidt-type rearrangements of PCU-8-one (**1**) under a variety of experimental conditions.

The reaction of **1** with hydroxylamine *O*-sulfonic acid in the presence of formic acid⁷ results in Schmidt rearrangement, thereby affording two isomeric lactams (**2a**) and (**2b**) (Scheme 1, product ratio **2a** : **2b** = 1:2). Unequivocal assignment of each of the structures of **2a** (as 12-azapentacyclo[5.5.0.0^{2,6}.0^{3,10}.0^{5,9}]dodecan-11-one) and **2b** (as 11-azapentacyclo[5.5.0.0^{2,6}.0^{3,10}.0^{5,9}]dodecan-12-one) was secured *via* application of X-ray crystallographic methods.

Schmidt reaction of PCU-8,11-dione with NaN₃·MsOH has been reported⁸ to be accompanied by extensive skeletal rearrangement of the pentacyclic cage system. In our hands, the corresponding reaction of **1** with HN₃·Tf₂O afforded two products, a substituted polycyclic urea (**3**) (16%) and a tricyclic nitrile (**4**) (18%, Scheme

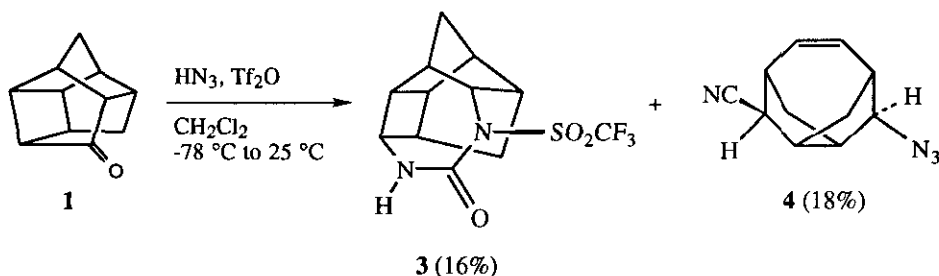
†Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

Scheme 1



2). X-Ray structure drawings of **3** and **4** are shown in Figures 1 and 2, respectively. The latter compound is closely analogous to the kinds of rearranged polycyclic ketonitriles that were reported previously for the reaction of PCU-8,11-dione with NaN_3 - MsOH .⁸

Scheme 2



Compound (**3**) appears to have been produced from **1** via a "double Schmidt rearrangement". The formation of a cyclic urea by double ring-homologation of a cyclic ketone is highly unusual but not entirely unprecedented.⁹ Thomas¹⁰ has reported that tetrazoles can be prepared conveniently via reaction of aliphatic secondary amides with NaN_3 - Tf_2O . In addition, when treated with acyl halides, 5-substituted tetrazoles are known to undergo *N*-acylation accompanied by fragmentation of the tetrazole ring with concomitant loss of N_2 . This procedure has been employed extensively to synthesize 1,3,4-oxadiazoles¹¹ and is an example of the familiar "Huisgen rearrangement".¹²

The formation of cyclic urea (**3**) as a product of the reaction of **1** with HN_3 - Tf_2O can be rationalized in terms of the mechanism postulated in Scheme 3. Here, Schmidt rearrangement leads initially to **2a** and **2b**. Further reaction with HN_3 - Tf_2O appears to occur selectively with **2b**, thereby resulting in formation of the corresponding tetrazole (**5**). *N*-acylation of **5** can occur subsequently via reaction with Tf_2O , ultimately affording the corresponding triflyl enol ether (**8**).¹³ Finally, hydrolysis of triflyl enol ether, which occurs during aqueous workup, leads to the observed reaction product (**3**).

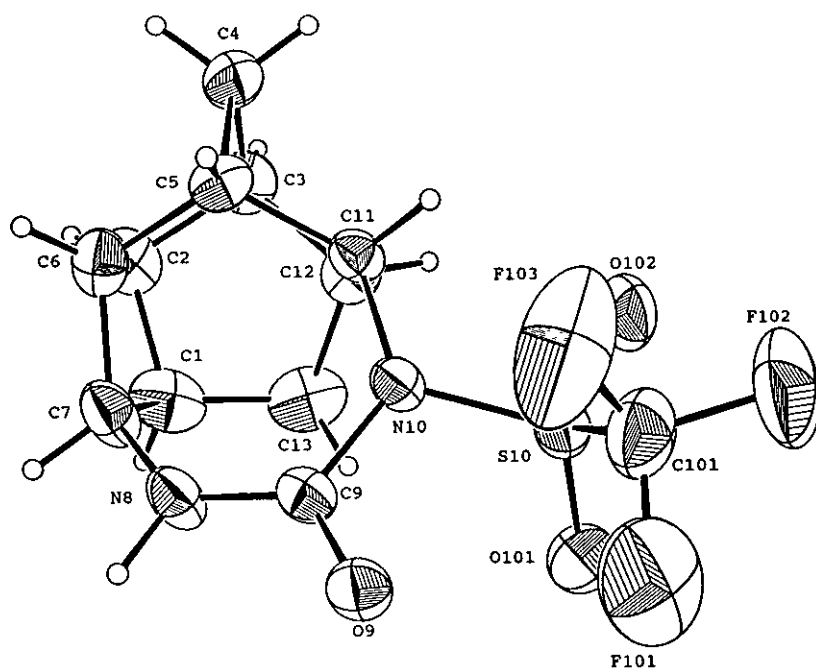


Figure 1. X-ray structure drawing of 3.

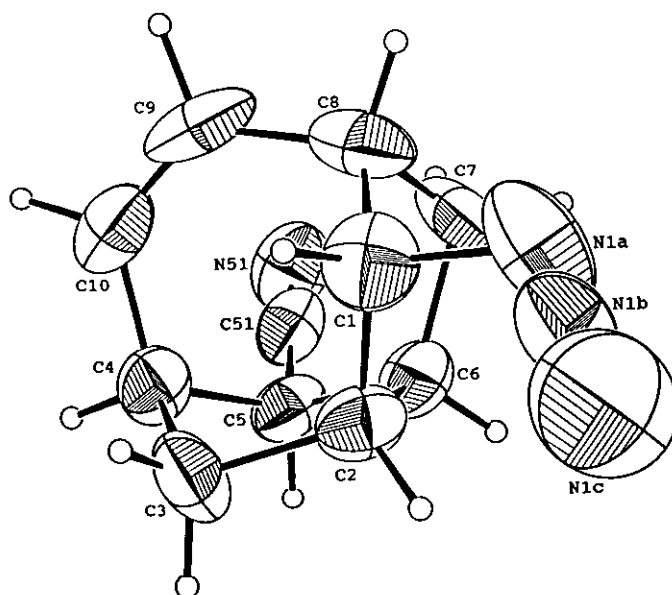
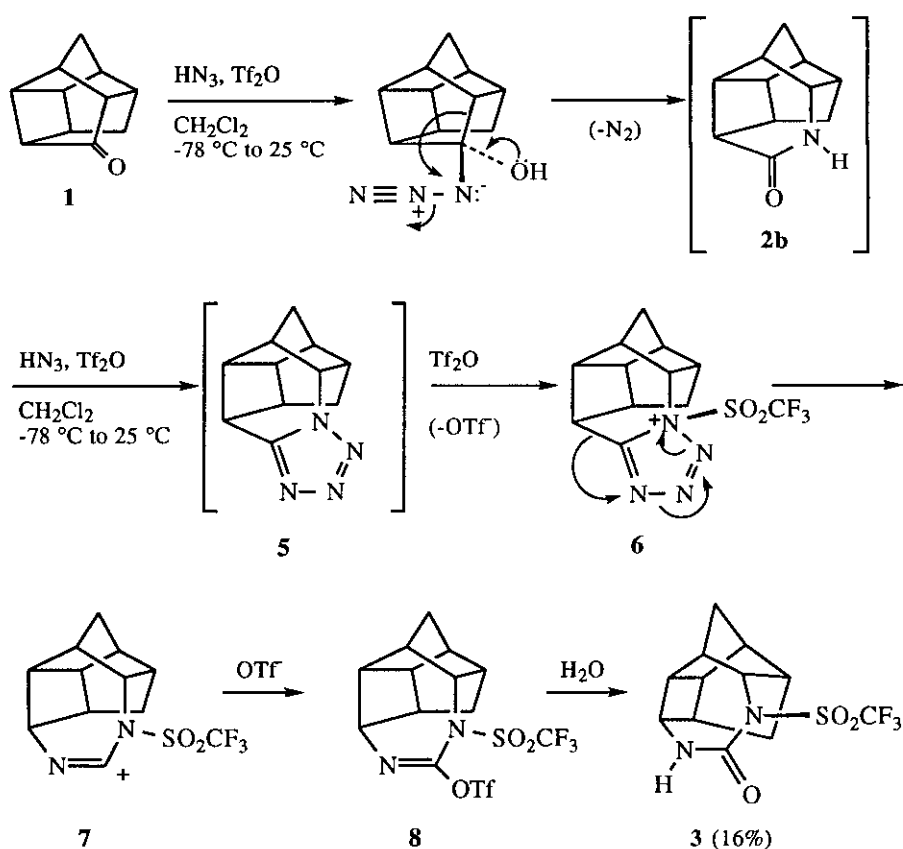


Figure 2. X-ray structure drawing of 4.

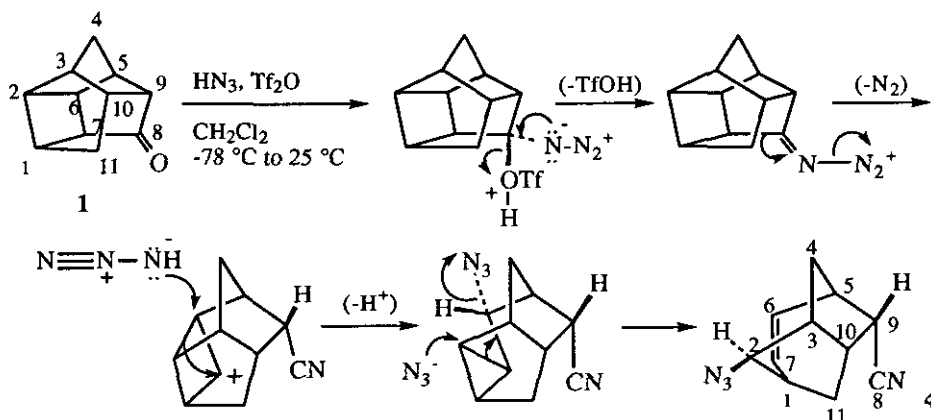
Our suggestion that **2b** (rather than **2a**) is the key intermediate in the reaction of **1** with $\text{HN}_3\text{-Tf}_2\text{O}$ which is transformed selectively into **3** has been verified by the results of a control experiment. Thus, a 1:2 mixture of **2a** and **2b** was subjected to the reaction conditions which are identical to those shown in Scheme 2. Unreacted starting material was recovered, and the composition of this material was subjected subsequently to ^1H nmr spectroscopic analysis. Integration of the ^1H nmr spectrum of the mixture of recovered **2a** and **2b** indicated that the ratio of **2a** : **2b** had dropped to 1:1.3, a result that is consistent with the mechanism shown in Scheme 3 (see the Experimental Section).

Scheme 3



The formation of **4** as a product of the reaction of **1** with $\text{HN}_3\text{-Tf}_2\text{O}$ is rationalized by the mechanism shown in Scheme 4. This mechanism is consistent with that which was forwarded previously to account for the course of the corresponding reaction of PCU-8,11-dione with $\text{NaN}_3\text{-MsOH}$.⁸

Scheme 4



EXPERIMENTAL

Melting points are uncorrected. Elemental microanalyses were performed by M-H-W Laboratories, Phoenix, AZ.

Schmidt Rearrangement of 1. A solution of 1 (1.6 g, 10 mmol) and hydroxylamine *O*-sulfonic acid ($\text{H}_2\text{NOSO}_3\text{H}$, 1.5 g, 15 mmol) in HCO_2H (15 ml) was refluxed for 24 h. The reaction mixture was concentrated *in vacuo* to remove formic acid, and water (50 ml) was added to the residue. The resulting suspension was extracted with CHCl_3 (3 x 15 ml). The combined organic layers were washed sequentially with 10% aqueous NaHCO_3 (20 ml), water (20 ml), and brine (20 ml). The organic layer was dried (MgSO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by using a gradient elution scheme (10-50% EtOAc -hexane mixed solvent). The first chromatography fraction afforded an oil (0.5 g) which was not identified. The second fraction afforded a mixture of lactams (**2a**) and (**2b**) (800 mg, 46%, product ratio **2a**:**2b** = 1:2). Individual pure isomers were obtained by fractional recrystallization of this product mixture from EtOAc . Pure **2a** was thereby obtained as a colorless microcrystalline solid; mp 251°C (decomp.); ir (KBr) 3186 (m), 2941 (s), 1656 (vs), 1463 (w), 1401 cm^{-1} (w); ^1H nmr (CDCl_3) δ 1.39 (AB, J_{AB} = 10.5 Hz, 1 H), 1.60 (AB, J_{AB} = 10.5 Hz, 1 H), 1.55 (s, 2 H), 2.30 (br s, 1 H), 2.50 (s, 3 H), 2.55-2.70 (m, 1 H), 2.70-2.95 (m, 2 H), 3.86 (dt, J = 6.2, 8.5 Hz, 1 H), 7.12 (br s, 1 H); ^{13}C nmr (CDCl_3) δ 30.09 (t), 36.35 (t), 38.65 (d), 39.12 (d), 40.61 (d), 41.98 (d), 42.88 (d), 45.83 (d), 47.85 (d), 50.00 (d), 177.2 (s). Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}$: C, 75.40; H, 7.48. Found: C, 75.34; H, 7.32.

Compound (**2b**) was obtained as a colorless microcrystalline solid, mp 237°C ; ir (KBr) 3187 (m), 3071 (m), 2928 (s), 1671 (s), 1470 (w), 1402 cm^{-1} (w); ^1H nmr (CDCl_3) δ 1.41 (AB, J_{AB} = 10.5 Hz, 1 H), 1.62 (AB, J_{AB} = 10.5 Hz, 1 H), 1.55 (s, 2 H), 2.13 (t, J = 3.9 Hz, 1 H), 2.40 (m, 1 H), 2.47-2.68 (m, 2 H), 2.75-2.95 (m, 2 H), 3.10 (m, 1 H), 3.63 (m, 1 H), 7.26 (br s, 1 H); ^{13}C nmr (CDCl_3) δ 31.05 (t), 33.09 (t), 35.06 (d), 37.11 (d), 38.42 (d), 38.68 (d), 42.49 (d), 44.15 (d), 48.14 (d), 56.30 (d), 173.8 (s). Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}$: C, 75.40; H, 7.48. Found: C, 75.15; H, 7.53.

Reaction of 1 with HN_3 - Tf_2O . A solution of **1** (2.00 g, 12.5 mmol) and HN_3 (37 ml of a 1.7 M solution in CH_2Cl_2 , 2.69 g, 62.8 mmol) under argon was cooled externally to -78°C (dry ice-acetone bath). To this cold solution was added Tf_2O (3.55 g, 12.6 mmol) dropwise with stirring. After the addition of Tf_2O had been completed, the cold bath was removed, and the stirred reaction mixture was allowed to warm gradually to room temperature during 3 h. A solid, which precipitated during the course of the reaction, was removed by filtration. The filtrate was extracted with 10% aqueous NaHCO_3 (100 ml). The layers were separated, and the aqueous layer was extracted with CHCl_3 (3 x 25 ml). The combined organic layers were washed sequentially with water (100 ml) and brine (100 ml). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue, a pale yellow oil, was dissolved in EtOAc (4 ml). The resulting solution was concentrated slowly *via* evaporation under ambient conditions, during which time crystals gradually formed and precipitated from solution. After several days, the precipitated solid was collected by suction filtration, thereby affording **3** (647 mg, 16%) as a colorless microcrystalline solid: mp $196\text{--}197^\circ\text{C}$; ir (KBr) 3223 (m), 3110 (m), 2973 (s), 1683 (s), 1445 (m), 1382 (s), 1194 (vs), 1088 cm^{-1} (s); ^1H nmr (CDCl_3) δ 1.41 (AB, $J_{\text{AB}} = 11.3$ Hz, 1 H), 1.66 (AB, $J_{\text{AB}} = 11.3$ Hz, 1 H), 1.60-2.05 (m, 2 H), 2.65 (m, 4 H), 2.94 (m, 1 H), 3.12 (m, 1 H), 3.82 (dd, $J = 17.6, 8.7$ Hz, 1 H), 4.45 (dd, $J = 9.1, 2.7$ Hz, 1 H), 6.28 (d, $J = 7.8$ Hz, 1 H); ^{13}C nmr (CDCl_3) δ 29.10 (t); 37.69 (t), 40.55 (d), 41.31 (d), 42.58 (d), 44.39 (d), 46.12 (d), 46.48 (d), 46.93 (d), 63.83 (d), 119.7 (q, $^1J_{\text{CF}} = 322$ Hz), 154.3 (s); ^{19}F nmr (CDCl_3 ; CFCl_3 internal standard) -70.72 (d). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_3\text{F}_3\text{S}$: C, 44.72; H, 4.06; N, 8.69. Found: C, 44.91; H, 4.07; N, 8.57.

The mother liquor which remained after removal of **3** was concentrated *in vacuo*. The residual yellow oil was purified *via* column chromatography on silica gel by eluting with 20% EtOAc-hexane. The initial chromatography fractions afforded an oil (180 mg), which was not characterized. Continued elution of the chromatography column with 50% EtOAc-hexane afforded pure **4** (450 mg, 18%) as a colorless microcrystalline solid: mp $85\text{--}86^\circ\text{C}$; ir (KBr) 2950 (s), 2876 (m), 2226 (m), 2088 (vs), 1650 (m), 1444 (m), 1243 cm^{-1} (m); ^1H nmr (CDCl_3) δ 1.60-2.20 (m, 4 H), 2.60 (m, 1 H), 2.85 (m, 3 H), 3.12 (m, 1 H), 3.75 (s, 1 H), 6.08 (m, 2 H); ^{13}C nmr (CDCl_3) δ 34.39 (t), 39.68 (d), 40.43 (t), 40.92 (d), 44.08 (d, 2 C), 49.53 (d), 73.35 (d), 120.1 (s), 133.5 (d), 134.8 (d). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.86; H, 6.00; N, 27.84.

Control Experiment: Reaction of 2a + 2b with HN_3 - Tf_2O . A solution of **2a** and **2b** (ratio **2a** : **2b** = 1:2, 1.0 g, 5.7 mmol) and HN_3 (20 ml of a 1.7 M solution in CH_2Cl_2 , 1.46 g, 34 mmol) under argon was cooled externally to -78°C (dry ice-acetone bath). To this cold solution was added Tf_2O (1.6 g, 5.7 mmol) dropwise with stirring. After the addition of Tf_2O had been completed, the cold bath was removed, and the stirred reaction mixture was allowed to warm gradually to room temperature during 3.5 h. A pale yellow oil separated from solution during the course of the reaction. The supernatant liquid was decanted and then was washed sequentially with water (50 ml), 10% aqueous NaHCO_3 (50 ml), and brine (25 ml). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residual solid was recrystallized from EtOAc, thereby affording **3** (280 mg, 15%). The ^1H and ^{13}C nmr spectra of this material were identical in

all respects with the corresponding spectra of **3** that had been obtained perviously from the reaction of **1** with $\text{HN}_3 \cdot \text{Tf}_2\text{O}$ (*vide supra*).

The remaining mother liquor was concentrated *in vacuo*, and the residue was purified *via* column chromatography on silica gel by eluting with 50% EtOAc-hexane. The initial chromatography fractions afforded an oil (160 mg) which was not further characterized. Continued elution of the chromatography column gave a mixture of **2a** and **2b** (ratio **2a** : **2b** = 1:1.3). These results suggest that **2a** and **2b** are formed via reaction of **1** with $\text{HN}_3 \cdot \text{Tf}_2\text{O}$, and that **3** is formed selectively by subsequent *in situ* reaction of **2b** with $\text{HN}_3 \cdot \text{Tf}_2\text{O}$.

X-Ray Structures of 2a, 2b, 3, and 4. All data were collected on an Enraf-Nonius CAD-4 diffrac-tometer by using the ω -2 θ scan technique, Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) and a graphite monochromator. Standard procedures used in our laboratory for this purpose have been described previously.¹⁴ Pertinent X-ray data are given in Table 1.¹⁵ Data were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods [i.e., SIR¹⁶ (**2a**, **2b**, and **4**) and SHELXS-86¹⁷ (**3**)], and the model was refined by using full-matrix least-squares techniques. Anisotropic parameters were incorporated for all non-hydrogen atoms. Hydrogen atoms were located on difference maps and then were included in the model in idealized positions [$U(\text{H}) = 1.3 B_{\text{eq}}(\text{C})$]. All computations other than those specified were performed by using MolEN.¹⁸ Scattering factors were taken from the usual sources.¹⁹

Table 1. X-ray structure data for **2a**, **2b**, **3**, and **4**.

Compound	2a	2b	3	4
Formula	$\text{C}_{11}\text{H}_{13}\text{NO}$	$\text{C}_{11}\text{H}_{13}\text{NO}$	$\text{C}_{12}\text{H}_{13}\text{F}_3 \text{ N}_2\text{O}_3\text{S}$	$\text{C}_{11}\text{H}_{12}\text{N}_4$
Size (mm)	.08 x .22 x .24	.21 x .23 x .27	.42 x .44 x .48	.48 x .49 x .52
Space Group	P1	P2 ₁ /c	P2 ₁ /c	P2 ₁ 2 ₁ 2 ₁
a (Å)	6.4423 (5)	10.964 (4)	12.795 (1)	8.0082 (7)
b (Å)	6.5451 (5)	6.629 (1)	8.990 (1)	9.443 (1)
c (Å)	11.0543 (6)	12.817 (2)	12.306 (2)	13.515 (2)
α (°)	95.175 (6)			
β (°)	94.450 (6)	115.21 (2)	115.60 (1)	
γ (°)	114.105 (6)			
V (Å ³)	420.27 (6)	842.8 (4)	1276.6 (3)	1022.2 (2)
Z	2	4	4	4
D _c (g·cm ⁻³)	1.385	1.381	1.677	1.301
μ (cm ⁻¹)	0.83	0.83	2.90	0.78
ω -2 θ (2 θ_{max})	44	44	44	44
Total refl.	1027	1204	1756	1442
Unique refl.	1027	1156	1679	1260
R _{int}	-	0.027	0.019	0.026
I $\geq$ 3 σ (I)	734	771	1295	834
Parameters	118	118	190	136
R, wR	.0450, .0461	.0454, .0453	.0464, .0463	.0621, .0663
(Δ/σ) _{max}	<0.01	<0.01	<0.01	<0.01
ρ_{min} ; ρ_{max}	0.19; -0.21	0.15; -0.12	0.64; -0.42	0.30; -0.25

ACKNOWLEDGMENT

We thank the Robert A. Welch Foundation (Grant B-963 to A. P. M., B-1202 to S. G. B.) and the University of North Texas Faculty Research Committee for financial support of this study.

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Received, 17th March, 1994