Reaction of 5-Amino-1-phenylpyrazole-4-carbonitriles with Dimethyl Acetylenedicarboxylate. Synthesis and Structural Determination of Trimethyl 4,8-Dioxo-1-phenyl-4,5,5a,8-tetrahydro-1*H*-pyrazolo[3,4-*e*]indolizine-5,5a,6-tricarboxylate Derivatives

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The reaction of 5-amino-1-phenylpyrazole-4-carbonitriles **1a-c** with dimethyl acetylenedicarboxylate in the presence of potassium carbonate in dimethyl sulfoxide gave trimethyl 4,5,5a,8-tetrahydro-1-phenyl-4,8-dioxo-1*H*-pyrazolo[3,4-*e*]indolizine-5,5a,6-tricarboxylate derivatives **3a-c** from the basic solution. The products were formed by a double Michael reaction of **1** with dimethyl acetylenedicarboxylate followed by cyclization to the cyano group. The structure of product **3a** was established by X-ray crystallography.

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Dimethyl acetylenedicarboxylate plays a very important role not only as a reagent 1,3-dipolarophile and dienophile in 1,3-dipolar cycloadditions and Diels-Alder reactions but also as a building block in the formation of heterocycles [1,2]. The reaction of dimethyl acetylenedicarboxylate with various nucleophiles occassionally affords unexpected products open to new reactions which could be applied to prepare useful substances. For example, the reaction of cyclic aminonitrile derivatives with dimethyl acetylenedicarboxylate is a versatile method for the synthesis of a variety of dimethyl fused pyridinedicarboxylates [3-6]. Recently, it has been reported that the reaction of 1-substituted 5-aminopyrazole-4-carbonitriles with dimethyl acetylenedicarboxylate gives mainly dimethyl 1-substituted 4-amino-1*H*-pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates which are key intermediates for the preparation of pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine derivatives [7,8]. The type of product obtained is influenced by the substitution pattern attached at the pyrazole 1-position of the starting *o*-aminonitriles.

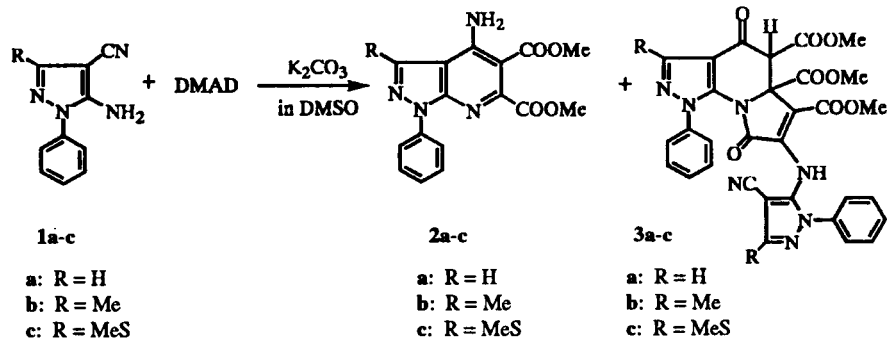
The reaction of 5-amino-1-phenylpyrazole-4-carbonitrile (**1a**) with dimethyl acetylenedicarboxylate in the presence of potassium carbonate gave the expected product, dimethyl 4-amino-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**2a**) along with an unknown product. This unknown product **3a** was crystallized from the reaction mixture by treatment with dilute hydrochloric acid. We now wish to report the synthesis and structural determination of trimethyl 7-(4-cyano-1-phenylpyrazol-5-yl)-amino-4,5,5a,8-tetrahydro-1-phenyl-4,8-dioxo-1*H*-pyrazolo[3,4-*e*]indolizine-5,5a,6-tricarboxylates **3**, which were obtained by the reaction of **1** with dimethyl acetylenedicarboxylate.

The reaction of **1** with dimethyl acetylenedicarboxylate in the presence of potassium carbonate in dimethyl sulfoxide gave dimethyl 4-amino-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5,6-dicarboxylate (**2a**) from the basic solution in 31% yield [7]. After filtration of this product, the mother liquid was acidified with 10% hydrochloric acid to give a tan powdered product which could not be crystallized from methanol and various other solvents. Treatment of this product with 1*N* methanolic hydrogen chloride and allowed to stand at room temperature for one week afforded a crystalline compound **3a** in 1.4% yield. Compound **3a** formed as colorless needles which were recrystallized from methanol.

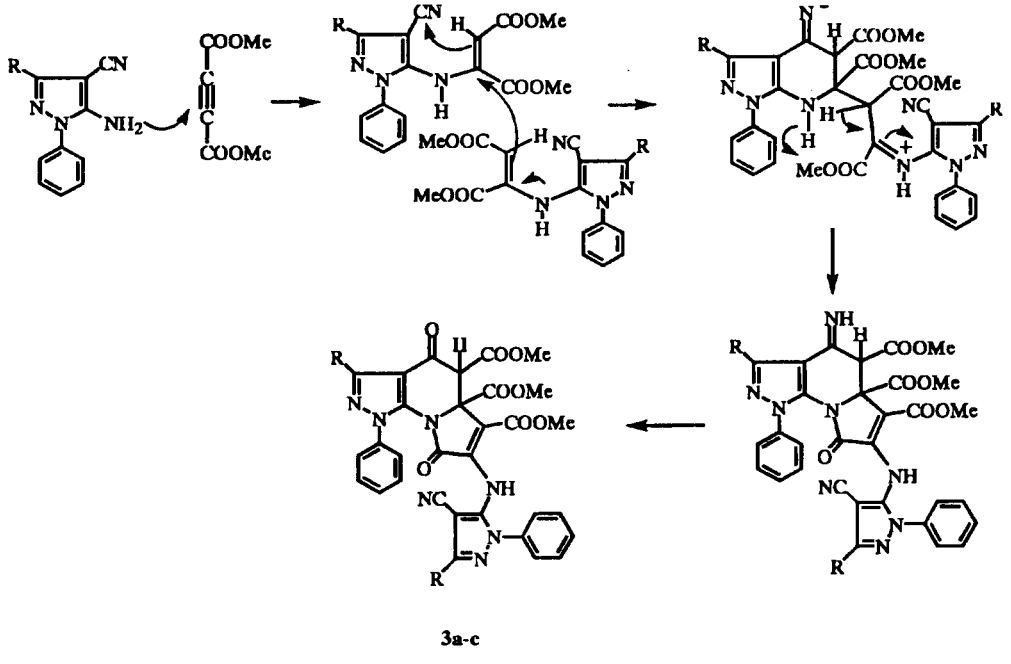
The mechanism of formation of **3a** can be postulated as shown in Scheme 2. Evidently, the Michael adduct produced by addition of dimethyl acetylenedicarboxylate to **1a**, in the first step of the process, was then dimerized, followed first by 1,6-cyclization of the cyano group and the enamino carbon and then a second cyclization of the amino group and ester group to give the 3-iminopyrazolo[3,4-*b*]indolizine derivative, followed by hydrolysis of the imino group to the final product.

The reaction of 3-substituted 4-amino-1-phenylpyrazole-4-carbonitriles **1b,c** with dimethyl acetylenedicarboxylate also gave the corresponding 3-substituted pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates **2b,c** [7] along with 2-substituted pyrazolo[3,4-*e*]indolizine derivatives **3b,c**.

Scheme 1



Scheme 2



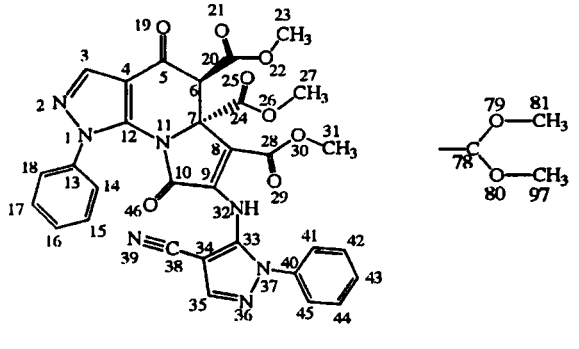


Figure 1. Atomic Numbering.

The structure of **3a** was established by X-ray crystallography that is shown in Figure 1. The symmetric unit of the crystalline compound consists of two chemically identical but crystallographically independent molecules which will be designated as **I** and **II**. Molecules **I** and **II** are shown in Figures 2 and 3, respectively. A disordered methoxycarbonyl group at the 6-position of **3a** was observed in molecule **II**. Each site is approximately 50% populated.

In conclusion, the structure of the by-product, trimethyl 7-(4-cyano-1-phenyl-5-pyrazolyl)amino-4,5,5a,8-tetrahydro-1-phenyl-4,8-dioxo-1*H*-pyrazolo[3,4-*e*]indolizine-5,5a,6-tricarboxylate, along with dimethyl 4-amino-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate obtained by the reaction of 5-amino-1-phenylpyrazole-4-carboni-

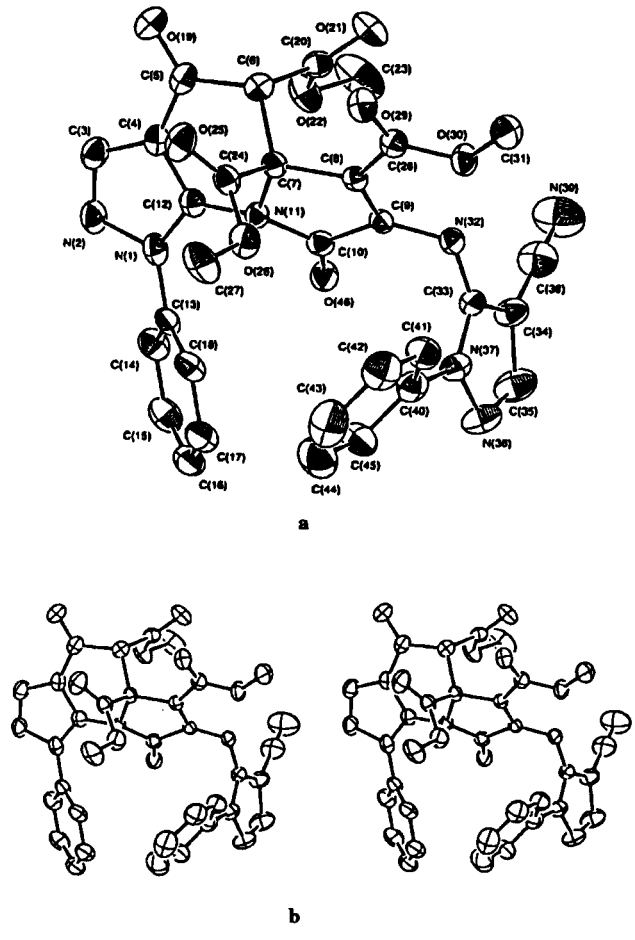


Figure 2. a, Perspective view of molecule I with the atom-numbering scheme; b, Stereoscopic view molecule I.

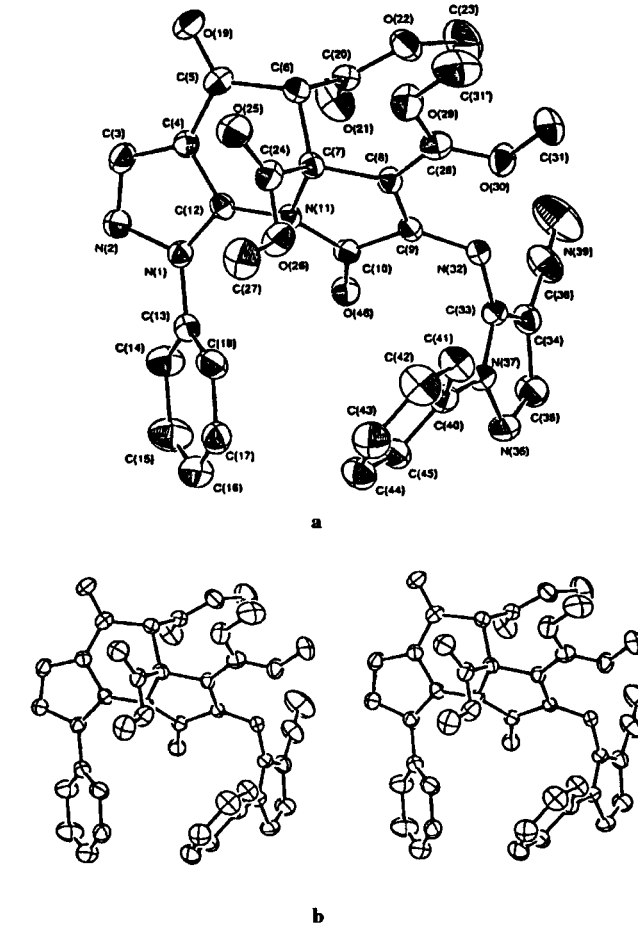


Figure 3. a, Perspective view of molecule II with the atom-numbering scheme; b, Stereoscopic view of molecule II.

trile with dimethyl acetylenedicarboxylate was determined by X-ray crystallography. This reaction is the first example of the construction of the novel tricyclic heterocycle, pyrazolo[3,4-*e*]indolizine derivative by the reaction of *o*-aminocyanopyrazoles with dimethyl acetylenedicarboxylate.

EXPERIMENTAL

All melting points were determined in a capillary tube and are uncorrected. Infrared (ir) spectra were recorded as potassium bromide pellets on a JASCO 810 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi 323 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on a JEOL-PS-100 (100 MHz), JEOL-FX-90Q (90 MHz), and JEOL-GX-400 (400 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL-JMS-01SG mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis at Nagasaki University.

The Reaction of 5-Aminopyrazole-4-carbonitrile Derivatives with Dimethyl Acetylenedicarboxylate.

To a mixture of 9.2 g (50 mmoles) of 5-amino-1-phenylpyrazole-4-carbonitrile (**1a**), 27.6 g (200 mmoles) of anhydrous potassium carbonate and 300 ml of dimethyl sulfoxide, a solution of 10.0 g (70 mmoles) of dimethyl acetylenedicarboxylate in 20 ml of dimethyl sulfoxide was added dropwise during 30 minutes with ice-water cooling. Stirring was continued for an additional 60 hours at room temperature. The color of the reaction mixture changed from brown to dark greenish brown. The reaction mixture was poured into 500 ml of ice-water and stirred for 30 minutes. The dark brown solid that appeared was collected by filtration. After drying in air, the product was suspended in 20 ml of methanol. The white crystalline product that appeared was collected by filtration and recrystallized from methanol to give 3.50 g (21%) of colorless prisms, mp 178-180°. This compound was identified as dimethyl 4-amino-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**2a**) [7]. The filtrate was acidified with 10% hydrochloric acid solution. The resulting precipitate was collected by filtration. After drying in air the color of the product changed from tan to a black solid. This black solid was dissolved in 30 ml of methanol and 5 ml of 1*N*-hydrochloric acid solution. This solution was allowed to stand for about 6-7 days. The precipitate that appeared was col-

Table 1

Fractional Coordinates and Equivalent Isotropic Thermal Parameters for the Non-hydrogen Atoms, with their E.S.D.'s in Parenthesis. The Methyl Ester Moiety of C(28), O(29), O(30) and C(31) in the Molecule II is Disordered. The C(31) and C(31') Atoms have Occupancy Factors of 0.5

Atom	X	Y	Z	U(EQ)
Molecule I				
N(1)	0.2107(1)	0.1361(5)	0.2267(1)	0.055(2)
N(2)	0.2327(1)	0.2005(6)	0.2133(1)	0.068(2)
C(3)	0.2152(2)	0.1695(7)	0.1734(2)	0.067(3)
C(4)	0.1817(1)	0.0883(6)	0.1589(2)	0.053(3)
C(5)	0.1525(2)	0.0363(6)	0.1186(2)	0.061(3)
C(6)	0.1182(1)	-0.0258(6)	0.1172(2)	0.048(2)
C(7)	0.1282(1)	-0.1063(6)	0.1584(2)	0.042(2)
C(8)	0.0950(1)	-0.1310(5)	0.1622(1)	0.039(2)
C(9)	0.0966(1)	-0.0423(6)	0.1913(1)	0.040(2)
C(10)	0.1316(1)	0.0496(6)	0.2116(2)	0.046(2)
N(11)	0.1514(1)	-0.0063(5)	0.1946(1)	0.044(2)
C(12)	0.1802(1)	0.0710(6)	0.1940(2)	0.049(2)
C(13)	0.2234(1)	0.1439(6)	0.2695(2)	0.049(2)
C(14)	0.2392(2)	0.2784(7)	0.2906(2)	0.064(3)
C(15)	0.2517(2)	0.2859(8)	0.3324(2)	0.072(3)
C(16)	0.2488(2)	0.1597(8)	0.3524(2)	0.075(3)
C(17)	0.2332(2)	0.0265(7)	0.3306(2)	0.071(3)
C(18)	0.2208(1)	0.0158(6)	0.2890(2)	0.057(3)
O(19)	0.1538(1)	0.0428(5)	0.0874(1)	0.073(2)
C(20)	0.0896(1)	0.0993(6)	0.1074(2)	0.053(3)
O(21)	0.0574(1)	0.0869(5)	0.0839(1)	0.071(2)
O(22)	0.1058(1)	0.2211(4)	0.1311(1)	0.071(2)
C(23)	0.0811(2)	0.3483(9)	0.1259(2)	0.114(4)
C(24)	0.1496(1)	-0.2555(6)	0.1622(2)	0.053(3)
O(25)	0.1606(1)	-0.2871(5)	0.1401(1)	0.086(2)
O(26)	0.1541(1)	-0.3400(4)	0.1934(1)	0.077(2)
C(27)	0.1756(2)	-0.4825(8)	0.2013(2)	0.094(4)
C(28)	0.0662(1)	-0.2400(6)	0.1341(2)	0.050(3)
O(29)	0.06842(9)	-0.3148(4)	0.1089(1)	0.063(2)
O(30)	0.03849(9)	-0.2458(4)	0.1408(1)	0.061(2)
C(31)	0.0094(2)	-0.3611(7)	0.1166(2)	0.073(3)
N(32)	0.0707(1)	-0.0144(5)	0.2017(1)	0.050(2)
C(33)	0.0783(1)	0.0343(6)	0.2401(2)	0.051(2)
C(34)	0.0666(2)	0.1609(7)	0.2508(2)	0.067(3)
C(35)	0.0826(2)	0.1480(8)	0.2937(2)	0.096(4)
N(36)	0.1028(2)	0.0226(6)	0.3088(1)	0.083(3)
N(37)	0.0996(1)	-0.0490(5)	0.2752(1)	0.059(2)
C(38)	0.0448(2)	0.2815(8)	0.2243(2)	0.089(4)
N(39)	0.0272(2)	0.3810(8)	0.2029(2)	0.133(4)
C(40)	0.1199(2)	-0.1883(7)	0.2814(2)	0.066(3)
C(41)	0.1032(2)	-0.3111(7)	0.2547(2)	0.076(3)
C(42)	0.1224(2)	-0.4462(8)	0.2601(2)	0.100(4)
C(43)	0.1588(2)	-0.4535(9)	0.2931(3)	0.132(5)
C(44)	0.1755(2)	-0.334(1)	0.3199(3)	0.116(5)
C(45)	0.1562(2)	-0.1973(9)	0.3145(2)	0.086(4)
O(46)	0.14092(9)	0.1529(4)	0.2361(1)	0.058(2)
Molecule II				
N(1)	0.1151(1)	0.3175(5)	0.0305(1)	0.050(2)
N(2)	0.1299(1)	0.4044(5)	0.0665(1)	0.060(2)
C(3)	0.1655(2)	0.4146(6)	0.0800(2)	0.058(3)
C(4)	0.1744(1)	0.3381(6)	0.0540(2)	0.053(3)
C(5)	0.2081(2)	0.3190(7)	0.0536(2)	0.060(3)
C(6)	0.2033(1)	0.2428(7)	0.0147(2)	0.054(3)
C(7)	0.1712(1)	0.1222(6)	-0.0040(2)	0.046(2)
C(8)	0.1597(1)	0.0741(6)	-0.0471(2)	0.045(2)
C(9)	0.1255(1)	0.1252(6)	-0.0741(2)	0.044(2)

Table 1 (cont.)

Atom	X	Y	Z	U(EQ)
Molecule II				
C(10)	0.1109(1)	0.2103(6)	-0.0517(2)	0.045(2)
N(11)	0.1373(1)	0.1932(5)	-0.0102(1)	0.043(2)
C(12)	0.1414(1)	0.2804(6)	0.0223(2)	0.046(2)
C(13)	0.0775(2)	0.2661(7)	0.0113(2)	0.056(3)
C(14)	0.0511(2)	0.3690(7)	0.0076(2)	0.080(3)
C(15)	0.0148(2)	0.3168(9)	-0.0102(2)	0.105(4)
C(16)	0.0055(2)	0.1677(9)	-0.0232(2)	0.087(3)
C(17)	0.0319(2)	0.0694(7)	-0.0189(2)	0.077(3)
C(18)	0.0687(2)	0.1175(7)	-0.0012(2)	0.070(3)
O(19)	0.2391(1)	0.3595(6)	0.0815(1)	0.086(2)
C(20)	0.1938(1)	0.3671(7)	-0.0176(2)	0.057(3)
O(21)	0.1729(1)	0.4705(5)	-0.0246(1)	0.104(3)
O(22)	0.2090(1)	0.3366(5)	-0.0395(1)	0.081(2)
C(23)	0.1968(2)	0.434(1)	-0.0760(2)	0.131(5)
C(24)	0.1821(1)	-0.0152(7)	0.0257(2)	0.056(3)
O(25)	0.2117(1)	-0.0303(5)	0.0569(1)	0.080(2)
O(26)	0.1545(1)	-0.1129(4)	0.0112(1)	0.068(2)
C(27)	0.1602(2)	-0.2530(8)	0.0357(2)	0.095(4)
C(28)	0.1833(2)	-0.0150(7)	-0.0567(2)	0.060(3)
O(29)	0.2144(1)	-0.0609(5)	-0.0267(1)	0.077(2)
O(30)	0.1712(1)	-0.0429(5)	-0.0944(1)	0.069(2)
C(31)	0.1944(3)	-0.139(1)	-0.1046(4)	0.082(7)
C(31')	0.2369(4)	-0.149(2)	-0.0386(5)	0.118(9)
N(32)	0.1064(1)	0.1174(5)	-0.1163(1)	0.051(2)
C(33)	0.0682(1)	0.1433(6)	-0.1423(2)	0.045(2)
C(34)	0.0505(2)	0.2594(7)	-0.1698(2)	0.059(3)
C(35)	0.0130(2)	0.2237(8)	-0.1883(2)	0.074(3)
N(36)	0.0073(1)	0.0968(6)	-0.1736(1)	0.064(2)
N(37)	0.0423(1)	0.0452(5)	-0.1450(1)	0.050(2)
C(38)	0.0676(2)	0.3899(8)	-0.1748(2)	0.090(4)
N(39)	0.0823(2)	0.4943(8)	-0.1776(2)	0.158(5)
C(40)	0.0467(2)	-0.0895(6)	-0.1209(2)	0.055(3)
C(41)	0.0745(2)	-0.1926(7)	-0.1116(2)	0.079(3)
C(42)	0.0784(2)	-0.3215(8)	-0.0883(2)	0.097(4)
C(43)	0.0549(2)	-0.3460(8)	-0.0742(2)	0.092(4)
C(44)	0.0274(2)	-0.2415(8)	-0.0835(2)	0.088(4)
C(45)	0.0231(2)	-0.1129(7)	-0.1068(2)	0.070(3)
O(46)	0.08191(9)	0.2804(4)	-0.0661(1)	0.056(2)

lected by filtration to give 0.42 g (0.676 mmole, 1.4%) as colorless needles. An analytical sample was recrystallized from methanol to give colorless needles, mp 249-251°. This compound was trimethyl 7-(4-cyano-1-phenylpyrazol-5-yl)amino-4,5,5a,8-tetrahydro-1-phenyl-4,8-dioxo-1*H*-pyrazolo[3,4-*e*]indolizine-5,5a,6-tricarboxylate (**3a**); ir (potassium bromide): ν cm^{-1} 3470, 3335 (NH or OH), 3360 (NH or OH), 1710, 1690 (CO), 1614, 1590, 1235; uv (ethanol): λ max nm (log ε) 248 (4.88), 319 (4.38); ^1H nmr (deuteriochloroform): δ 3.51 (3H, s, OMe), 3.84 (3H, s, OMe), 3.86 (3H, s, OMe), 4.61 (1H, s, 5-H), 7.26-7.57 (10H, m, phenyl-H), 7.80 (1H, s, 3-H or 3'-H), 8.09 (1H, s, 3-H or 3'-H), 8.12 (1H, bs, NH); ms: (LR) m/z (%) 622 (M^++1, 15), 621 (M^+, 42), 563 (35), 562 (100), 531 (17), 530 (49), 458 (17).

Anal. Calcd. for $C_{31}H_{23}N_7O_8$ (621.57): C, 59.90; H, 3.73; N, 15.77. Found: C, 59.53; H, 3.87; N, 15.62.

Dimethyl 4-Amino-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**2b**).

This compound (0.927 g, 2.73 mmoles) was synthesized in 14% yield from 5-amino-3-methylpyrazole-4-carbonitrile (**1b**) (3.96 g, 20 mmoles) and dimethyl acetylenedicarboxylate (2.84 g, 20 mmoles) in a manner similar to that described for the

Table 2

Thermal Parameters for the Non-hydrogen Atoms, with their E.S.D.'s in Parentheses

Atom	U11	U22	U33	U12	U13	U23
Molecule I						
N(1)	0.036(2)	0.045(3)	0.066(3)	-0.003(2)	0.026(2)	0.005(2)
N(2)	0.045(3)	0.060(3)	0.076(3)	-0.005(3)	0.035(3)	0.014(3)
C(3)	0.060(4)	0.051(4)	0.071(4)	0.005(3)	0.045(3)	0.014(3)
C(4)	0.041(3)	0.041(3)	0.059(4)	0.001(3)	0.031(3)	0.001(3)
C(5)	0.061(4)	0.039(3)	0.066(4)	0.012(3)	0.045(3)	0.012(3)
C(6)	0.052(3)	0.030(3)	0.047(3)	-0.003(3)	0.028(3)	-0.004(3)
C(7)	0.034(3)	0.034(3)	0.043(3)	-0.002(2)	0.020(3)	0.001(3)
C(8)	0.034(3)	0.029(3)	0.040(3)	0.004(2)	0.018(3)	0.005(2)
C(9)	0.030(3)	0.039(3)	0.038(3)	0.004(2)	0.016(2)	0.006(3)
C(10)	0.043(3)	0.040(3)	0.040(3)	0.005(3)	0.020(3)	0.006(3)
N(11)	0.034(2)	0.040(3)	0.044(3)	-0.005(2)	0.022(2)	0.003(2)
C(12)	0.041(3)	0.035(3)	0.053(3)	0.006(3)	0.024(3)	0.006(3)
C(13)	0.030(3)	0.050(4)	0.046(3)	0.003(3)	0.013(3)	0.006(3)
C(14)	0.049(4)	0.051(4)	0.065(4)	-0.008(3)	0.021(3)	0.004(3)
C(15)	0.050(4)	0.065(4)	0.067(4)	-0.008(3)	0.016(3)	-0.011(4)
C(16)	0.049(4)	0.090(5)	0.057(4)	-0.004(4)	0.016(3)	0.013(4)
C(17)	0.053(4)	0.067(4)	0.063(4)	-0.011(3)	0.019(3)	0.018(3)
C(18)	0.043(3)	0.046(4)	0.054(4)	-0.003(3)	0.012(3)	0.010(3)
O(19)	0.077(3)	0.061(3)	0.065(3)	-0.002(2)	0.050(2)	0.001(2)
C(20)	0.053(3)	0.042(3)	0.044(3)	0.000(3)	0.025(3)	0.001(3)
O(21)	0.043(2)	0.068(3)	0.067(3)	0.006(2)	0.010(2)	-0.002(2)
O(22)	0.048(2)	0.045(3)	0.086(3)	0.011(2)	0.023(2)	-0.005(2)
C(23)	0.092(6)	0.079(6)	0.105(6)	0.044(5)	0.013(5)	-0.031(5)
C(24)	0.039(3)	0.040(3)	0.058(4)	-0.002(3)	0.023(3)	0.005(3)
O(25)	0.084(3)	0.057(3)	0.096(3)	0.018(2)	0.065(3)	0.005(2)
O(26)	0.065(3)	0.053(3)	0.087(3)	0.023(2)	0.045(2)	0.028(2)
C(27)	0.066(4)	0.058(5)	0.113(6)	0.031(4)	0.031(4)	0.026(4)
C(28)	0.045(3)	0.037(3)	0.051(3)	0.008(3)	0.027(3)	0.006(3)
O(29)	0.051(2)	0.045(2)	0.070(3)	-0.002(2)	0.033(2)	-0.012(2)
O(30)	0.043(2)	0.062(3)	0.061(2)	-0.012(2)	0.030(2)	-0.015(2)
C(31)	0.054(4)	0.072(5)	0.067(4)	-0.031(4)	0.028(3)	-0.015(4)
N(32)	0.034(2)	0.061(3)	0.040(3)	-0.009(2)	0.018(2)	-0.008(2)
C(33)	0.042(3)	0.055(4)	0.041(3)	-0.004(3)	0.023(3)	0.002(3)
C(34)	0.075(4)	0.052(4)	0.052(4)	0.011(3)	0.037(3)	0.002(3)
C(35)	0.122(6)	0.070(5)	0.067(4)	0.003(4)	0.059(4)	-0.014(4)
N(36)	0.103(4)	0.066(4)	0.055(3)	0.001(3)	0.049(3)	-0.003(3)
N(37)	0.060(3)	0.053(3)	0.046(3)	-0.006(3)	0.031(2)	-0.004(2)
C(38)	0.096(5)	0.064(5)	0.075(5)	0.004(4)	0.043(4)	-0.013(4)
N(39)	0.150(6)	0.084(5)	0.107(5)	0.038(5)	0.053(5)	0.016(4)
C(40)	0.062(4)	0.051(4)	0.064(4)	-0.002(3)	0.039(3)	0.007(3)
C(41)	0.068(4)	0.062(4)	0.070(4)	0.013(4)	0.034(4)	0.013(4)
C(42)	0.097(5)	0.073(5)	0.099(5)	0.006(4)	0.059(5)	0.013(4)
C(43)	0.122(7)	0.076(6)	0.160(8)	0.031(5)	0.096(6)	0.038(6)
C(44)	0.082(5)	0.106(7)	0.117(6)	0.023(5)	0.044(5)	0.037(5)
C(45)	0.057(4)	0.097(6)	0.072(5)	0.007(4)	0.023(4)	0.015(4)
O(46)	0.045(2)	0.060(3)	0.052(2)	-0.009(2)	0.026(2)	-0.013(2)
Molecule II						
N(1)	0.049(3)	0.041(3)	0.042(3)	-0.005(2)	0.025(2)	-0.006(2)
N(2)	0.056(3)	0.054(3)	0.051(3)	-0.005(3)	0.031(2)	-0.011(2)
C(3)	0.063(4)	0.048(4)	0.041(3)	-0.011(3)	0.025(3)	-0.009(3)
C(4)	0.051(3)	0.047(4)	0.043(3)	-0.008(3)	0.027(3)	-0.005(3)
C(5)	0.049(4)	0.061(4)	0.047(3)	-0.010(3)	0.019(3)	-0.010(3)
C(6)	0.036(3)	0.067(4)	0.044(3)	0.000(3)	0.023(3)	-0.003(3)
C(7)	0.036(3)	0.050(4)	0.038(3)	0.009(3)	0.021(3)	0.007(3)
C(8)	0.038(3)	0.046(3)	0.036(3)	0.008(3)	0.020(3)	0.001(3)
C(9)	0.041(3)	0.038(3)	0.039(3)	-0.001(3)	0.025(3)	-0.000(3)
C(10)	0.037(3)	0.043(3)	0.039(3)	0.002(3)	0.019(3)	0.005(3)
N(11)	0.037(2)	0.044(3)	0.034(2)	0.005(2)	0.017(2)	0.001(2)
C(12)	0.044(3)	0.036(3)	0.044(3)	0.004(3)	0.028(3)	0.000(3)

Table 2 (cont.)

Atom	U11	U22	U33	U12	U13	U23
Molecule II						
C(13)	0.052(3)	0.053(4)	0.046(3)	-0.002(3)	0.030(3)	-0.002(3)
C(14)	0.058(4)	0.058(4)	0.094(5)	0.002(3)	0.040(4)	-0.011(4)
C(15)	0.051(4)	0.107(6)	0.121(6)	0.023(4)	0.043(4)	0.008(5)
C(16)	0.067(4)	0. 093(5)	0.072(4)	-0.011(4)	0.036(4)	0.0(4)
C(17)	0.084(5)	0.064(4)	0.059(4)	-0.023(4)	0.043(4)	-0.014(3)
C(18)	0.064(4)	0.059(4)	0.069(4)	-0.010(3)	0.044(4)	-0.006(3)
O(19)	0.050(2)	0.124(4)	0.057(3)	-0.020(3)	0.020(2)	-0.035(3)
C(20)	0.044(3)	0.062(4)	0.046(3)	-0.008(3)	0.024(3)	-0.001(3)
O(21)	0.109(4)	0.069(3)	0.105(4)	0.028(3)	0.073(3)	0.027(3)
O(22)	0.060(3)	0.100(4)	0.065(3)	0.004(3)	0.041(2)	0.012(3)
C(23)	0.135(7)	0.138(8)	0.088(6)	-0.006(6)	0.073(6)	0.045(6)
C(24)	0.047(3)	0.058(4)	0.043(3)	0.013(3)	0.020(3)	-0.003(3)
O(25)	0.056(3)	0.096(3)	0.058(3)	0.015(2)	0.019(2)	0.029(3)
O(26)	0.072(3)	0.049(3)	0.051(2)	-0.000(2)	0.022(2)	0.008(2)
C(27)	0.117(6)	0.052(4)	0.078(5)	-0.000(4)	0.051(5)	0.019(4)
C(28)	0.049(3)	0.051(4)	0.058(4)	0.000(3)	0.025(3)	-0.000(3)
O(29)	0.060(3)	0.086(3)	0.060(3)	0.027(2)	0.028(2)	0.004(2)
O(30)	0.054(2)	0.087(3)	0.048(2)	0.014(2)	0.026(2)	-0.009(2)
C(31)	0.082(9)	0.067(9)	0.079(9)	0.024(7)	0.060(8)	-0.008(7)
C(31')	0.08(1)	0.08(1)	0.16(2)	0.016(9)	0.07(1)	-0.03(1)
N(32)	0.042(3)	0.061(3)	0.037(2)	-0.004(2)	0.025(2)	-0.005(2)
C(33)	0.039(3)	0.043(3)	0.039(3)	0.001(3)	0.020(3)	0.001(3)
C(34)	0.053(4)	0.060(4)	0.048(3)	0.009(3)	0.029(3)	0.010(3)
C(35)	0.048(4)	0.096(5)	0.057(4)	0.012(4)	0.024(3)	0.021(4)
N(36)	0.037(3)	0.083(4)	0.052(3)	-0.001(3)	0.017(2)	0.004(3)
N(37)	0.039(3)	0.052(3)	0.042(3)	-0.002(2)	0.018(2)	-0.002(2)
C(38)	0.089(5)	0.070(5)	0.089(5)	0.025(4)	0.063(4)	0.032(4)
N(39)	0.165(7)	0.083(5)	0.187(7)	0.010(5)	0.134(6)	0.040(5)
C(40)	0.054(4)	0.046(4)	0.044(3)	-0.010(3)	0.024(3)	-0.001(3)
C(41)	0.079(4)	0.055(4)	0.080(5)	0.009(4)	0.051(4)	0.008(4)
C(42)	0.096(5)	0.058(5)	0.103(6)	0.023(4)	0.058(5)	0.021(4)
C(43)	0.095(5)	0.063(5)	0.086(5)	-0.005(4)	0.050(4)	0.005(4)
C(44)	0.088(5)	0.070(5)	0.082(5)	-0.024(4)	0.056(4)	-0.003(4)
C(45)	0.063(4)	0.063(4)	0.066(4)	-0.005(3)	0.040(3)	0.001(3)
O(46)	0.044(2)	0.058(3)	0.047(2)	0.010(2)	0.024(2)	0.004(2)

preparation of **2a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 190-191°; ir (potassium bromide): ν cm^{-1} 3500, 3320 (NH_2), 1745, 1690 (CO), 1620, 1590; ^1H nmr (deuteriochloroform): δ 2.74 (3H, s, Me), 3.86 (3H, s, OMe), 3.95 (3H, s, OMe), 7.27-7.55 (3H, m, phenyl-H), 8.05-8.20 (2H, m, phenyl-H); ms: (LR) m/z (%) 341 (M^++1, 20), 340 (M^+, 100), 309 (11), 281 (11), 250 (15), 224 (39), 222 (20).

Anal. Calcd. for $C_{17}H_{16}N_4O_4$ (340.34): C, 60.00; H, 4.74; N, 16.46. Found: C, 60.18; H, 4.75; N, 16.52.

Trimethyl 7-(4-Cyano-3-methyl-1-phenyl-5-pyrazolyl)amino-4,5,5a,8-tetrahydro-3-methyl-1-phenyl-4,8-dioxo-1*H*-pyrazolo-[3,4-*e*]indolizine-5,5a,6-tricarboxylate (**3b**).

This compound (0.72 g, 1.11 mmoles) was obtained in 5.6% yield from 5-amino-3-methyl-1-phenylpyrazole-4-carbonitrile (**1b**) (3.96 g, 20 mmoles) and dimethyl acetylenedicarboxylate (2.84 g, 20 mmoles) in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless crystals, mp 263-266°; ir (potassium bromide): ν cm^{-1} 3240 (NH), 2225 (CN), 1750 (shoulder), 1740, 1682, 1640 (CO); uv (ethanol): λ max nm (log ε) 250 (shoulder, 4.54), 393 (3.29); ^1H nmr (deuteriochloroform): δ 2.34 (3H, s, Me), 2.52 (3H, s, Me), 3.51 (3H, s, OMe), 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 4.58 (1H, s, 5-H), 7.33-7.55 (10H, m, phenyl-H), 8.07 (1H, s, NH); ms: (LR) m/z (%) 650 (M^++1, 28), 649 (M^+, 68), 591 (37), 590 (100), 559 (22), 558 (60), 226 (14).

Anal. Calcd for $C_{33}H_{27}N_7O_8$ (649.63): C, 61.01; H, 4.19; N, 15.09. Found: C, 60.85; H, 4.27; N, 14.94.

Trimethyl 7-(4-Cyano-3-methylthio-1-phenyl-5-pyrazolyl) amino-4,5,5a,8-tetrahydro-3-methylthio-1-phenyl-4,8-dioxo-1*H*-pyrazolo[3,4-*e*]indolizine-5,5a,6-tricarboxylate (**3c**).

This compound (0.52 g, 0.73 mmole) was synthesized in 1.5% yield from 5-amino-3-methylthio-1-phenylpyrazole-4-carbonitrile (**1c**) (11.5 g, 50 mmoles), dimethyl acetylenedicarboxylate (9.0 g, 63 mmoles), and potassium carbonate (20 g, 145 mmoles) in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 255-257°; ir (potassium bromide): ν cm^{-1} 3340 (NH), 2210 (CN), 1725, 1705, 1692 (CO); uv (ethanol): λ max nm (log ε) 215 (4.60), 300 (4.51), 395 (4.56); ^1H nmr (deuteriochloroform): δ 2.55 (3H, s, SMe), 2.59 (3H, s, SMe), 2.52 (3H, s, Me), 3.50 (3H, s, OMe), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 4.58 (1H, s, 5-H), 7.42-7.58 (10H, m, phenyl-H), 8.04 (1H, s, NH) ms: (LR) m/z (%) 714 (M^++1, 27), 713 (M^+, 64), 654 (51), 653 (100), 622 (15), 593 (22).

Table 3

Fractional Coordinates and Isotropic Thermal Parameters for the Hydrogen Atoms, with their E.S.D.'s in Parentheses

Atom	X	Y	Z	U
Molecule I				
H(3)	0.223(1)	0.199(5)	0.155(1)	0.05(1)
H(6)	0.1072(9)	-0.096(4)	0.096(1)	0.009(9)
H(14)	0.241(1)	0.363(5)	0.275(1)	0.05(1)
H(15)	0.260(1)	0.368(6)	0.344(1)	0.06(2)
H(16)	0.256(1)	0.160(6)	0.381(1)	0.08(2)
H(17)	0.230(1)	-0.068(5)	0.346(1)	0.05(1)
H(18)	0.209(1)	-0.076(5)	0.273(1)	0.06(1)
H(23A)	0.091(1)	0.397(7)	0.149(2)	0.09(2)
H(23B)	0.079(5)	0.29(2)	0.157(5)	0.5(1)
H(23C)	0.072(1)	0.359(6)	0.099(2)	0.09(2)
H(27A)	0.200(2)	-0.458(8)	0.219(2)	0.14(3)
H(27B)	0.165(2)	-0.541(8)	0.176(2)	0.14(3)
H(27C)	0.172(2)	-0.51(1)	0.231(3)	0.22(4)
H(31A)	-0.015(2)	-0.30(1)	0.107(2)	0.17(3)
H(31B)	0.007(2)	-0.385(8)	0.089(2)	0.12(2)
H(31C)	0.009(1)	-0.411(6)	0.136(2)	0.09(2)
H(32)	0.051(1)	-0.058(5)	0.186(1)	0.03(1)
H(35)	0.079(1)	0.215(6)	0.309(2)	0.08(2)
H(41)	0.078(1)	-0.297(5)	0.232(1)	0.05(1)
H(42)	0.108(2)	-0.53(1)	0.236(2)	0.18(3)
H(43)	0.169(1)	-0.547(7)	0.295(2)	0.10(2)
H(44)	0.201(2)	-0.323(9)	0.349(2)	0.17(3)
H(45)	0.166(2)	-0.103(8)	0.340(2)	0.14(3)
Molecule II				
H(3)	0.179(1)	0.472(4)	0.104(1)	0.03(1)
H(6)	0.225(1)	0.197(6)	0.018(2)	0.08(2)
H(4)	0.060(1)	0.474(7)	0.020(2)	0.09(2)
H(5)	-0.004(2)	0.378(7)	-0.017(2)	0.11(2)
H(6)	-0.024(2)	0.135(8)	-0.041(2)	0.13(2)
H(7)	0.024(1)	-0.034(6)	-0.032(1)	0.07(2)
H(8)	0.088(1)	0.043(6)	0.002(1)	0.06(2)
H(23A)	0.208(2)	0.39(1)	-0.094(3)	0.19(4)
H(23B)	0.205(1)	0.518(7)	-0.068(2)	0.09(2)
H(23C)	0.170(4)	0.37(2)	-0.110(4)	0.39(8)
H(27A)	0.136(2)	-0.305(8)	0.019(2)	0.12(2)
H(27B)	0.178(2)	-0.307(9)	0.034(2)	0.17(3)
H(27C)	0.167(2)	-0.221(8)	0.064(2)	0.13(2)
H(32)	0.117(1)	0.085(5)	-0.130(1)	0.05(1)
H(35)	-0.007(1)	0.271(6)	-0.210(2)	0.08(2)
H(41)	0.090(1)	-0.177(5)	-0.125(1)	0.05(1)
H(42)	0.098(2)	-0.392(8)	-0.081(2)	0.12(2)
H(43)	0.063(1)	-0.431(7)	-0.054(2)	0.09(2)
H(44)	0.011(1)	-0.252(6)	-0.073(2)	0.08(2)
H(45)	0.006(1)	-0.024(5)	-0.110(1)	0.05(1)

Anal. Calcd. for $C_{33}H_{27}N_7O_8S_2$ (713.75): C, 55.53; H, 3.81; N, 13.74, S, 8.98. Found: C, 55.43; H, 3.88; N, 13.65; S, 9.10.

Table 4

Bond Distances, with their E.S.D.'s in Parentheses

Atom		Molecule I	Molecule II
N(1)	-N(2)	1.394(8)	1.391(6)
N(1)	-C(12)	1.362(6)	1.347(9)
N(1)	-C(13)	1.421(7)	1.434(7)
N(2)	-C(3)	1.320(8)	1.322(8)
C(3)	-C(4)	1.416(8)	1.40(1)
C(4)	-C(5)	1.446(6)	1.45(1)
C(4)	-C(12)	1.38(1)	1.376(6)
C(5)	-C(6)	1.530(9)	1.533(9)
C(5)	-O(19)	1.214(9)	1.230(6)
C(6)	-C(7)	1.558(8)	1.566(7)
C(6)	-C(20)	1.525(8)	1.524(8)
C(7)	-C(8)	1.506(9)	1.500(8)
C(7)	-N(11)	1.481(6)	1.467(7)
C(7)	-C(24)	1.549(8)	1.539(8)
C(8)	-C(9)	1.321(8)	1.338(6)
C(8)	-C(28)	1.472(6)	1.46(1)
C(9)	-C(10)	1.496(7)	1.487(9)
C(9)	-N(32)	1.370(8)	1.366(6)
C(10)	-N(11)	1.393(9)	1.381(5)
C(10)	-O(46)	1.201(6)	1.217(6)
N(11)	-C(12)	1.404(8)	1.381(7)
C(13)	-C(14)	1.377(8)	1.383(9)
C(13)	-C(18)	1.375(9)	1.361(8)
C(14)	-C(15)	1.38(1)	1.395(9)
C(15)	-C(16)	1.38(1)	1.37(1)
C(16)	-C(17)	1.376(9)	1.35(1)
C(17)	-C(18)	1.382(9)	1.402(9)
C(20)	-O(21)	1.182(6)	1.193(8)
C(20)	-O(22)	1.325(6)	1.323(9)
O(22)	-C(23)	1.466(9)	1.47(1)
C(24)	-O(25)	1.186(9)	1.200(5)
C(24)	-O(26)	1.323(8)	1.314(7)
O(26)	-C(27)	1.474(8)	1.475(8)
C(28)	-O(29)	1.202(8)	1.271(6)
C(28)	-O(30)	1.331(8)	1.266(7)
O(30)	-C(31)	1.478(7)	1.49(2)
O(29)	-C(31')		1.47(2)
N(32)	-C(33)	1.386(8)	1.407(6)
C(33)	-C(34)	1.357(9)	1.362(7)
C(33)	-N(37)	1.363(6)	1.354(8)
C(34)	-C(35)	1.401(9)	1.395(8)
C(34)	-C(38)	1.413(8)	1.42(1)
C(35)	-N(36)	1.319(9)	1.318(9)
N(36)	-N(37)	1.362(8)	1.375(5)
N(37)	-C(40)	1.434(8)	1.438(7)
C(38)	-N(39)	1.152(9)	1.138(11)
C(40)	-C(41)	1.386(8)	1.373(9)
C(40)	-C(45)	1.388(7)	1.38(1)
C(41)	-C(42)	1.39(1)	1.38(1)
C(42)	-C(43)	1.389(9)	1.38(1)
C(43)	-C(44)	1.36(1)	1.37(1)
C(44)	-C(45)	1.40(1)	1.39(1)

X-Ray Crystallographic Analysis of **3a**.

A yellow irregularly shaped crystal (0.3 x 0.1 x 0.1 mm) was obtained from a methanol solution: $C_{31}H_{23}N_7O_8$, molecular weight = 621.57; monoclinic, space group C2/c, a = 42.48(4), b = 8.707(7), c = 37.99(2)Å, β = 121.70(6)°, V = 11950(20)Å^3, Z = 16; μ (CuK_α radiation, λ =1.5418 Å) = 8.7 cm^{-1}. The cell dimesious and diffraction intensities were measured on a MAC Sciences (MXC18) diffractometer using graphite-monochromated CuK_α radiation ($-42 \le h \le 42$, $-8 \le k \le 0$, $0 \le 1 \le 37$). The ω-2θ scan mode with a scan rate of 8°/minute was employed for data collection with the ω scan range (1.0 + 0.2 x tans)°. Of the 6151 independent reflections which were collected, 4268 reflection ($I > 2\ \sigma$) were used for the structure determination and refinement. The structure was solved using direct methods utilizing programs in CRYSTAN-GM (Ver. 6.11, MAC Science). All non-hydrogen atoms not located by direct methods were

Table 5

Bond Angles, with their E.S.D.'s in Parentheses

Atom			Molecule I	Molecule II
N(2)	-N(1)	-C(12)	109.5(5)	110.9(4)
N(2)	-N(1)	-C(13)	118.3(4)	118.5(5)
C(12)	-N(1)	-C(13)	132.2(6)	130.1(5)
N(1)	-N(2)	-C(3)	104.8(5)	104.6(5)
N(2)	-C(3)	-C(4)	113.2(7)	112.0(4)
C(3)	-C(4)	-C(5)	134.0(7)	134.2(4)
C(3)	-C(4)	-C(12)	103.2(5)	105.1(5)
C(5)	-C(4)	-C(12)	122.8(6)	120.6(6)
C(4)	-C(5)	-C(6)	114.6(6)	115.3(4)
C(4)	-C(5)	-O(19)	124.5(6)	125.0(6)
C(6)	-C(5)	-O(19)	120.8(4)	119.7(6)
C(5)	-C(6)	-C(7)	112.0(4)	111.8(6)
C(5)	-C(6)	-C(20)	112.2(4)	108.3(5)
C(7)	-C(6)	-C(20)	109.1(5)	108.1(4)
C(6)	-C(7)	-C(8)	112.7(4)	112.9(5)
C(6)	-C(7)	-N(11)	111.3(4)	109.7(4)
C(6)	-C(7)	-C(24)	107.8(5)	109.4(3)
C(8)	-C(7)	-N(11)	101.3(5)	102.3(3)
C(8)	-C(7)	-C(24)	113.9(5)	112.5(5)
N(11)	-C(7)	-C(24)	109.6(3)	109.7(5)
C(7)	-C(8)	-C(9)	111.0(4)	110.1(5)
C(7)	-C(8)	-C(28)	119.0(5)	123.3(4)
C(9)	-C(8)	-C(28)	129.9(6)	126.6(5)
C(8)	-C(9)	-C(10)	110.1(5)	109.7(5)
C(8)	-C(9)	-N(32)	130.4(4)	128.2(6)
C(10)	-C(9)	-N(32)	119.1(5)	121.8(4)
C(9)	-C(10)	-N(11)	104.7(4)	105.4(4)
C(9)	-C(10)	-O(46)	129.3(6)	128.4(4)
N(11)	-C(10)	-O(46)	126.0(5)	126.2(6)
C(7)	-N(11)	-C(10)	111.5(4)	111.6(5)
C(7)	-N(11)	-C(12)	115.3(5)	115.9(3)
C(10)	-N(11)	-C(12)	125.7(4)	127.3(4)
N(1)	-C(12)	-C(4)	109.3(5)	107.4(5)
N(1)	-C(12)	-N(11)	127.1(6)	127.5(4)
C(4)	-C(12)	-N(11)	123.5(4)	125.0(6)
N(1)	-C(13)	-C(14)	118.8(5)	118.4(5)
N(1)	-C(13)	-C(18)	119.2(5)	120.1(6)
C(14)	-C(13)	-C(18)	122.0(5)	121.4(6)
C(13)	-C(14)	-C(15)	118.8(6)	118.0(6)
C(14)	-C(15)	-C(16)	120.2(6)	121.3(7)
C(15)	-C(16)	-C(17)	119.6(6)	119.5(6)
C(16)	-C(17)	-C(18)	121.3(6)	121.0(6)
C(13)	-C(18)	-C(17)	118.1(5)	118.9(6)
C(6)	-C(20)	-O(21)	125.2(5)	124.5(7)
C(6)	-C(20)	-O(22)	110.1(4)	110.7(5)
O(21)	-C(20)	-O(22)	124.7(5)	124.4(6)
C(20)	-O(22)	-C(23)	115.7(4)	115.4(6)
C(7)	-C(24)	-O(25)	124.0(5)	124.5(5)
C(7)	-C(24)	-O(26)	110.5(6)	109.7(4)
O(25)	-C(24)	-O(26)	125.5(5)	125.9(6)
C(24)	-O(26)	-C(27)	115.6(6)	117.1(4)
C(8)	-C(28)	-O(29)	123.0(6)	118.0(5)
C(8)	-C(28)	-O(30)	111.5(5)	117.5(4)
O(29)	-C(28)	-O(30)	125.4(4)	124.5(6)
C(28)	-O(30)	-C(31)	116.1(5)	118.1(6)
C(28)	-O(29)	-C(31')		115.2(7)
C(9)	-N(32)	-C(33)	125.4(4)	124.8(6)
N(32)	-C(33)	-C(34)	130.2(5)	128.8(6)
N(32)	-C(33)	-N(37)	122.4(5)	123.0(4)
C(34)	-C(33)	-N(37)	107.3(5)	108.1(4)
C(33)	-C(34)	-C(35)	104.7(5)	104.2(6)
C(33)	-C(34)	-C(38)	126.5(6)	125.7(5)
C(35)	-C(34)	-C(38)	128.7(7)	129.9(5)
C(34)	-C(35)	-N(36)	112.3(7)	112.9(5)
C(35)	-N(36)	-N(37)	104.5(5)	104.2(4)
C(33)	-N(37)	-N(36)	111.2(5)	110.6(4)
C(33)	-N(37)	-C(40)	130.1(6)	129.5(4)
N(36)	-N(37)	-C(40)	118.6(4)	119.6(5)
C(34)	-C(38)	-N(39)	179.2(7)	177.9(6)
N(37)	-C(40)	-C(41)	120.0(4)	120.3(7)
N(37)	-C(40)	-C(45)	118.8(5)	119.3(5)
C(41)	-C(40)	-C(45)	121.2(6)	120.4(6)
C(40)	-C(41)	-C(42)	120.8(5)	119.6(8)
C(41)	-C(42)	-C(43)	117.6(6)	120.4(7)
C(42)	-C(43)	-C(44)	122.3(8)	119.4(7)
C(43)	-C(44)	-C(45)	120.3(6)	120.9(8)
C(40)	-C(45)	-C(44)	117.9(6)	119.3(6)

found using the successive difference Fourier maps. Hydrogen atoms were included at calculated positions. The methyl group (C(31), C(31')) of the methyl ester group bonded to C(8) of **II** is disordered (See Figure 3). In the refinement process the disordered carbon-sites were assigned occupancy factors of 0.5. The structure was refined using a full-matrix least-squares procedure with isotropic thermal parameters for hydrogen atoms and the carbon atoms of the disordered methyl ester group and with anisotropic thermal parameters for the rest of the non-hydrogen atoms. The final R and Rw values were 0.050 and 0.050, respectively.

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