Synthesis and Some Reactions of Ethyl 2-[2-(Substituted Methyleneamino)anilino]cyclohepta[*b*]pyrrole-3-carboxylates

Noritaka ABE* and Akikazu KAKEHI†
Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi 753
†Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380
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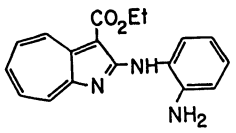
We synthesized Schiff bases, ethyl 2-[2-(benzilideneamino)anilino]cyclohepta[*b*]pyrrole-3-carboxylate (**2a**) and ethyl 2-[2-(2-butenylideneamino)anilino]cyclohepta[*b*]pyrrole-3-carboxylate (**2b**), from ethyl 2-(2-aminoanilino)-cyclohepta[*b*]pyrrole-3-carboxylate (**1**) in excellent yields by treating **1** with benzaldehyde or 2-butenal in the presence of molecular sieves 4A, respectively. Further, the cyclization and cycloaddition reactions of the Schiff bases were investigated. Treatment of **2a** with iron(III) chloride or Pd–C gave ethyl 2-(2-phenylbenzimidazol-1-yl)cyclohepta[*b*]pyrrole-3-carboxylate and 12*H*-5,13-dihydrocyclohepta[1′,2′:4,5]pyrrolo[2,3-*b*][1,5]benzodiazepin-12-one (**4**). A similar treatment of **2b**, however, gave ethyl 2-(4-methylqinolin-8-yl)aminocyclohepta[*b*]pyrrole-3-carboxylate and **4**. The reaction of **2a** with dimethyl acetylenedicarboxylate (DMAD) gave 15a-ethyl 5,6,7,15-tetramethyl 15,15a-dihydro-14*H*-pyrrolo[2′,1′:1,2]isoquino[3,4-*b*][1,5]benzodiazepine-5,6,7,15,15a-pentacarboxylate (**6**) and methyl 4-(3-ethoxycarbonylcyclohepta[*b*]pyrrol-2-yl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-ylideneacetate (**7**). The reaction of **2b** with DMAD, however, gave the 1,4-dihydropyridine derivative as a Diels–Alder adduct, along with **7**. The structures of **6** and **7** were confirmed by single-crystal X-ray analyses.

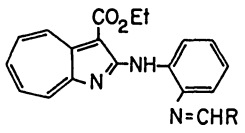
The reactions of aromatic and heteroaromatic Schiff bases with dimethyl acetylenedicarboxylate (DMAD) are of interest and some reports have been given.[1–3] Reactions in this fields have been reviewed twice.[4,5] Normally, reactions of Schiff bases with DMAD afforded the corresponding 1,2-dihydropyridine derivatives. Recently, we reported that 2-(2-aminoanilino)-cyclohepta[*b*]pyrroles are useful materials for the synthesis of novel azaazulene-fused heterocycles.[6] In a continuation of our work, we synthesized the Schiff bases (**2a**, **2b**) of ethyl 2-(2-aminoanilino)cyclohepta-[*b*]pyrrole-3-carboxylate[6] (**1**), and investigated some reactions of the Schiff bases, especially cycloaddition reactions with DMAD. We found that the Schiff base (**2a**) underwent an interesting cycloaddition reaction, as well as subsequent ring transformations.

The treatment of **1** with benzaldehyde or 2-butenal in the presence of molecular sieves 4A for 4 d at room temperature gave Schiff bases (**2a** and **2b**) in excellent yields. The Schiff base **2a** was easily hydrolyzed, giving **1**.

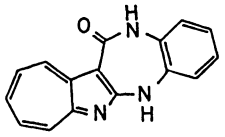
Treatment of **2a** with iron(III) chloride in refluxing ethanol for 30 h gave ethyl 2-(2-phenylbenzimidazol-1-yl)cyclohepta[*b*]pyrrole-3-carboxylate (**3**) (42% yield) and 12*H*-5,13-dihydrocyclohepta[1′,2′:4,5]pyrrolo[2,3-*b*][1,5]benzodiazepin-12-one[6] (**4**) (11% yield). These structures were deduced by their spectroscopic data as well as elemental analyses. The formation of the former is appreciable as ordinary benzimidazole syntheses.[7] The latter would be formed from **1**, which is presumably a hydrolyzed product of **2a**. The reaction of **2a** with Pd–C in refluxing *t*-butylbenzene gave rise to similar results, giving **3** (34% yield) and **4** (14% yield). In contrast, the reaction of **2b** with iron(III) chloride gave no benzimidazole derivative; instead, it gave ethyl



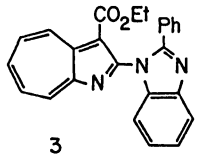
1



2a: R = Ph
2b: R = -CH=CHCH3



4



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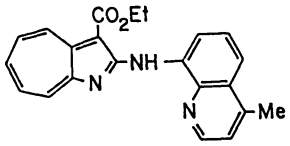
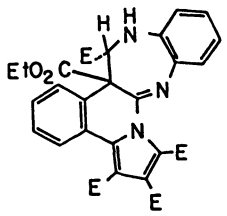


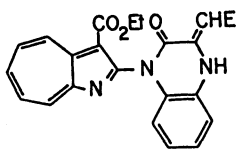
5

2-(4-methylqinolin-8-yl)amino-cyclohepta[*b*]pyrrole-3-carboxylate (**5**) (16% yield) and **4** (13% yield).

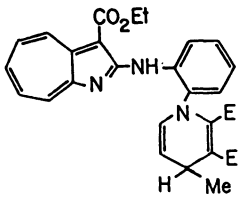
The reaction of **2a** with DMAD in refluxing acetonitrile for 48 h gave a complex mixture. Two products, 15a-ethyl 5,6,7,15-tetramethyl 15,15a-dihydro-14*H*-pyrrolo[2′,1′:1,2]isoquino[3,4-*b*][1,5]benzodiazepine-5,6,7,15,15a-pentacarboxylate (**6**) (14% yield) as 1 : 2-adduct and methyl 4-(3-ethoxycarbonylcyclohepta[*b*]pyrrol-2-yl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-ylideneacetate



6: E = CO_2Me



7: E = CO_2Me



8: E = CO_2Me

(**7**) (24% yield) as 1 : 1-adduct, were isolated from the mixture by silica-gel column chromatography. No other 1 : 1-adduct was isolated. Through the reaction of **2a** with DMAD, no normal 1 : 2-cycloadducts (1,2-dihydropyridines)[1–5] which could react on the methylideneamine moiety were observed.

The structures of these compounds were determined by elemental analyses and spectral inspections, and confirmed by single-crystal X-ray analyses. From an inspection of the ^{1}H NMR spectrum of **6** (signals resonated at δ=6.7—7.9), it is considered that a cyclohepta[*b*]pyrrole ring does not exist. Instead, the exitence of two benzene rings is suggested. One methine proton at δ=5.42 (J=7.9 Hz) is coupled with an NH proton at δ=5.11. Although three methyl ester signals were observed under an ordinary resonating field, one methyl ester signal was shielded and observed at δ=3.33. These facts suggest that a ring transformation attended cycloaddition. From an inspection of the ^{1}H NMR spectrum of **7** (signals resonated at δ=8.0—9.9), it is considered that a cyclohepta[*b*]pyrrole ring remains. One methyl ester exists (δ=3.80). From an inspection of the IR spectrum, the existence of amido carbonyl (1630 cm^{-1}) has been considered. These considerations led us to assuming the structures. A PLUTO drawing[8] of **6** is shown in Fig. 1, and an ORTEP drawing[9] of **7** is shown in Fig. 2.

One possible mechanism for the formation of **6** is shown in Scheme 1. The 1 : 2 molar addct (**A**) would be formed first, which would then cyclize as an arrow to give intermediates **B** and **C**, furnishing **6**. The formation of a 1 : 2-adduct, such as intermediate **A**, is often observed.[4,5] Although the existence of a cyclopentadiene derivative, or its further reacted product, as a counterpart of **C**, was not confirmed, it is probable, considering that isocyanides react with DMAD to give cyclopentadienylideneamine derivatives.[4,12,13] The formation of **7** resembles the case of 2-(4-nitrobenzylidene)-

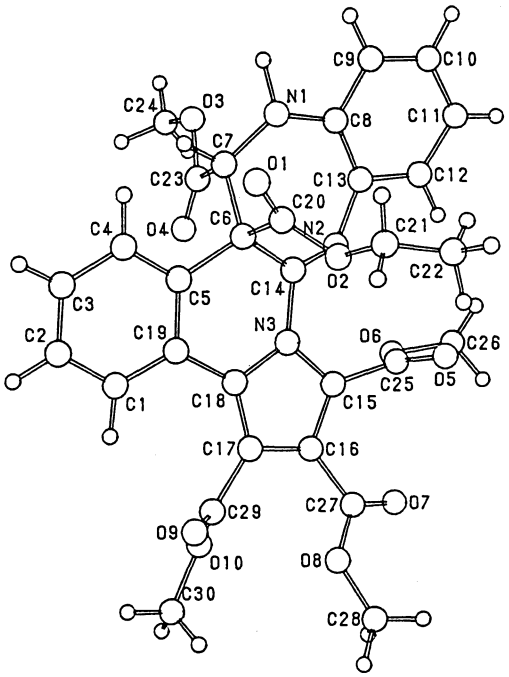


Fig. 1. PLUTO drawing of **6**.

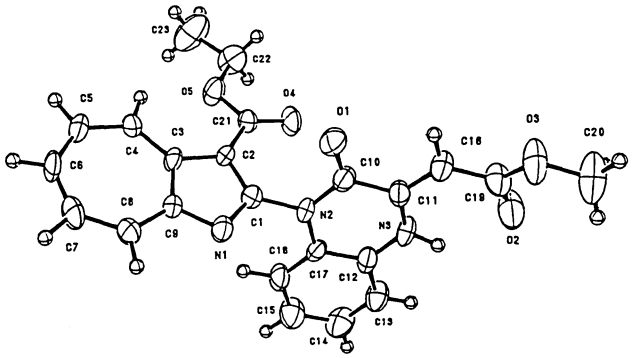
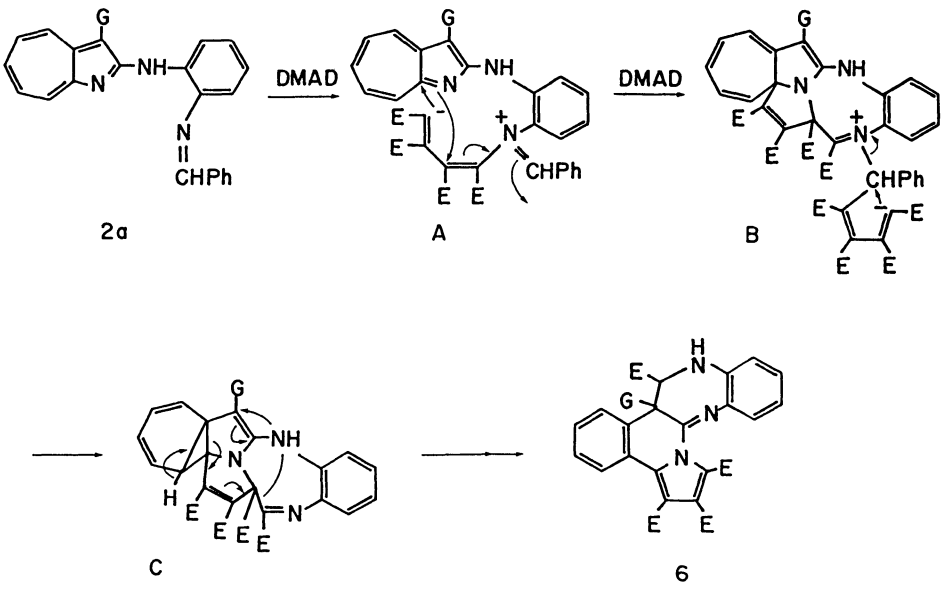


Fig. 2. ORTEP drawing of **7**.

aminoaniline with DMAD.[4]

The reaction of **2b** with DMAD is different from that of **2a**; two compounds, 1,4-dihydropyridine derivative **8** (37% yield) and **7** (36% yield), were isolated. The structure of **8** was determined by elemental analyses and spectral inspections. In the ^{1}H NMR spectrum of **8**, one methyl signal at δ=1.56 (d, J=6.7 Hz), which coupled with a methine proton at δ=5.85 (dq, J=7.3 and 6.7 Hz), two vinylic protons at δ=5.45 (dd, J=7.3 and 1.8 Hz) and 6.90—7.05 (overlapped with three benzene ring protons), and one deshielded proton on the benzene ring at δ=8.07 (d, J=7.3 Hz) were seen, along with signals of one ethyl ester, two methyl esters, and the protons on the cyclohepta[*b*]pyrrole ring. The signals of the protons on the cyclohepta[*b*]pyrrole ring appeared under an ordinary resonance field. In its IR spectrum, three ester carbonyl signals were seen at 1746, 1710, and 1682 cm^{-1}. These observations were consist-



Scheme 1.

ant with the structure. Compound **8** is a Diels–Alder adduct of the 2-butenylideneamine moiety of **2b** with DMAD. Upon the reaction of cinnamylideneamine derivatives with DMAD, no such products were obtained.[3–5]

Experimental

All of the melting points are uncorrected. The ^{1}H (250 MHz) NMR spectra were taken on a Hitachi R-250H spectrometer using $CDCl_3$ as a solvent (TMS as an internal standard). The IR spectra were recorded for Nujol mulls with a Hitachi 270-50 infrared spectrophotometer. The mass spectra were determined with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. Column chromatography was performed on a Kieselgel 60.

Synthesis of 2a and 2b. A mixture of **1**[6] (0.617 g), benzaldehyde (0.4 ml), and molecular sieves 4A (5.0 g) in dry benzene (50 ml) was stirred for 4 d at room temperature; the solvent was then filtered and the molecular sieves washed with chloroform. The combined filtrate was evaporated and the residue recrystallized from cyclohexane to give **2a** (0.757 g, 95%) as yellow needles, mp 170—171 °C. ^{1}H NMR δ=1.46 (3H, t, J=7.3 Hz), 4.52 (2H, q, J=7.3 Hz), 7.08 (1H, dd, J=7.9 and 7.3 Hz), 7.29 (1H, t, J=7.9 Hz), 7.39 (1H, dd, J=7.9 and 7.3 Hz), 7.45—7.55 (4H, m), 7.65 (1H, t, J=10.4 Hz), 7.69 (1H, t, J=10.4 Hz), 8.17—8.23 (2H, m), 8.30 (1H, d, J=10.4 Hz), 8.69 (1H, s), 8.94 (1H, d, J=10.4 Hz), 9.19 (1H, d, J=7.9 Hz), and 11.12 (1H, brs) ; IR 3260 (NH), 1660 (C=O), and 1626 cm^{-1} (C=N). Found: C, 75.77; H, 5.36; N, 10.69%. Calcd for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63%.

In a similar manner, **2b** was synthesized from **1** and 2-butenal in 94% yield.

2b: Yellow needles (from hexane), mp 145—146 °C. ^{1}H NMR δ=1.52 (3H, t, J=7.0 Hz), 2.02 (3H, d, J=6.1 Hz), 4.57 (2H, q, J=7.0 Hz), 6.45—6.70 (2H, m), 7.00—7.13 (2H, m), 7.28—7.40 (1H, m), 7.58 (1H, t, J=9.8 Hz), 7.68 (1H, t, J=9.8 Hz), 7.72 (1H, dd, J=10.4 and 9.8 Hz), 8.24 (1H, d, J=8.5 Hz), 8.32 (1H, d, J=10.4 Hz), 9.02 (1H, d, J=9.8 Hz), 9.11 (1H, d, J=7.9 Hz), and 10.63 (1H, brs); IR 3228 (NH), 1666 (C=O), and 1646 cm^{-1} (C=N). Found: C, 73.81; H, 5.80; N, 11.81%. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69%.

Hydrolysis of 2a. After a mixture of **2a** (0.395 g) and TsOH (0.05 g) in ethanol (20 ml) was refluxed for 4 h, the solvent was evaporated. The residue was chromatographed with chloroform to give **1** (0.285 g, 93%).

Reaction of 2a with Iron(III) Chloride. To a solution of **2a** (0.380 g) in ethanol (20 ml) saturated aq iron(III) chloride solution (2 ml) was added; after the mixture was refluxed for 30 h, the solvent was evaporated. Water was added to the residue; the mixture was then acidified with dil HCl, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. The residue was chromatographed with chloroform to give **1** (0.018 g, 6%) and **3** (0.159 g, 42%). Elution with chloroform–ethyl acetate (1 : 1) gave **4**[6] (0.028 g, 11%).

3: Yellow needles (from hexane–dichloromethane), mp 138—139.5 °C. ^{1}H NMR δ=0.85 (3H, t, J=7.0 Hz), 3.84 (1H, dq, J=10.4 and 7.0 Hz), 3.98 (1H, dq, J=10.4 and 7.0 Hz), 7.15—7.40 (6H, m), 7.57 (2H, d, J=6.7 Hz), 7.90 (1H, d, J=7.9 Hz), 8.03 (1H, t, J= 9.8 Hz), 8.08 (1H, t, J=9.8 Hz), 8.18 (1H, t, J=9.8 Hz), 8.93 (1H, d, J=9.8 Hz), and 9.64 (1H, d, J=9.8 Hz); IR 1676 cm^{-1} (C=O). Found: C, 76.38; H, 4.80; N, 10.81%. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68%.

Reaction of 2a with Pd-C. After a mixture of **2a** (0.110 g) and 5% Pd-C (0.200 g) in *t*-butylbenzene (10 ml) was refluxed for 4 d, the solvent was evaporated. The residue was chromatographed and gave **1** (0.030 g, 35%), **3** (0.037 g, 34%), and **4** (0.010 g, 14%), successively.

Reaction of 2b with Iron(III) Chloride. A mixture of **2b** (0.360 g) and saturated aq iron(III) chloride solution (2 ml) in ethanol (20 ml) was refluxed for 20 h and worked up in the same way as for **2a**. Chromatography of the residue gave **5** (0.058 g, 16%) and **4** (0.035 g, 13%), successively.

5: Yellow needles (from hexane), mp 172—173 °C. ^{1}H NMR δ=1.59 (3H, t, J=7.3 Hz), 2.86 (3H, s), 4.67 (2H, q,

J=7.3 Hz), 7.35 (1H, d, J=8.6 Hz), 7.44 (1H, d, J=7.9 Hz), 7.57 (1H, t, J=8.6 Hz), 7.59 (1H, t, J=9.8 Hz), 7.72 (1H, t, J=9.8 Hz), 7.74 (1H, dd, J=10.4 and 9.8 Hz), 8.06 (1H, d, J=8.6 Hz) 8.38 (1H, d, J= 9.8 Hz), 9.12 (1H, d, J=10.4 Hz), 9.40 (1H, d, J=7.9 Hz) and 11.83 (1H, brs); IR 3292 (NH) and 1686 cm^{-1} (C=O). Found: C, 73.98; H, 5.61; N, 11.69%. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76%.

Reaction of 2a with DMAD. After a mixture of **2a** (0.500 g) and DMAD (0.540 g) in dry acetonitrile (50 ml) was refluxed for 48 h, the solvent was evaporated. The residue was chromatographed with benzene–chloroform (1 : 1) to give **1** (0.047 g, 15%) and **6** (0.103 g, 14%), successively. Elution with chloroform gave **7** (0.129 g, 24%).

6: Pale yellow prisms (from hexane–dichloromethane), mp 193—194 °C. ^{1}H NMR δ=0.87 (3H, t, J=7.3 Hz), 3.33 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 3.98 (3H, s), 3.70—4.10 (2H, m), 5.11 (1H, brd, J=7.9 Hz), 5.42 (1H, d, J=7.9 Hz), 6.78 (1H, d, J=7.9 Hz), 6.89 (1H, dd, J=7.9 and 7.3 Hz), 7.11 (1H, dd, J=7.9 and 7.3 Hz), 7.25—7.40 (3H, m), 7.58 (1H, dm, J=7.9 Hz), and 7.82 (1H, dm, J=7.9 Hz); IR 3428 (NH), 1732, and 1714 cm^{-1} (C=O); MS m/z (rel intensity) 589 (16, M^+), 557 (11), 530 (100), 498 (15), 466 (53), 438 (12), 280 (86), and 236 (6). Found: C, 61.46; H, 4.80; N, 7.20%. Calcd for $C_{30}H_{27}N_3O_{10}$: C, 61.12; H, 4.62; N, 7.13%.

7: Yellow needles (from hexane), mp 151—152 °C. ^{1}H NMR δ=1.04 (3H, t, J=7.0 Hz), 3.80 (3H, s), 4.05—4.25 (2H, m), 5.92 (1H, s), 6.30 (1H, d, J=8.5 Hz), 6.75—6.90 (1H, m), 7.05—7.15 (2H, m), 8.05—8.30 (3H, m), 8.94 (1H, d, J=10.4 Hz), 9.85 (1H, d, J=10.4 Hz), and 11.27 (1H, brs); IR 3210 (NH), 1698, 1652, and 1630 cm^{-1} (C=O). Found: C, 66.38; H, 4.86; N, 10.09%. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07%.

Reaction of 2b with DMAD. After a mixture of **2b** (0.500 g), DMAD (0.750 g), and 5% Pd–C (0.500 g) in dry acetonitrile (50 ml) was refluxed for 4 h, the solvent was evaporated. The residue was chromatographed with benzene–chloroform (1 : 1) to give **8** (0.256 g, 37%). Elution with chloroform gave **7** (0.210 g, 36%).

8: Orange needles (from hexane), mp 110—112 °C. ^{1}H NMR δ=1.35 (3H, t, J=7.0 Hz), 1.56 (3H, d, J=6.7 Hz), 3.71 (3H, s), 3.98 (3H, s), 4.39 (1H, dd, J=10.4 and 7.0 Hz), 4.50 (1H, dd, J=10.4 and 7.0 Hz), 5.30 (1H, s), 5.45 (1H, dd, J=7.3 and 1.8 Hz), 5.85 (1H, dq, J=7.3 and 6.7 Hz), 6.90—7.05 (4H, m), 7.70—7.85 (3H, m), 8.07 (1H, d, J=7.3 Hz), 8.41 (1H, d, J=9.6 Hz), and 9.09 (1H, dd, J=9.2 and 2.4 Hz); IR 1746, 1710, and 1682 cm^{-1} (C=O). Found: C, 66.79; H, 5.57; N, 8.32%. Calcd for $C_{28}H_{27}N_3O_6$: C, 67.05; H, 5.43; N, 8.38%.

Single-Crystal X-Ray Structure Determination of 6 and 7. A single crystal of **6** was grown from a hexane–dichloromethane solution; a single crystal of **7** was grown from a hexane solution. A yellow monoclinic crystal for **6** and yellow triclinic crystal for **7** were used for structure determinations. The X-ray analysis data are shown in Table 1. Tables of the coordinates, bond lengths, bond and torsion angles, as well as F_o-F_c tables, are deposited as Document No. 8998 at the Office of the Editor of Bull. Chem. Soc. Jpn. A PLUTO drawing of **6** is shown in Fig. 1, and an ORTEP drawing of **7** is

Table 1. Crystal and Structure Analyses Data of Compounds **6**, **7**

	6	**7**
Formula	$C_{30}H_{27}N_3O_{10}$	$C_{23}H_{19}N_3O_5$
Formula weight	589.56	417.42
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/a$; Z=4	$P\bar{1}$; Z=2
Lattice paramaters		
a/Å	16.461(9)	9.994(3)
b/Å	9.824(2)	12.257(4)
c/Å	17.472(2)	9.305(5)
α/°		109.27(3)
β/°	92.06(3)	107.92(3)
γ/°		91.91(3)
V/Å^3	2824(2)	1012.1(7)
D_{calcd}/g cm^{-1}	1.387	1.370
Crystal size/mm^3	0.08×0.20×0.42	0.14×0.36×0.38
Diffractometer	Rigaku AFC5S	Rigaku AFC5S
Radiation	Mo $K\alpha$ (λ=0.71069 Å)	Mo $K\alpha$ (λ=0.71069 Å)
Monochrometer	Graphite	Graphite
Scan type	ω–2θ	ω–2θ
2θ Max	55.0°	55.0°
Computer program	TEXSAN System[a)]	TEXSAN System[a)]
Structure solution	Direct method; MITHRIL[b)]	Direct method; MITHRIL[b)]
Hydrogen atom treatment	Calculated, not refined	Calculated, not refined
Refinement	Full-matrix, anisotropic	Full-matrix, anisotropic
Least-squares weight	$4F_o^2/\sigma(F_o^2)$	$4F_o^2/\sigma(F_o^2)$
No. of measurement ref.	Total: 5799, Unique: 5562	Total: 4889, Unique: 4624
No. of observations[c)]	917	1462
No. of variables	388	280
Residuals R; R_w	0.056; 0.052	0.067; 0.071
Max shift/Error	2.59	0.01
$\Delta\rho_{max}$/e$^-$ Å^{-3}	0.22	0.58

a) See Ref. 10. b) See Ref. 11. c) $I<3.00\sigma$ (I).

shown in Fig. 2.

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