

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

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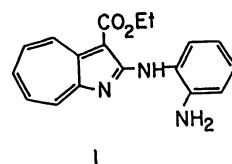
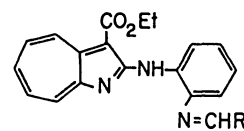
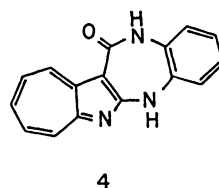
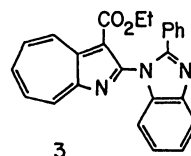
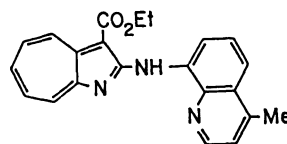
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We synthesized Schiff bases, ethyl 2-[2-(benzylideneamino)anilino]cyclohepta[b]pyrrole-3-carboxylate (**2a**) and ethyl 2-[2-(2-butenylideneamino)anilino]cyclohepta[b]pyrrole-3-carboxylate (**2b**), from ethyl 2-(2-aminoanilino)-cyclohepta[b]pyrrole-3-carboxylate (**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-methylquinolin-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-carboxylate⁶⁾ (**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.

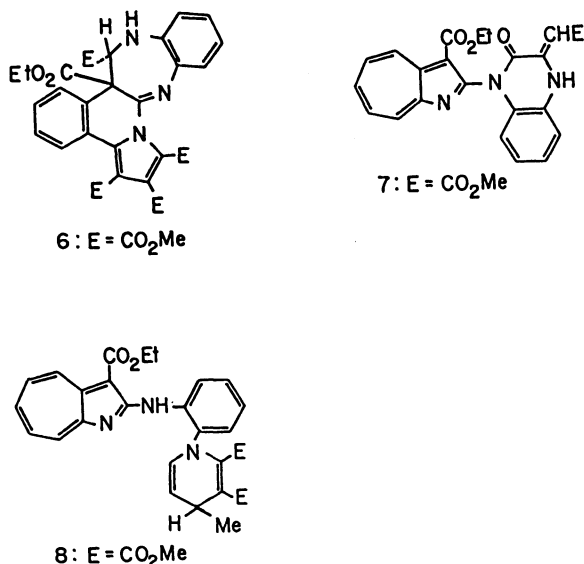
The treatment of **1** with benzaldehyde or 2-butenal in the presence of molecular sieves 4A for 4 d at room temperature gave Schiff bases (**2a** and **2b**) in excellent yields. The Schiff base **2a** was easily hydrolyzed, giving **1**.

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-one⁶⁾ (**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****3****5**

2-(4-methylquinolin-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



(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 methylenimine 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 ¹H NMR spectrum of **6** (signals resonated at $\delta=6.7-7.9$), it is considered that a cyclohepta[*b*]pyrrole ring does not exist. Instead, the existence of two benzene rings is suggested. One methine proton at $\delta=5.42$ ($J=7.9$ Hz) is coupled with an NH proton at $\delta=5.11$. Although three methyl ester signals were observed under an ordinary resonating field, one methyl ester signal was shielded and observed at $\delta=3.33$. These facts suggest that a ring transformation attended cycloaddition. From an inspection of the ¹H NMR spectrum of **7** (signals resonated at $\delta=8.0-9.9$), it is considered that a cyclohepta[*b*]pyrrole ring remains. One methyl ester exists ($\delta=3.80$). 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 drawing⁸⁾ of **6** is shown in Fig. 1, and an ORTEP drawing⁹⁾ of **7** is shown in Fig. 2.

One possible mechanism for the formation of **6** is shown in Scheme 1. The 1:2 molar adduct (**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 cyclopentadienyldieneamine derivatives.^{4,12,13)} The formation of **7** resembles the case of 2-(4-nitrobenzylidene)-

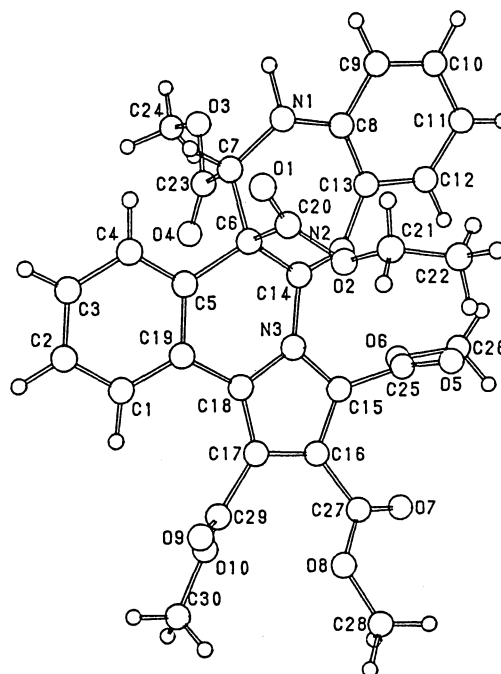


Fig. 1. PLUTO drawing of **6**.

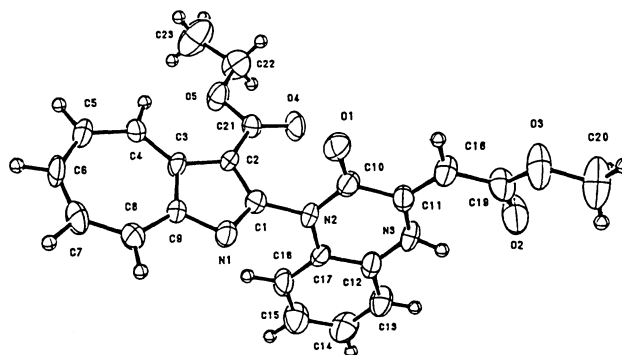
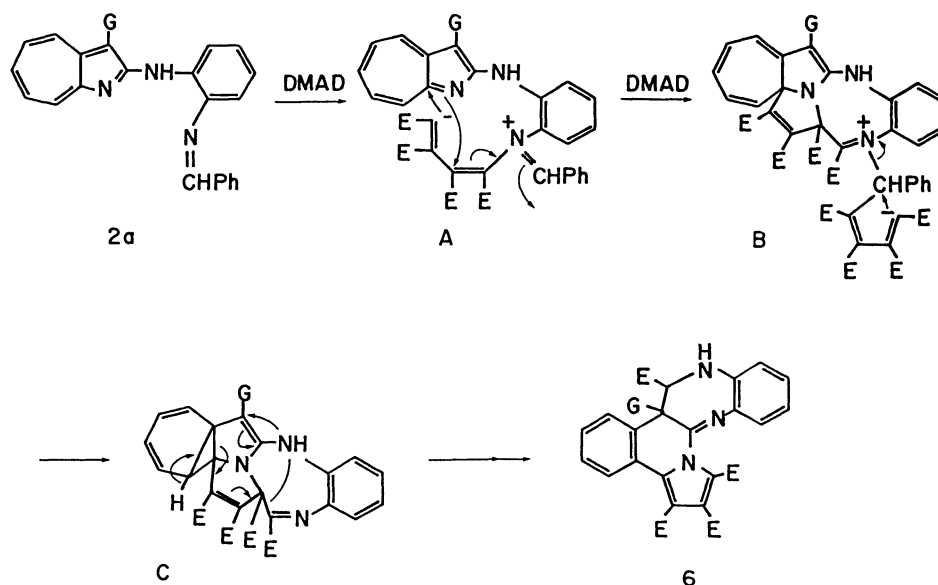


Fig. 2. ORTEP drawing of **7**.

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 ¹H NMR spectrum of **8**, one methyl signal at $\delta=1.56$ (d, $J=6.7$ Hz), which coupled with a methine proton at $\delta=5.85$ (dq, $J=7.3$ and 6.7 Hz), two vinylic protons at $\delta=5.45$ (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 $\delta=8.07$ (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 ^1H (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. ^1H 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 $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2$: 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. ^1H 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 $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2$: 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. ^1H 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 $\text{C}_{25}\text{H}_{19}\text{N}_3\text{O}_2$: 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. ^1H 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 $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2$: 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. ^1H NMR $\delta=0.87$ (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 $\text{C}_{30}\text{H}_{27}\text{N}_3\text{O}_{10}$: C, 61.12; H, 4.62; N, 7.13%.

7: Yellow needles (from hexane), mp 151–152 °C. ^1H NMR $\delta=1.04$ (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 $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_5$: 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. ^1H NMR $\delta=1.35$ (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 $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_6$: 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	$\text{C}_{30}\text{H}_{27}\text{N}_3\text{O}_{10}$	$\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_5$
Formula weight	589.56	417.42
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/a$; $Z=4$	$P\bar{1}$; $Z=2$
Lattice parameters		
$a/\text{\AA}$	16.461(9)	9.994(3)
$b/\text{\AA}$	9.824(2)	12.257(4)
$c/\text{\AA}$	17.472(2)	9.305(5)
$\alpha/^\circ$		109.27(3)
$\beta/^\circ$	92.06(3)	107.92(3)
$\gamma/^\circ$		91.91(3)
$V/\text{\AA}^3$	2824(2)	1012.1(7)
$D_{\text{calcd}}/\text{g cm}^{-3}$	1.387	1.370
Crystal size/ mm^3	$0.08 \times 0.20 \times 0.42$	$0.14 \times 0.36 \times 0.38$
Diffractionmeter	Rigaku AFC5S	Rigaku AFC5S
Radiation	Mo $K\alpha$ ($\lambda=0.71069$ \AA)	Mo $K\alpha$ ($\lambda=0.71069$ \AA)
Monochromator	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
$\Delta\rho_{\text{max}}/\text{e}^- \text{\AA}^{-3}$	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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