Beckmann Reaction of Oximes of 3a-Aryl-5,6a-diphenyl-3a,6a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(3*H*)-dione and Its Derivatives

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Synopsis. In the reaction with pyrrolidine, the (*Z*)-6-oxime (**2**) of 3a-aryl-5,6a-diphenyl-3a,6a-dihydro-2*H*-furo-[3,2-*b*]pyrrole-2,6(3*H*)-dione (**1**) gave the (*Z*)-oxime (**3**) in which the lactone ring was opened. (*Z*)-Oxime **3** isomerized on silica gel to give (*E*)-oxime **4**. Treatment of **2** with tosyl chloride in aqueous ethanolic sodium hydroxide afforded 5-aryl-2-cyano-2-phenyl-1*H*-pyrrol-3(2*H*)-ones (**7**) in yields of 41—90%, while both **3a** and **4a** gave the pyrroline-ring-opened product **8** in moderate yields.

Recently it was reported that in the reaction with nucleophiles, 3a,5,6a-triaryl-3a,6a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(3*H*)diones[1,2] **1** undergo a ring-transformation to give 3-aroyl-2,5-diarylpyrrole derivatives.[3] The crucial feature of this transformation is the cleavage of the central C(3a)–C(6a) bond, after the lactone ring of **1** has been opened by nucleophiles. The Beckmann rearrangement of the oxime (**2**) of **1** and its derivatives **3** and **4** was expected to give ring-expanded products via the cleavage of either the C(6)–C(5) or C(6a)–C(6) bond.

The present paper describes the results of the Beckmann rearrangementof oximes **2**, **3**, and **4**.

Results and Discussion

Preparation of Oximes 2, 3, and 4. Oximes **2** of 3a-aryl-5,6a-diphenyl-3a,6a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(3*H*)-dione (**1**) were prepared by treatment with hydroxylammonium chloride in the presence of sodium acetate in ethanol under reflux conditions. The lactone ring of **2** was then cleaved with pyrrolidine at room temperature to give (*Z*)-oxime **3**, the geometry of which was established by X-ray crystallographic analysis of **3a** (Fig. 1). Compound **2** was determined to have (*Z*)-geometry. Compounds **3a** and **3b** isomerized to (*E*)-oximes **4a** and **4b** upon chromatography on silica gel (ethyl acetate–dichloromethane), while **2** and **3c** were inert to the treatment mentioned above. Both (*Z*)-oxime **3a** and (*E*)-oxime **4a** eliminated pyrrolidine, giving **2a** in 85—>99% yields, upon being refluxed in ethanol. In the presence of additional pyrrolidine, **3a** gave a mixture of **2a** and **3a** in refluxing ethanol (Scheme 1). The facts mentioned above might suggest that (*Z*)-oxime **2** is stabilized by an intramolecular hydrogen bond and that in the lactone-ring-opened oximes **3** and **4**, steric crowding in the vicinity of the oxime moiety makes (*E*)-oxime **4** more favorable than (*Z*)-oxime **3**.

Carbamoylmethyl-substituted ketone **5**[3] formed neither **3a** nor **4a** in the reaction with hydroxylamine in ethanol under reflux conditions; pyrrole-3-carboxamide **6**[3] and **2a** were obtained in 14 and 28% yields, respectively.

Beckmann Reaction. Oximes **2**, **3a**, and **4a** were treated with tosyl chloride in the presence of sodium hydroxide[4] (Scheme 2). Compound **2a** gave 2-cyano-2,5-

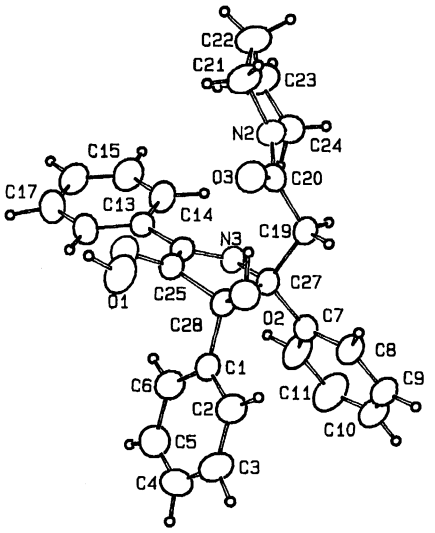
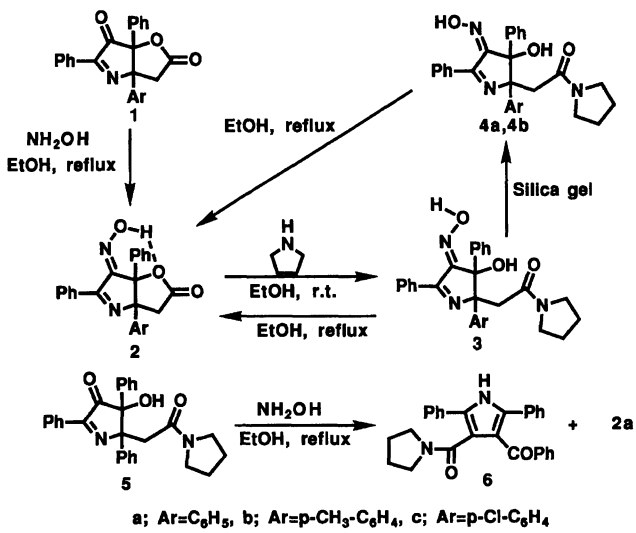
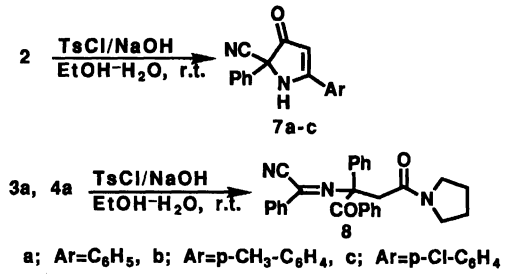


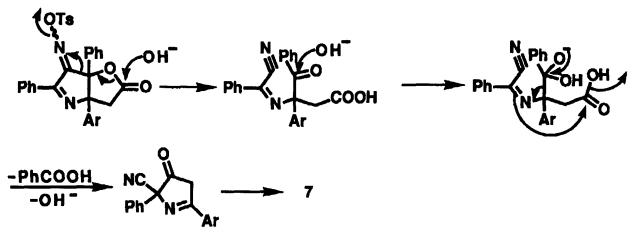
Fig. 1. ORTEP drawing of **3a**.



Scheme 1.



Scheme 2.



Scheme 3.

diphenyl-1*H*-pyrrol-3(2*H*)-one (**7a**) in a 90% yield. The structure of **7a** was elucidated on the basis of its elemental analysis and its spectral data. With deuterium oxide, the vinylic proton of **7a** could be exchanged, although slowly, with deuterium via the enamine–iminomethylene tautomerism.

When **2b** and **2c**, each having one para-substituted phenyl group at the 3a position, were similarly treated, the expected **7b** and **7c** were formed in yields of 77 and 41%, respectively. Their mass spectra showed peaks attributable to the corresponding *p*-substituted phenylacetylenes (*p*-R–$C_6H_4C_2H$; R=CH_3 and Cl) with relative intensities of 12 and 13%, respectively. Thus it was established that the *p*-substituted phenyl group of starting materials **2b** and **2c** is in the 2-position of the produced 1*H*-pyrrol-3(2*H*)-one ring of **7**. This finding is informative for the elucidation of the reaction pathway (Scheme 3).

On the other hand, under the same reaction conditions, both (*Z*)-oxime **3a** and (*E*)-oxime **4a** gave nitrile **8** (31 and 39% yields, respectively), also via cleavage of the C(3)–C(4) bond.

Experimental

All of the melting points were determined on a Mitamurariken MELT THERMO and are uncorrected. The IR spectra were measured as KBr pellets on a Nippon-Bunko IR-700. The NMR spectra were recorded at 270 MHz with a JEOL GSX-270 and 100 MHz with a JEOL FT-100 using TMS as an internal standard. The UV spectra were measured on a Hitachi 220A spectrophotometer. The mass spectra were obtained on a JEOL JMS-O1SG-2 mass spectrometer at 75 eV using a direct inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300).

Preparation of 2. Typical Procedure. After a mixture of **1a** (420 mg, 1.10 mmol), hydroxylammonium chloride (200 mg, 2.88 mmol), and sodium acetate (340 mg, 4.14 mmol) in ethanol (15 ml) was heated under reflux for 8 h, it was cooled to room temperature. The solvent was evaporated in vacuo, leaving a residue which was washed with water (30 ml) and recrystallized from benzene to give the **(*Z*)-6-Oxime of 3a,5,6a-Triphenyl-3a,6a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(3*H*)-dione (2a)** (403 mg, 92%) as colorless needles: Mp 271—272°C; IR 3144, 3028, 2772 (broad band), and 1792 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.50 (1H, d, J=15 Hz), 3.72 (1H, d, J=15 Hz), 6.69—7.69 (13H, m), 8.10—8.40 (2H, m), and 12.41 (1H, s, D_2O-exchanged); ^{13}C NMR δ=42.85, 83.65, 91.67, 124.59, 126.59, 126.73, 127.53, 127.79, 127.89, 128.52, 129.54, 131.26, 131.82, 135.82, 138.81, 158.43, 166.23, and 174.02; MS m/z 382 (M^+). Found: C, 75.31; H, 4.93; N, 7.20%. Calcd for $C_{24}H_{18}N_2O_3$: C, 75.37; H, 4.74; N, 7.33%.

Similarly **2b** and **2c** were quantitatively prepared. Their physical and spectral data are given below.

(*Z*)-6-Oxime of 5,6a-Diphenyl-3a-(*p*-tolyl)-3a,6a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(3*H*)-dione (2b): Colorless needles (benzene–ethanol); mp 242—244°C; IR 3154, 3030, 2794, (broad band), and 1792 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (3H, s), 3.26 (1H, d, J=19 Hz), 3.52 (1H, d, J=19 Hz), 6.74—7.60 (12H, m), 8.32—8.36 (2H, m), and 11.94 (1H, s, D_2O-exchanged); ^{13}C NMR δ=20.81, 40.01, 83.21, 91.73, 124.62, 126.39, 127.07, 127.50, 128.23, 128.25, 128.38, 129.53, 131.34, 135.65, 136.18, 136.89, 156.35, 166.60, and 174.34; MS m/z 396 (M^+). Found: C, 75.75; H, 5.23; N, 7.06%. Calcd for $C_{25}N_{20}N_2O_3$: C, 75.74; H, 5.23; N, 7.07%.

(*Z*)-6-Oxime of 3a-(*p*-Chlorophenyl)-5,6a-diphenyl-3a,6a-dihydro-2*H*-furo[3,2-*b*]pyrrole-2,6(3*H*)-dione (2c): Colorless needles (benzene); mp 253—254 °C; IR 3162, 3032, 2814 (broad band), and 1796 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.27 (1H, d, J=19 Hz), 3.82 (1H, d, J=19 Hz), 6.84—7.12 (9H, m), 7.58—7.61 (3H, m), 8.26 (2H, d, J=6 Hz), and 12.44 (1H, s, D_2O-exchanged); ^{13}C NMR δ=41.18, 82.81, 90.91, 124.59, 127.09, 127.37, 127.50, 128.22, 128.26, 128.65, 129.30, 131.39 131.85, 135.72, 137.82, 156.09, 166.20, and 173.98; MS m/z 418 (M^+) and 416 (M^+). Found: C, 68.88; H, 4.37; N, 6.69%. Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.14; H, 4.17; N, 6.72%.

Preparation of 3. Typical Procedure. A mixture of **2a** (312 mg, 0.82 mmol) and pyrrolidine (0.68 ml, 8.2 mmol) was stirred at room temperature for 5 h, giving the **(*Z*)-Oxime of 4-Hydroxy-2,4,5-triphenyl-5-(1-pyrrolidinylcarbonylmethyl)-4,5-dihydro-3*H*-pyrrol-3-one (3a)** (230 mg, 62%): Colorless needles (ethanol); mp 183—184 °C (decomp); IR 3258 (broad band), 2958, 2880, and 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.42—1.89 (4H, m), 3.18 (1H, d, J=13.5 Hz), 3.24—3.41 (3H, m), 3.56 (1H, d, J=13.5 Hz), 3.71—3.81 (1H, m), 6.92—7.57 (13H, m), 8.36—8.40 (2H, m), and 9.11 (1H, s, D_2O-exchanged); ^{13}C NMR ($CDCl_3$) δ=24.24, 25.71, 44.98, 46.40, 47.94, 83.70, 84.87, 125.75, 126.47, 126.59, 126.75, 127.33, 127.51, 127.73, 129.05, 129.56, 132.04, 139.91, 142.32, 163.18, 166.43, and 170.28; MS m/z 453 (M^+). Found: C, 74.31; H, 6.12; N, 8.80%. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27%.

Similarly **3b** and **3c** were obtained in 61% and 80% yields, respectively.

(*Z*)-Oxime of 4-Hydroxy-2,4-diphenyl-5-(*p*-tolyl)-5-(1-pyrrolidinylcarbonylmethyl)-4,5-dihydro-3*H*-

pyrrol-3-one (3b): Colorless needles (ethanol); mp 198—199 °C (decomp); IR 3056 (broad band), 2874, 2700 (broad band), and 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.41—1.79 (4H, m), 2.15 (3H, s), 3.18 (1H, d, J=13 Hz), 3.21—3.39 (3H, m), 3.52 (1H, d, J=13 Hz), 3.54—3.79 (1H, m), 6.82—7.12 (9H, m), 7.43—7.56 (3H, m), 8.35—8.38 (2H, m), and 9.05 (1H, s, D_2O-exchanged); ^{13}C NMR ($CDCl_3$) δ=20.92, 24.24, 25.73, 45.14, 46.40, 47.92, 83.57, 84.92, 125.75, 126.11, 126.75, 127.35, 128.19, 128.34, 129.05, 131.26, 132.07, 135.95, 139.39, 139.87, 163.38, 166.20, and 170.35; MS m/z 467 (M^+). Found: C, 74.35; H, 6.29; N, 8.99%. Calcd for $C_{29}H_{29}N_3O_3$: C, 74.49; H, 6.25; N, 8.99%.

(*Z*)-Oxime of 4-Hydroxy-5-(*p*-chlorophenyl)-2,4-diphenyl-5-(1-pyrrolidinylcarbonylmethyl)-4,5-dihydro-3*H*-pyrrol-3-one (3c): Colorless needles (ethanol); mp 199—203 °C; IR 3056, 2874, 2800 (broad band), and 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.41—1.82 (4H, m), 3.10 (1H, d, J=13 Hz), 3.16—3.39 (3H, m), 3.48 (1H, d, J=13 Hz), 3.54—3.76 (1H, m), 6.82—7.20 (9H, m), 7.42—7.56 (3H, m), 8.35—8.38 (2H, m), and 8.87 (1H, s, D_2O-exchanged); ^{13}C NMR ($CDCl_3$) δ=24.24, 25.73, 45.01, 46.45, 47.96, 83.36, 84.69, 125.62, 127.02, 127.35, 127.56, 127.67, 128.37, 129.07, 131.41, 131.91, 132.24, 139.73, 141.00, 162.85, 166.83, and 169.95; MS m/z 489 (M^+) and 487 (M^+). Found: C, 68.70; H, 5.39; N, 8.00%. Calcd for $C_{28}H_{26}N_3O_3Cl$: C, 68.91; H, 5.37; N, 8.61%.

Isomerization of 3. Typical Procedure. Compound **3a** (239 mg) was chromatographed using an 8 : 2-mixture of dichloromethane–ethyl acetate, giving the **(*E*)-Oxime of 4-Hydroxy-2,4,5-triphenyl-5-(1-pyrrolidinylcarbonylmethyl)-4,5-dihydro-3*H*-pyrrol-3-one (4a)** (238 mg, 100%): Colorless needles (ethanol); mp 183—187 °C; IR 3222 (broad band), 2942, and 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.41—1.81 (4H, m), 3.12 (1H, d, J=13.5 Hz), 3.14—3.49 (3H, m), 3.55 (1H, d, J=13.5 Hz), 3.67—3.78 (1H, m), 6.87—7.56 (13H, m), 8.27—8.40 (2H, m), 8.98 (1H, s, D_2O-exchanged), and 9.60 (1H, s, D_2O-exchanged); ^{13}C NMR ($CDCl_3$) δ=24.21, 25.70, 44.91, 46.38, 47.91, 83.67, 84.87, 125.73, 126.24, 126.45, 126.74, 127.31, 127.49, 128.30, 129.04, 131.25, 132.02, 139.87, 142.30, 163.23, 166.36, and 170.24; MS m/z 453 (M^+). Found: C, 74.12; H, 5.94; N, 9.45%. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27%.

Compound **4b** was similarly obtained in a 97% yield.

(*E*)-Oxime of 4-Hydroxy-2,4-diphenyl-5-(*p*-tolyl)-5-(1-pyrrolidinylcarbonylmethyl)-4,5-dihydro-3*H*-pyrrol-3-one (4b): Colorless needles (ethanol); mp 188—190 °C; IR 3028, 2874, 2800, (broad band), and 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.41—1.81 (4H, m), 2.15 (3H, s), 3.15 (1H, d, J=13.5 Hz), 3.21—3.39 (3H, m), 3.52 (1H, d, J=13.5 Hz), 3.70—3.79 (1H, m), 6.82—7.12 (9H, m), 7.43—7.56 (3H, m), 8.34—8.38 (2H, m), 9.09 (1H, s, D_2O-exchanged), and 9.66 (1H, s, D_2O-exchanged); ^{13}C NMR ($CDCl_3$) δ=20.92, 24.24, 25.73, 45.16, 46.40, 47.92, 83.57, 84.96, 125.75, 126.11, 126.77, 127.35, 128.19, 128.34, 129.05, 131.26, 132.06, 135.97, 139.37, 139.87, 163.43, 166.16, and 170.35; MS m/z 467 (M^+). Found: C, 74.33; H, 6.28; N, 8.99%, Calcd for $C_{29}H_{29}N_3O_3$: C, 74.49; H, 6.25; N, 8.99%.

2-Cyano-2,5-diaryl-1*H*-pyrrol-3(2*H*)-one (7). Typical Procedure. Tosyl chloride (1.36 g, 7.1 mmol) was added in one portion to a mixture of **2a** (300 mg, 0.78 mmol), sodium hydroxide (301 mg, 7.1 mmol), water (9 ml), and ethanol (9 ml) and the reaction mixture was stirred at room temperature for 30 min. It was then poured into water (60 ml) and extracted with benzene (100 ml×2). The extract was dried ($MgSO_4$) and evaporated in vacuo to leave a residue which was chromatographed using dichloromethane–ethyl acetate as eluent, giving **2-Cyano-2,5-diphenyl-1*H*-pyrrol-3(2*H*)-one (7a)** (183 mg, 90%) as a colorless crystalline powder: mp 161—165 °C; IR 3318, 2248, and 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.57 (s, 1H, D_2O-exchanged), 6.43 (s, 1H, D_2O-exchanged), and 7.25—7.88 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=65.79, 94.87, 116.15, 125.24, 127.05, 128.71, 129.37, 129.46, 129.57, 132.95, 133.39, 176.34, and 192.23; UV (MeOH) λ_{max}; 349 (ε 8500) nm; MS m/z 260 (M^+). Found: C, 78.77; H, 4.76; N, 10.66%. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76%.

Similarly, **7b** and **7c** were obtained in yields of 70 and 41%, respectively.

2-Cyano-5-phenyl-5-(*p*-tolyl)-1*H*-pyrrol-3(2*H*)-one (7b): Colorless needles (benzene–chloroform); mp 220—222 °C; IR 3184, 2270, and 1657 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.42 (3H, s), 5.72 (1H, s, D_2O-exchanged), 7.36—7.59 (7H, m), 7.77 (2H, d J=8.1 Hz), and 9.91 (1H, s, D_2O-exchanged); ^{13}C NMR δ=21.12, 65.02, 90.87, 116.68, 124.89, 125.38, 127.58, 128.04, 129.15, 129.67, 133.30, 143.75, 176.37, and 191.20; UV (MeOH) λ_{max}; 349 (ε 10700) nm; MS m/z 274 (M^+). Found: C, 78.76; H, 5.31; N, 10.23%. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21%.

5-(*p*-Chlorophenyl)-2-cyano-5-phenyl-1*H*-pyrrol-3-(2H)-one (7c): Colorless plates (benzene–chloroform); mp 222—224 °C; IR 3124, 2240, and 1654 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.81 (1H, s), 7.36—7.51 (5H, m), 7.54 (2H, d, J=2.7 Hz), 8.03 (2H, d, J=2.7 Hz), and 10.01 (1H, s, D_2O-exchanged); ^{13}C NMR δ=65.11, 91.89, 116.48, 124.91, 127.04, 129.20, 129.25, 129.40, 133.04, 137.94, 175.27, and 191.48 UV (MeOH) λ_{max}; 349 (ε 9900) nm; MS m/z 296 (M^+) and 294 (M^+). Found: C, 69.24; H, 3.90; N, 9.64%. Calcd for $C_{17}H_{11}N_2OCl$: C, 69.28; H, 3.76; N, 9.50%.

Preparation of 8. A mixture of tosyl chloride (1.26 g, 6.6 mmol), **3a** (300 mg, 0.78 mmol), sodium hydroxide (264 mg, 6.6 mmol), water (8 ml), and ethanol (8 ml) was stirred at room temperature for 1 h and then poured into water (100 ml). The mixture was extracted with dichloromethane (50 ml×4). The extract was dried ($MgSO_4$) and evaporated in vacuo to leave a residue which was chromatographed. Tosyl chloride was first eluted with benzene. The fraction eluted with ethyl acetate was evaporated in vacuo and then the residue was sonicated in a mixed solvent of ethyl acetate and hexane, giving **8** (90 mg, 31%): Colorless crystalline powder (ethyl acetate–hexane); mp 182—184 °C; IR 3060, 2976, 2872, 2210, 1683, 1641, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.52—1.81 (4H, m), 2.67—2.76 (1H, m), 3.13—3.36 (3H, m), 3.68 (1H, d, J=15 Hz), 3.89 (1H, d, J=15 Hz), 7.19—7.72 (13H, m), and 8.02—8.06 (2H, m); ^{13}C NMR ($CDCl_3$) δ=24.19, 25.99, 44.15, 45.57, 46.76, 77.20, 110.56, 126.27, 127.87, 127.94, 128.81, 128.90, 131.11, 132.40, 133.96, 134.79, 141.02, 141.31, 166.63, and 197.23; MS m/z 435 (M^+). Found: C, 77.65; H, 5.79; N, 9.74%. Calcd for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65%.

Similarly **4a** gave **8** in a 39% yield. Compound **3b** afforded a complex mixture of unidentified products and **3c** gave **7c** in an 18% yield.

X-Ray Analysis of 3a. Crystallographic Section.

$C_{28}H_{25}O_3N_3$, $M_m=451.50$, triclinic, space group $P1/a$, $a=8.832(1)$, $b=9.750(1)$, $c=14.124(1)$ Å, $\alpha=101.96(7)°$, $\beta=96.44(7)°$, $\gamma=97.16(7)°$, $V=1168.3$ Å^3, $Z=2$, $D_x=1.289$ g cm^{-3}.

Data Collection. Diffractometer: CAD 4 (ENRAF-NONIUS), crystal size: 0.2×0.2×0.1 mm, radiation: Cu $K\alpha$ (1.54184 Å), monochrometer: graphite, data collecting mode: ω–2θ scan, number of reflections: 2952 (observed), temperature, 298 K.

Structure Analysis. Solution: SIR, $R=0.050$, $R_w=0.062$, software: MOLEN.

Supplementary Material Available. The tables of bond distances (2 pages), bond angles (3 pages), structure factors (32 pages), positional parameters and their estimated standard deviations (3 pages), refined displacement parameter expressions (2 pages), and general displacement parameter expressions (4 pages) of the X-ray crystallography of **3a** are deposited as Document No. 66009 at the Office of the Editor of the Bull. Chem. Soc. Jpn.

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