# Meisenheimer Rearrangement of Azetopyridoindoles. VII.[1] Ring Expansion of 2-Phenylhexahydroazeto[1′,2′:1,2]pyrido[3,4-*b*]indoles by Oxidation with *m*-Chloroperbenzoic Acid

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**Oxidation of methyl (1,2-*cis*)-2-phenyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (8a) with *m*-chloroperbenzoic acid (MCPBA) (3 eq) in methylene dichloride at room temperature unexpectedly gave 4,10-dioxooctahydroisoxazolo[3,2-*c*][1,4]benzdiazonine (10) (44%), together with the two [1,2]-Meisenheimer rearrangement products [11 (5%) and 12 (14%)]. The structure of 10 was unambiguously established by an X-ray analysis. On the other hand, the peracid oxidation of the corresponding 1,2-*trans* isomer (17) gave hexahydroisoxazolo[2′,3′:1,2]pyrido[3,4-*b*]indole (18) (37%) *via* the [1,2]-Meisenheimer rearrangement of the N-oxide as well as dihydro-β-carboline N-oxide (19) (60%) and methyl cinnamate (20) (61%). The remarkable difference in the results of peracid oxidation between the two isomers (8a and 17) was rationalized on the basis of the molecular energy calculations using a combination of molecular mechanics (MM) and molecular orbitals (MO) methods.**

**Key words** Meisenheimer rearrangement; azetopyridoindole; benzdiazonine; *m*-chloroperbenzoic acid oxidation; X-ray analysis; energy calculation

The thermal [1,2]- and [2,3]-rearrangements of tertiary amine N-oxides bearing benzyl or allyl groups are known as the Meisenheimer rearrangement. Previously we reported[3] that *m*-chloroperbenzoic acid (MCPBA) oxidations of 1,2-*cis*- and *trans*-2-vinylazetopyridoindoles (**1a** and **1b**) gave oxazepinopyridoindole (**3**) from the former *via* the [2,3]-Meisenheimer rearrangement and isoxazolopyridoindole (**4**) from the latter *via* the [1,2]-Meisenheimer rearrangement of the corresponding N-oxides. We also obtained 3,6-epoxyazocinoindole (**5**) by the peracid oxidation of 2-ethylazetopyridoindole (**2**)[4] (Chart 1). For structure–activity relationship investigation of eudistomins, which have a unique oxathiazepinopyridoindole ring system, 12-carbaeudistomin and related compounds have been synthesized from the oxazepinopyridoindole (**3**),[1] and their biological evaluation is in progress. As a continuation of our work on the Meisenheimer rearrangement, we were interested in the MCPBA oxidation of azetopyridoindoles (**8** and **17**) bearing a phenyl group instead of a vinyl group at the C-2 position, expecting the formation of a benzoxazepinopyridoindole (see Chart 3) *via* the [2,3]-Meisenheimer rearrangement followed by aromatization.

The substrate (**8a**), 1,2-*cis*-10-methyl-2-phenylazetopyridoindole, was synthesized from tetrahydro-β-carboline-1-acetate (**6a**) by the same procedure (see Chart 2) as described for the 2-vinylazetidine (**1a**)[5]. The crude oil finally obtained was purified by column chromatography to give **8a** in 80% overall yield, accompanied with a small amount of the 1,3-oxazinone (**9a**) (9%). The structure of **8a** was easily confirmed by a comparison of the $^1$H-NMR spectral data ($J_{1,2}=9.0$ Hz and $J_{1,10b}=2.0$ Hz) with those of the 2-vinylazetidine (**1a**)[5] ($J_{1,2}=8.0$ Hz, and $J_{1,10b}=3.0$ Hz). The minor product (**9a**) was identified as indolopyrido-3,5-oxazin-4-one with the stereochemistry shown in Chart 2, based on our previous observation.[5]

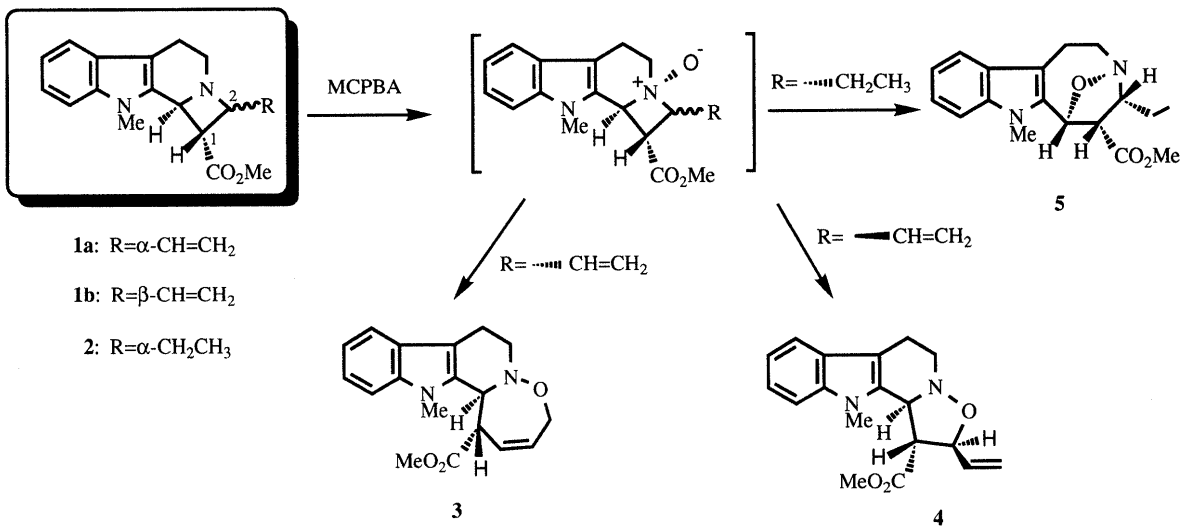


Chart 1

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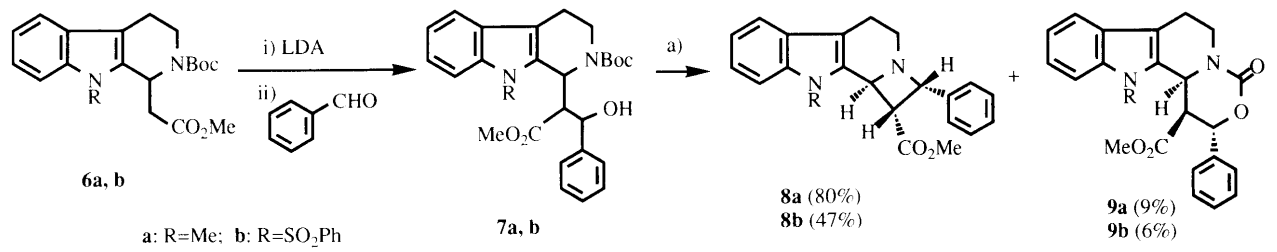


Reagents a) i) $MeSO_2Cl$ / $Et_3N$; ii) dry HCl / EtOAc; iii) DBU / DMSO

Chart 2

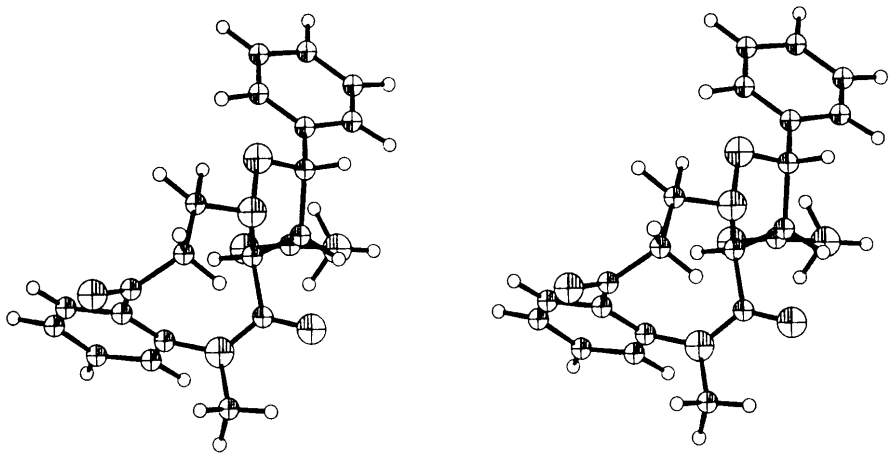

Fig. 1. Stereoscopic View of **10**

Although the oxidation of **8a** with 1 eq of MCPBA in methylene dichloride ($CH_2Cl_2$) proceeded slowly at room temperature, use of 3 eq of MCPBA completed the oxidation instantly to give three products [**10** (44%), **11** (5%), and **12** (14%) (Chart 3)], which could be separated by column chromatography. The MS showed that **11** and **12** were products of the Meisenheimer rearrangement of the corresponding N-oxides of **8a**. As the spectral data could not distinguish clearly between isoxazolopyridoindole and epoxyazocinoindole structures, the reductive cleavage (Zn in acetic acid) of the N–O bond of **11** and **12** was carried out to give the amino alcohols (**13** and **14**, respectively). The amino alcohol (**13**)[6] obtained from **11** was identical with an authentic sample separated from a diastereomeic mixture of **13**, which was alternatively prepared by treatment of **7a** with dry hydrogen chloride in ethyl acetate. Therefore, the isoxazolopyridoindole structure was assigned to **11**, whose stereochemistry was established by the positive $^1$H-nuclear Overhauser effect between 1-H and 2-H (10.6%). The stereochemistry of **12** was determined by a comparison of the $^1$H-NMR spectral data ($J_{4,5}=9.2$ Hz and $J_{5,6}=3.3$ Hz) with those of **5**[4] ($J_{4,5}=8.0$ Hz and $J_{5,6}=4.0$ Hz). The MS [*m/z* 394 ($M^+$)] of the major product (**10**) revealed the incorporation of three oxygen atoms into **8a**. Though the $^1$H-NMR spectrum showed the presence of three neighboring methine protons and two methylene protons, the characteristic absorption band due to the indole skeleton was not observed in the UV spectrum. The $^{13}$C-NMR spectral data ($\delta$ 167.02, 170.47, and 202.81) showed the presence of three carbonyl carbons. On the basis of these results, the structure of **10** was assigned as methyl 5-methyl-4,10-dioxo-2-phenyl-2,3,3a,4,5,10,11,12-octahydroisoxazolo[3,2-*c*][1,4]benzdiazonine-3-carboxylate. Finally, definitive evidence for the stereostructure of **10** was obtained by an X-ray crystallographic analysis; a stereoscopic view of the molecule is shown in Fig. 1.

Oxidation of 2,3-disubstituted indoles with peracid is well known.[7] Hino *et al.* have reported[8] the oxidations of tetrahydrocarbazole and *N*-methyltetrahydrocarbazole with MCPBA (1 eq, $-60$°C in $CH_2Cl_2$), but the ketoamides corresponding to **10** were not isolated. However, 4a-hydroxytetrahydro-4a*H*-carbazole is known to be oxidized to the corresponding ketoamide by perbenzoic acid (2 eq, 0°C in $CHCl_3$) oxidation in good yield.[9] It is noteworthy that the ketoamide (**10**) was isolated for the first time in our research on the oxidation of azetopyridoindoles. Thus, in order to elucidate the reaction pathway for the formation of **10**, MCPBA oxidation of 10-benzenesulfonyl-2-phenylazetidine (**8b**) was examined. When the azetidine (**8b**) was treated with 1 eq of MCPBA, the reaction readily proceeded to give only a mixture of normal [1,2]-Meisenheimer rearrangement products [**15** (19%) and **16** (70%)], whose structures were determined by the comparison of their spectral data with those of **11** and **12**, and the corresponding ketoamides were not isolated from the reaction mixture. Oxidation of the isoxazolidine (**11**) with MCPBA was then carried out, but gave no **10**; only a tarry mixture was obtained. On the basis of these results, a plausible mechanism for the formation of **10** is as follows: the hydroxyperbenzoate (**B**) may be formed initially *via* the first intermediate (**A** or **A'**) through epoxidation of **8a** followed by the addition of the

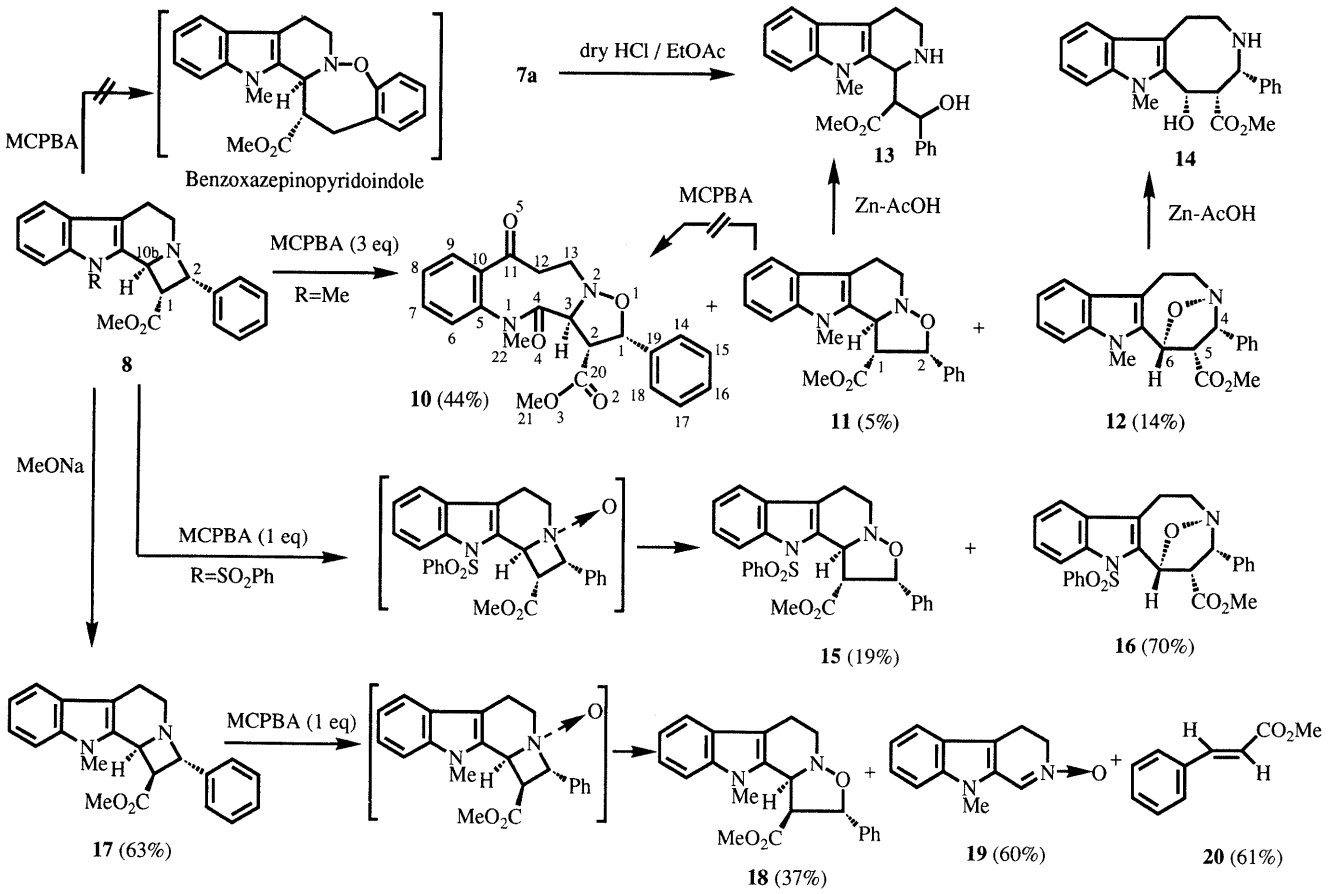


Chart 3

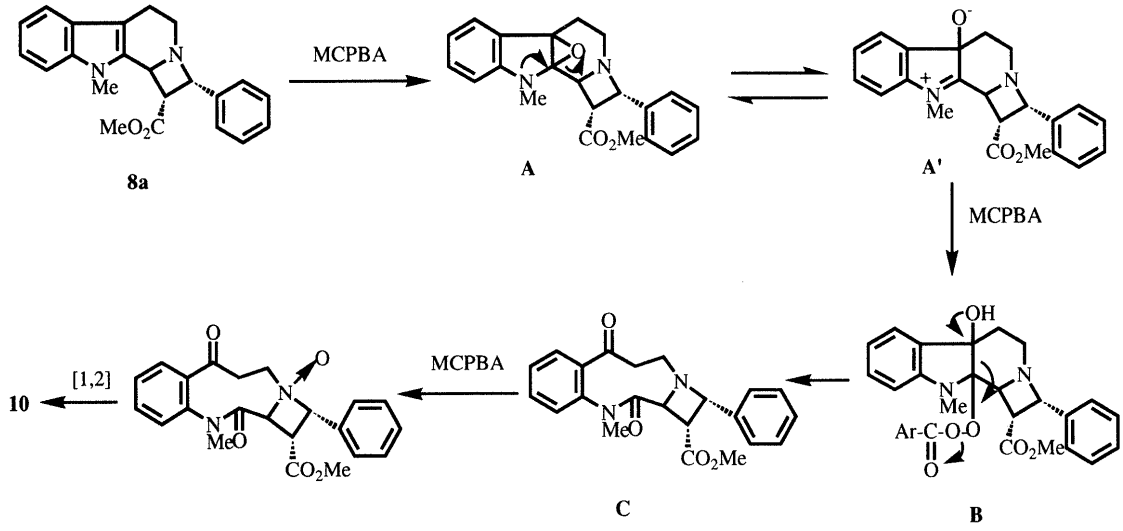


Chart 4

second MCPBA. Ring opening to give the ketoamide (**C**) then occurs. The subsequent *N*-oxidation of **C** followed by the [1,2]-Meisenheimer rearrangement ultimately leads to **10**, as shown in Chart 4.

Next, our attention was focused on the problem of the reason why the benzdiazonine (**10**) was obtained only in the case of the azetopyridoindole (**8a**) bearing a phenyl group at the C-2 position. Thus, we investigated the MCPBA oxidation of the 1,2-*trans* isomer (**17**), obtained by isomerization of **8a** with NaOMe. In contrast to the result for the 1,2-*cis* isomer (**8a**), the reaction proceeded smoothly with 1 eq of MCPBA at room temperature to give the [1,2]-Meisenheimer rearrangement product (**18**) (37%), accompanied with 3,4-dihydro-β-carboline-2-oxide (**19**)[10] and *trans*-methyl cinnamate (**20**) presumably obtained by thermal fragmentation of the N-oxide in a 1,2-fashion.

The remarkable difference between the results obtained by the MCPBA oxidation of 1,2-*cis* and -*trans* isomers (**8a** and **17**) may be explained by steric crowding around the lone pair of electrons of the nitrogen in the azetidine ring observed in **8a**, based on a molecular modeling study. To

test this possibility, computational evaluations of **8a** and **17** were performed using a combination of molecular mechanics (MM) and molecular orbitals (MO).[11] In the case of molecules having two rotable bonds with a phenyl and a methyl ester group, CNDO-SCAN[12] computations are useful to elucidate the most stable conformation. First, an MM calculation of **8a** was carried out to obtain a starting model. Next, a CNDO-SCAN energy map was prepared by continual rotation of two free torsional angles ($\omega 1$ and $\omega 2$) of the C-2 phenyl and C-1 ester groups in 10° increments from 0° to 360°. The result of the scanning of **8a** is shown in the contour map (Fig. 2). According to this map, the energetically most stable conformation of **8a** is located at point (a) [$\omega 1 = 300°$ and $\omega 2 = 330°$]. Theoretically the energies of the points (a) ($\omega 1 = 300°$) and (a') ($\omega 2 = 330°$) should be equal in the case of a symmetrical phenyl group. However, the energy of (a) is lower than that of (a') by 4.0 kcal/mol in the map. This may be due to lack of complete planarity of the phenyl group in the starting model prepared by MM calculation. Evaluation of the *trans*-isomer (**17**) was carried out in the same manner, and its contour map was prepared (Fig. 3). The point (b) ($\omega 1 = 270°$ and $\omega 2 = 90°$) was indicated as the most stable conformation. The two contour maps thus obtained clearly show that the *trans*-isomer (**17**) has a higher degree of freedom compared to *cis*-**8a**. Accordingly, it may be concluded that the phenyl group of the *trans*-isomer (**17**) is more flexible, whereas that of the *cis*-isomer (**8a**) is fixed at point (a).

The model obtained from the contour map of **8a** was further optimized by the modified neglect of differential overlap (MNDO) program.[13] The MNDO-optimized structure of **8a** (Fig. 4) shows that MCPBA oxidation of the azetidine nitrogen may be hindered by the fixed phenyl group, in accordance with the above suggestion.

In conclusion, it was clarified that the N-oxides of the

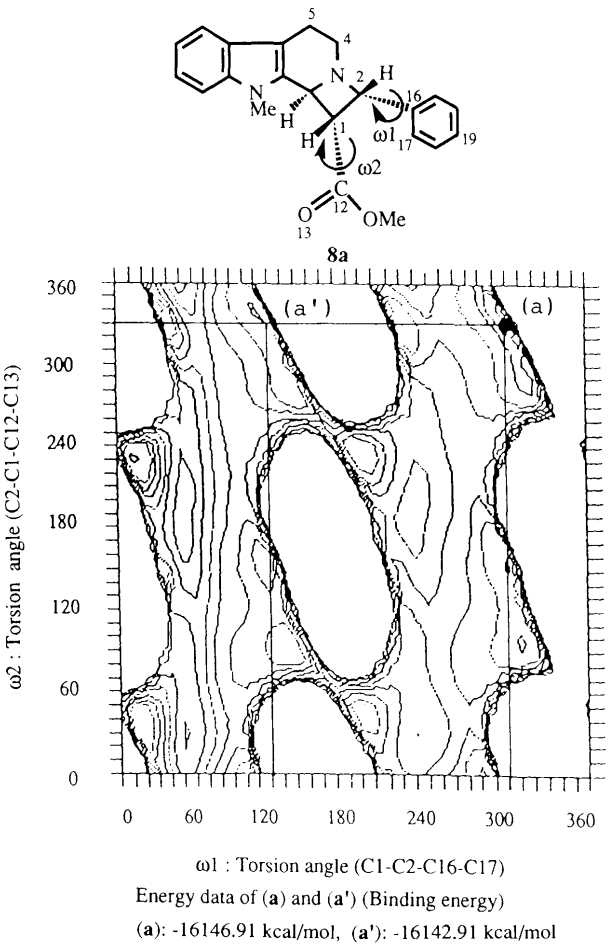


Fig. 2. CNDO-SCAN Energy Map for **8a**

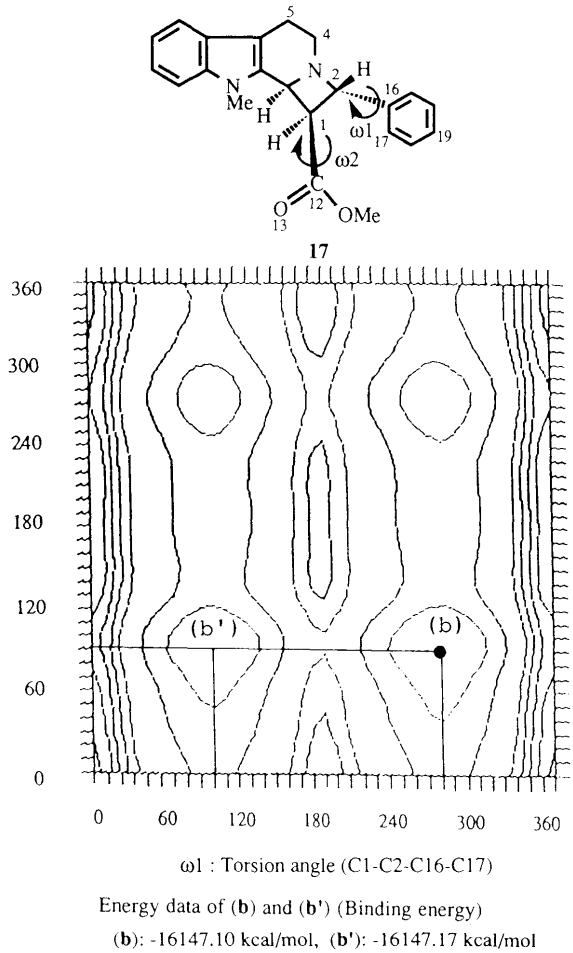


Fig. 3. CNDO-SCAN Energy Map for **17**

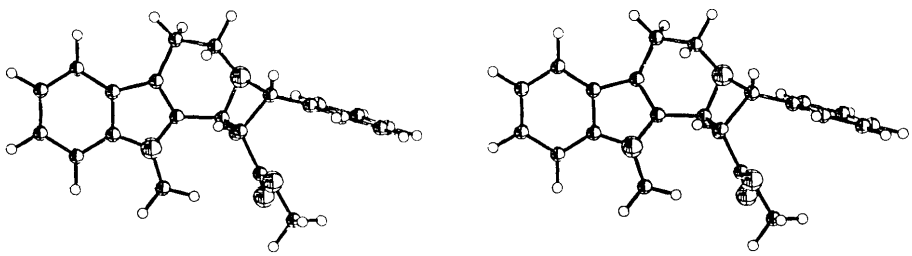

Fig. 4. Most Probable Molecular Conformation of **8a** Deduced from the Theoretical Calculation (CNDO/MNDO)

substrate **8** gave the [1,2]-Meisenheimer rearrangement products, but not the expected benzene-fused oxazepine *via* the [2,3]-rearrangement.

## Experimental

Melting points were determined on a Yanagimoto apparatus and are uncorrected. IR and UV spectra were recorded on Shimadzu IR-435 and JASCO UVIDEC-505 spectrophotometers. $^1$H- and $^{13}$C-NMR spectra were determined with a Varian Gemini-200 spectrometer in $CDCl_3$, and MS with a Hitachi M-4000H instrument. All reactions were carried out under a nitrogen atmosphere. MCPBA (80%) was purchased from Nacarai Tesque Inc. For column chromatography, $SiO_2$ (Merck Art 9385) was used.

**Methyl (1,2-*trans*)-10-Methyl-2-phenyl-1,2,4,5,10,10b-hexahydroazeto-[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (8a) and Methyl 12-Methyl-4-oxo-2-phenyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*]pyrido[1,2-*c*]-[1,3]oxazine-1-carboxylate (9a)** A solution of **6a** (3.58 g, 10 mmol) in tetrahydrofuran (THF) (30 ml) was added dropwise to a solution of lithium diisopropylamide (LDA) [prepared from diisopropylamine (1.7 ml, 12 mmol) and *n*-BuLi (15% hexane solution, 7.7 ml, 12 mmol)] in THF (30 ml) at −78 °C, and the mixture was stirred for 30 min. Then, benzaldehyde (2.04 ml, 20 mmol) was added to this solution, and the whole was stirred at −78°C for 1 h. The reaction was quenched with water, and THF was removed by evaporation. The residue was extracted with EtOAc, and the extract was washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo* to give methyl 2-(2-*tert*-butoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-hydroxy-3-phenylpropionic acid (**7a**) as an oil. The $^1$H-NMR spectrum was not sufficiently well resolved to permit assignment of all the signals, because a mixture of diastereomers was present. Then, triethylamine (TEA) (4.2 ml, 30 mmol) and methanesulfonyl chloride (MsCl) (1.2 ml, 15 mmol) were added successively to a solution of the crude alcohol (**7a**) obtained above in $CH_2Cl_2$ (35 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, and extracted with $CHCl_3$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was, without purification, dissolved in 2.3 N HCl in EtOAc (60 ml) and the solution was stirred for 2 h. After removal of the solvent by evaporation *in vacuo*, the residue was dissolved in dimethyl sulfoxide (DMSO) (15 ml) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.13 g, 20 mmol). This solution was allowed to stand for 2 h, diluted with water (250 ml), and extracted with EtOAc. The extract was washed with water and brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (elution with 10% EtOAc in hexane) to give **8a** (2.76 g, 80% overall yield from **6a**), which was recrystallized from EtOH to give crystals, mp 187—188 °C. IR (KBr) cm$^{-1}$: 1720 (CO). $^1$H-NMR ($CDCl_3$) δ: 2.71—3.13 (4H, m, 4-$H_2$, 5-$H_2$), 3.31 (3H, s, $NCH_3$), 3.33 (1H, dd, $J$=9.0, 2.0 Hz, 1-H), 3.58 (3H, s, $CO_2CH_3$), 4.99 (1H, d, $J$=9.0 Hz, 2-H), 5.22 (1H, d, $J$=2.0 Hz, 10b-H), 7.09—7.48 (8H, m, ArH), 7.58 (1H, d, $J$=7.5 Hz, ArH). MS $m/z$: 346 ($M^+$). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.20; H, 6.43; N, 8.04. The second eluate (EtOAc) gave **9a** (348 mg, 9%), which was recrystallized from MeOH to give crystals, mp 227—228 °C. IR (KBr) cm$^{-1}$: 1720, 1695 (CO). $^1$H-NMR ($CDCl_3$) δ: 2.74—3.08 (3H, m, 6-H, 7-$H_2$), 3.42 (3H, s, $NCH_3$), 3.51 (3H, s, $CO_2CH_3$), 3.67 (1H, dd, $J$=4.0, 2.0 Hz, 1-H), 4.87 (2H, m, 2-H, 6-H), 5.83 (1H, d, $J$=2.0 Hz, 12b-H), 7.06—7.29 (3H, m, ArH), 7.40—7.56 (6H, m, ArH). MS $m/z$: 390 ($M^+$). *Anal.* Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.68; H, 5.68; N, 7.13.

**Methyl 10-Benzenesulfonyl-2-phenyl-1,2,4,5,10,10b-hexahydroazeto-[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (8b) and Methyl 12-Benzenesulfonyl-4-oxo-2-phenyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*]pyrido[1,2-*c*][1,3]oxazine-1-carboxylate (9b)** The same procedure as described for the preparation of **8a** and **9a** provided a crude product from **6b** (4.84 g, 10 mmol). This was purified by column chromatography (elution with 20% EtOAc in hexane) to give **8b** (2.23 g, 47%), which was recrystallized from EtOH/hexane to give crystals, mp 160—161 °C. IR (KBr) cm$^{-1}$: 1730 (CO), 1365, 1170 ($SO_2$). $^1$H-NMR ($CDCl_3$) δ: 2.60—3.12 (4H, m, 4-$H_2$, 5-$H_2$), 3.35 (3H, s, $CO_2CH_3$), 3.62 (1H, dd, $J$=9.3, 2.8 Hz, 1-H), 4.92 (1H, d, $J$=8.0 Hz, 2-H), 5.35 (1H, br s, 10b-H), 7.23—7.63 (11H, m, ArH), 7.89 (2H, d, $J$=9.3 Hz, ArH), 8.23 (1H, d, $J$=7.5 Hz, ArH). MS $m/z$: 472 ($M^+$). *Anal.* Calcd for $C_{27}H_{24}N_2O_4S$: C, 68.63; H, 5.12; N, 5.93. Found: C, 68.65; H, 5.12; N, 5.83. The second eluate (EtOAc) gave **9b** (323 mg, 6.3%), which was recrystallized from MeCN to give crystals, mp 239—241°C. IR (KBr) cm$^{-1}$: 1730, 1715 (CO), 1370, 1170 ($SO_2$). $^1$H-NMR ($CDCl_3$) δ: 2.52—2.88 (3H, m, 6-H, 7-$H_2$), 3.48 (3H, s, $CO_2CH_3$), 4.50 (1H, dd, $J$=4.0, 1.8 Hz, 1-H), 4.82 (1H, br d, $J$=10.0 Hz, 6-H), 4.97 (1H, br d, $J$=4.0 Hz, 2-H), 5.90 (1H, d, $J$=1.8 Hz, 12b-H), 7.15—7.60 (13H, m, ArH), 8.10 (1H, d, $J$=7.5 Hz, ArH). MS $m/z$: 516 ($M^+$). *Anal.* Calcd for $C_{28}H_{24}N_2O_6S$: C, 65.10; H, 4.68; N, 5.42. Found: C, 65.18; H, 4.68; N, 5.46.

**Reaction of 8a with MCPBA** A solution of 80% MCPBA (2.62 g, 15.17 mmol) in $CH_2Cl_2$ (15 ml) was added to a solution of **8a** (1.5 g, 4.34 mmol) in $CH_2Cl_2$ (50 ml) at 0 °C. The reaction mixture was stirred for 24 h, then diluted with $CH_2Cl_2$ (50 ml). The solution was washed with 5% $Na_2CO_3$ solution and water, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 15% EtOAc in hexane) to give **11** (79 mg, 5%) from the first fraction, **12** (220 mg, 14%) from the second fraction and **10** (752 mg, 44%) from the third fraction (elution with 40% EtOAc in hexane).

Methyl (1,2-*trans*)-11-methyl-2-phenyl-1,2,5,6,11,11b-hexahydroisoxazolo[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (**11**) had mp 200—201 °C (from benzene). IR (KBr) cm$^{-1}$: 1735 (CO). $^1$H-NMR ($CDCl_3$) δ: 3.01 (2H, m, 6-$H_2$), 3.20 (3H, s, $NCH_3$), 3.32—3.57 (2H, m, 5-$H_2$), 3.54 (3H, s, $CO_2CH_3$), 3.83 (1H, dd, $J$=9.6, 7.7 Hz, 1-H), 5.33 (1H, d, $J$=7.7 Hz, 11b-H), 5.88 (1H, d, $J$=9.6 Hz, 2-H), 7.08—7.47 (8H, m, ArH), 7.54 (1H, d, $J$=7.5 Hz, ArH). $^{13}$C-NMR δ: 20.23 (t), 30.06 (q), 49.02 (t), 51.84 (q), 58.63 (d), 62.44 (d), 82.35 (d), 107.81 (s), 109.13 (d), 118.52 (d), 119.42 (d), 121.89 (d), 125.75 (d), 127.46 (d), 128.04 (d), 128.52 (d), 132.60 (s), 135.94 (s), 138.05 (s), 170.89 (s). MS $m/z$: 362 ($M^+$). *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.90; H, 6.12; N, 7.73. Found: C, 72.89; H, 6.12; N, 7.74.

Methyl 3,6-epoxy-7-methyl-4-phenyl-1,2,3,4,5,6-hexahydroazocino-[5,4-*b*]indole-5-carboxylate (**12**) had mp 155—156 °C (from EtOH). IR (KBr) cm$^{-1}$: 1725 (CO). $^1$H-NMR ($CDCl_3$) δ: 3.11 (2H, m, 1-$H_2$), 3.25 (3H, s, $NCH_3$), 3.91 (1H, m, 2-H), 4.23 (1H, dd, $J$=9.2, 3.3 Hz, 5-H), 4.95 (1H, d, $J$=9.2 Hz, 4-H), 6.07 (1H, d, $J$=3.3 Hz, 6-H), 7.08—7.38 (3H, m, ArH), 7.40—7.56 (6H, m, ArH). $^{13}$C-NMR ($CDCl_3$) δ: 20.23 (t), 30.06 (q), 49.02 (t), 51.84 (q), 58.63 (d), 62.44 (d), 82.36 (d), 107.81 (s), 109.13 (d), 118.52 (d), 119.42 (d), 121.89 (d), 125.75 (s), 127.46 (d), 128.04 (d), 128.52 (d), 132.60 (s), 135.94 (s), 138.05 (s), 170.89 (s). MS $m/z$: 362 ($M^+$). *Anal.* Calcd for $C_{22}H_{22}N_2O_3 \cdot 1/4\,H_2O$: C, 72.03; H, 6.14; N, 7.64. Found: C, 72.03; H, 6.28; N, 7.42.

Methyl 4,10-dioxo-5-methyl-2-phenyl-2,3,3a,4,5,10,11,12-octahydroisoxazolo[3,2-*c*][1,4]benzodiazonine-3-carboxylate (**10**) had mp 159—160 °C (from EtOH). IR ($CHCl_3$) cm$^{-1}$: 1730, 1660 (CO). $^1$H-NMR ($CDCl_3$) δ: 2.96—3.28 (3H, m, 11-$H_2$, 12-HH), 3.07 (3H, s, $NCH_3$), 3.25 (3H, s, $CO_2CH_3$), 3.71 (1H, qd, $J$=6.7, 4.2 Hz, 12-HH), 4.07 (1H, d, $J$=7.5 Hz, 3a-H), 4.33 (1H, dd, $J$=9.2, 7.5 Hz, 3-H), 5.43 (1H, d, $J$=9.2 Hz, 2-H), 7.11—7.38 (6H, m, ArH), 7.50—7.72 (3H, m, ArH). $^{13}$C-NMR ($CDCl_3$) δ: 38.41 (q), 41.75 (t), 51.55 (q), 53.03 (t), 58.05 (d), 69.15 (d), 80.91 (d), 127.02 (d), 128.08 (d), 128.49 (d), 128.66 (d), 128.87 (d), 129.43 (d), 132.96 (d), 135.54 (s), 138.78 (s), 139.52 (s), 167.02 (s), 170.47 (s), 202.81 (s). MS $m/z$: 394 ($M^+$). *Anal.* Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.00; H, 5.61; N, 7.10.

**Reaction of 8b with MCPBA** A solution of 80% MCPBA (356 mg, 1.65 mmol) in $CH_2Cl_2$ (10 ml) was added to a solution of **8b** (708 mg, 1.5 mmol) in $CH_2Cl_2$ (10 ml) at room temperature. The reaction mixture was stirred for 2 h, then diluted with $CH_2Cl_2$ (20 ml). The solution was washed with 5% $Na_2CO_3$ solution and water, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 5% EtOAc in benzene) to give **16** (516 mg, 70%) from the first fraction and **15** (139 mg, 19%) from the second fraction.

Methyl 7-benzenesulfonyl-3,6-epoxy-4-phenyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylate (**16**) had mp 162—163 °C (from EtOH). IR ($CHCl_3$) cm$^{-1}$: 1725 (CO), 1340, 1170 ($SO_2$). $^1$H-NMR ($CDCl_3$) δ: 2.80—3.25 (3H, m, 1-$H_2$, 2-H), 3.29 (3H, s, $CO_2CH_3$), 3.97 (1H, m, 2-H), 4.28 (1H, dd, $J$=8.0, 4.0 Hz, 5-H), 4.73 (1H, d, $J$=8.0 Hz, 4-H), 6.40 (1H, d, $J$=4.0 Hz, 6-H), 7.23—7.63 (11H, m, ArH), 7.88 (2H, d, $J$=9.0 Hz, ArH), 8.20 (1H, d, $J$=7.5 Hz, ArH). MS $m/z$: 488 ($M^+$). *Anal.* Calcd for $C_{27}H_{24}N_2O_5S$: C, 66.37; H, 4.95; N, 5.74. Found: C, 66.34; H, 4.97; N, 5.79.

Methyl (1,2-*cis*)-11-benzenesulfonyl-2-phenyl-1,2,5,6,11,11b-hexahydroisoxazolo[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (**15**) had mp 198—199 °C (from MeOH–MeCN). IR (KBr) cm$^{-1}$: 1750 (CO), 1380, 1170 ($SO_2$). $^1$H-NMR ($CDCl_3$) δ: 2.53 (1H, m, 6-H), 2.94—3.25 (2H, m, 5-H, 6-H), 3.30 (3H, s, $CO_2CH_3$), 3.91 (1H, m, 5-H), 4.32 (1H, dd,

$J$=8.8, 2.0 Hz, 1-H), 5.32 (1H, d, $J$=8.8 Hz, 11b-H), 5.46 (1H, d, $J$=2.0 Hz, 2-H), 7.18—7.55 (11H, m, ArH), 7.68 (2H, d, $J$=9.0 Hz, ArH), 8.21 (1H, d, $J$=7.5 Hz, ArH). MS $m/z$: 488 ($M^+$). *Anal.* Calcd for $C_{27}H_{24}N_2O_5S$: C, 66.38; H, 4.95; N, 5.73. Found: C, 66.43; H, 4.92; N, 5.67.

**Methyl (1,2-*cis*)-10-Methyl-2-phenyl-1,2,4,5,10,10b-hexahydroazeto-[1′,2′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (17)** A solution of NaOMe (28% MeOH solution, 0.39 ml, 2 mmol) was added to a solution of **8a** (346 mg, 1 mmol) in dry MeOH (50 ml) at room temperature, and the reaction mixture was refluxed for 6 h. After evaporation of the solvent, the residue was neutralized with 5% aqueous acetic acid and then extracted with EtOAc. The extract was washed with water and brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 25% EtOAc in hexane) to recover **8a** (83 mg, 24%) from the first fraction. The second fraction gave **17** (218 mg, 63%), which was recrystallized from EtOH to give crystals, mp 166—168 °C. IR (KBr) $cm^{-1}$: 1735 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 2.59—2.90 (2H, m, 5-$H_2$), 3.03—3.22 (2H, m, 4-$H_2$), 3.49 (3H, s, $NCH_3$), 3.63 (3H, s, $CO_2CH_3$), 3.78 (1H, t, $J$=7.8 Hz, 1-H), 4.99 (1H, d, $J$=7.8 Hz, 2-H), 5.29 (1H, d, $J$=7.8 Hz, 10b-H), 7.10—7.48 (6H, m, ArH), 7.48—7.67 (3H, m, ArH). MS $m/z$: 346 ($M^+$). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.47; H, 6.45; N, 8.03.

**Reaction of 17 with MCPBA** The same procedure as described for the reaction of **8b** with MCPBA provided a crude product from **17** (369 mg, 1.1 mmol) and 80% MCPBA (276 mg, 1.3 mmol). This was purified by column chromatography (elution with 20% EtOAc in hexane) to give methyl cinnamate (**20**) (106 mg, 61%), which was identical with an authentic sample with respect to the $^1$H-NMR spectral data. Further elution with 10% MeOH in $CHCl_3$ gave methyl (1,2-*trans*)-11-methyl-2-phenyl-1,2,5,6,11,11b-hexahydroisoxazolo[2′,3′:1,2]pyrido[3,4-*b*]-indole-1-carboxylate (**18**) (144 mg, 37%), which was recrystallized from EtOH to give crystals, mp 129—130 °C. IR (KBr) $cm^{-1}$: 1730 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 2.99 (2H, m, 5-$H_2$), 3.28 (3H, s, $NCH_3$), 3.49 (1H, m, 4-H), 3.67 (1H, dd, $J$=9.6, 7.0 Hz, 1-H), 3.68 (3H, s, $CO_2CH_3$), 3.82 (1H, m, 4-H), 5.15 (1H, d, $J$=9.6 Hz, 11b-H), 6.07 (1H, d, $J$=7.0 Hz, 2-H), 7.05—7.55 (9H, m, ArH). MS $m/z$: 362 ($M^+$). *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 73.16; H, 6.15; N, 7.71. The third eluate gave 9-methyl-3,4-dihydro-$\beta$-carboline 2-oxide (**19**) (128 mg, 60%), which was recrystallized from benzene to give crystals, mp 189—191 °C. IR (KBr) $cm^{-1}$: 1570 (=N–O). $^1$H-NMR ($CDCl_3$) $\delta$: 3.26 (2H, t, $J$=8.0 Hz, 4-H), 3.70 (3H, s, $NCH_3$), 4.28 (2H, t, $J$=8.0 Hz, 3-H), 7.20—7.55 (4H, m, ArH), 7.88 (1H, s, 1-H). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 72.02; H, 6.04; N, 13.80.

**Methyl 3-Hydroxy-2-(9-methyl-1,2,3,4-tetrahydro-$\beta$-carbolin-1-yl)-3-phenylpropionate (13)** A suspension of **11** (20 mg, 0.06 mmol) and Zn (35 mg, 0.5 mg-atom) in acetic acid (2 ml) was stirred at room temperature for 24 h. The reaction mixture was filtered through a Celite pad, and the filtrate was neutralized with 5% NaOH solution and extracted with EtOAc. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 30% EtOAc in hexane) to give **13** (12 mg, 60%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 160—161 °C. IR (KBr) $cm^{-1}$: 3420 (OH), 3350 (NH), 1725 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 2.91—3.08 (3H, m, C$\underline{H}_2$C$\underline{H}$HNH), 3.30 (1H, t, $J$=1.8 Hz, C$\underline{H}$$CO_2$Me), 3.39 (1H, m, CH$\underline{H}$NH), 3.54 (3H, s, $CO_2CH_3$), 3.70 (3H, s, $NCH_3$), 4.92 (1H, s, C$\underline{H}$OH), 5.03 (1H, d, $J$=1.8 Hz, CH$\underline{H}$$CO_2$Me), 7.07—7.42 (8H, m, ArH), 7.56 (1H, d, $J$=7.5 Hz, ArH). $^{13}$C-NMR ($CDCl_3$) $\delta$: 22.27 (t), 31.30 (q), 42.38 (t), 51.47 (q), 53.37 (d), 54.99 (d), 71.76 (d), 109.11 (d), 112.98 (s), 118.38 (d), 119.55 (d), 121.95 (d), 125.28 (d), 126.79 (d), 127.87 (d), 132.68 (s), 138.24 (s), 142.63 (s), 172.67 (s). MS $m/z$: 364 ($M^+$). *Anal.* Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.55; H, 6.68; N, 7.68. The same compound was alternatively obtained as follows. A crude product (**7a**) synthesized from **6a** (358 mg, 1 mmol) was dissolved in 2.3 N HCl in EtOAc (4.4 ml) and the solution was stirred at room temperature for 1 h. After removal of the solvent by evaporation *in vacuo*, the residue was dissolved in $CHCl_3$, and the solution was washed with saturated aqueous $NaHCO_3$ solution and brine, then dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography to give **13** (63 mg, 17%), which was identical with **13** obtained from **11**, based on a comparison of their spectral data.

**Methyl 6-Hydroxy-7-methyl-4-phenyl-1,2,3,4,5,6-hexahydroazocino-[5,4-*b*]indole-5-carboxylate (14)** The same procedure as described for the preparation of **13** provided a crude product from **12** (50 mg, 0.14 mmol) with Zn (90 mg, 1.4 mg-atom). This was purified by column chromatography (elution with 30% EtOAc in hexane) to give **14** (32 mg, 64%), which was recrystallized from MeCN to give crystals, mp 198—199 °C. IR (KBr) $cm^{-1}$: 3380 (OH), 3290 (NH), 1720 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 2.84 (2H, m, 1-$H_2$), 3.22 (1H, t, $J$=4.4 Hz, 5-H), 3.31—3.54 (2H, m, 2-$H_2$), 3.66 (3H, s, $NCH_3$), 3.80 (3H, s, $CO_2CH_3$), 3.98 (1H, d, $J$=4.4 Hz, 4-H), 5.68 (1H, d, $J$=4.4 Hz, 6-H), 7.08—7.40 (8H, m, ArH), 7.58 (1H, d, $J$=7.5 Hz, ArH). MS $m/z$: 364 ($M^+$). *Anal.* Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.20; H, 6.62; N, 7.69.

**X-Ray Structure Determination of the 10** Transparent, colorless, plate-like crystals were obtained from EtOH solution. Crystal data: $C_{22}H_{22}N_2O_5$, triclinic, space group $P$-1 $a$=14.321(3), $b$=8.543(9), $c$=8.392(7) Å, $\alpha$=75.97(7), $\beta$=90.80(7), $\gamma$=95.21(1)°, $V$=991.94(3) Å$^3$, $Z$=2, $D_c$=1.321, $\mu$ (Cu$K_\alpha$)=7.39 $cm^{-1}$, and $F(000)$=416. A single crystal was mounted on a Rigaku automated four-circle diffractometer. Using graphite-monochromated Cu$K_\alpha$ radiation ($l$=1.5418 Å), the unit cell constants were obtained by least-squares calculation with 2$\theta$ values of 25 high-angle reflections. Intensity data of 3184 independent reflections were obtained using the 2$\theta$–$\omega$ scanning technique ($\sin\theta/\mu$ <0.5617 Å$^{-1}$). The scan speed was 7°/min; the background was measured for 5$\sigma$. The intensities of four standard reflections measured every 100 reflection intervals showed no structural deterioration due to X-ray irradiation during the measurement of all reflections. Corrections were applied for Lorentz and polarization factors, but not for absorption effects. The structure was solved by the direct method by MULTAN 87[14] using 3106 reflections [$F_o > 2\sigma(F_o)$]. Reasonable parameters were refined by the block-diagonal least-squares method with anisotropic temperature factors for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. The final $R$-value was 0.105. The final positional and thermal parameters for all non-hydrogen atoms (atomic numbering is shown in Chart 3) are given in Table 1. All numerical calculations were performed using the UNICS programs.[15]

Table 1. Final Atomic Parameters with Their Estimated Standard Deviations in Parentheses

| Atom | $x$ | $y$ | $z$ | $B_{eq}$ |
|---|---|---|---|---|
| O1 | 0.2960 (2) | 0.1988 (3) | 0.2126 (3) | 3.9 (1) |
| C1 | 0.3727 (2) | 0.1904 (4) | 0.1122 (4) | 3.1 (2) |
| C2 | 0.3546 (2) | 0.0229 (4) | 0.0667 (4) | 3.0 (2) |
| C3 | 0.2701 (2) | −0.0561 (4) | 0.1753 (4) | 2.9 (1) |
| C4 | 0.2775 (2) | −0.2373 (4) | 0.2539 (4) | 3.1 (2) |
| N1 | 0.1992 (2) | −0.3355 (3) | 0.2772 (4) | 3.4 (1) |
| C5 | 0.1103 (2) | −0.2878 (4) | 0.2129 (4) | 3.3 (2) |
| C6 | 0.0848 (3) | −0.3047 (5) | 0.0576 (5) | 4.1 (2) |
| C7 | −0.0040 (3) | −0.2761 (6) | −0.0058 (5) | 5.1 (2) |
| C8 | −0.0682 (3) | −0.2158 (6) | 0.0859 (6) | 5.2 (2) |
| C9 | −0.0453 (3) | −0.2031 (5) | 0.2424 (5) | 4.6 (2) |
| C10 | 0.0455 (2) | −0.2347 (4) | 0.3079 (5) | 3.7 (2) |
| C11 | 0.0643 (3) | −0.2093 (5) | 0.4752 (5) | 4.0 (2) |
| C12 | 0.1565 (3) | −0.1256 (4) | 0.5131 (4) | 3.5 (2) |
| C13 | 0.1848 (3) | 0.0362 (4) | 0.3892 (4) | 3.8 (2) |
| N2 | 0.2765 (2) | 0.0308 (3) | 0.3085 (3) | 3.3 (1) |
| C14 | 0.4622 (3) | 0.3764 (5) | −0.1224 (5) | 4.2 (2) |
| C15 | 0.4711 (3) | 0.5079 (5) | −0.2587 (5) | 5.1 (2) |
| C16 | 0.3985 (4) | 0.6101 (6) | −0.2917 (6) | 6.6 (3) |
| C17 | 0.3172 (4) | 0.5801 (6) | −0.1929 (6) | 6.8 (3) |
| C18 | 0.3096 (3) | 0.4411 (5) | −0.0610 (5) | 5.0 (2) |
| C19 | 0.3809 (2) | 0.3400 (4) | −0.0292 (4) | 3.4 (2) |
| C20 | 0.3363 (2) | 0.0392 (4) | −0.1136 (4) | 3.3 (2) |
| O2 | 0.2596 (2) | 0.0462 (4) | −0.1786 (3) | 5.3 (2) |
| O3 | 0.4159 (2) | 0.0459 (3) | −0.1926 (3) | 4.1 (1) |
| C21 | 0.4127 (3) | 0.0883 (6) | −0.3710 (5) | 6.0 (3) |
| O4 | 0.3558 (2) | −0.2825 (3) | 0.3024 (3) | 4.3 (1) |
| C22 | 0.2050 (3) | −0.5060 (4) | 0.3676 (6) | 4.9 (2) |
| O5 | 0.0016 (2) | −0.2459 (5) | 0.5760 (4) | 7.4 (2) |

$B_{eq}=4/3(B_{11}a^2+B_{22}b^2+B_{33}c^2)$.

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