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Synthesis of a Tricyclic Benzodiazepine Derivative from Chlordiazepoxide and X-Ray Crystallographic Analysis of a Rearrangement Product, the Indolenine Derivative

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The oxazolidone-fused benzodiazepine derivative (1) was prepared by treatment of chlordiazepoxide (2) with sodium hydride and ethyl chloroformate followed by the N-oxide rearrangement of the resultant carbamate (3) with acetic anhydride. The first reaction was found to be accompanied by a multi-step rearrangement of the initially formed 3 as a side reaction giving rise to the indolenine derivative (4). The structure of 4 was determined by X-ray crystallographic analysis.

Keywords——1,4-benzodiazepine; oxazolidone-fused benzodiazepine; X-ray analysis; rearrangement; indolenine; ring contraction; chlordiazepoxide; reaction mechanism

The successful introduction by Hoffmann-La Roche of 1,4-benzodiazepine compounds as minor tranquilizers led medicinal chemists to investigate a wide variety of chemical modifications of the drugs. Our synthetic research on 1,4-benzodiazepines started with the synthesis of oxazolidine-fused benzodiazepines[1] and resulted in the introduction of tricyclic minor tranquilizers for medical use. As part of our studies on tricyclic benzodiazepines, we hoped to synthesize a new tricyclic benzodiazepine starting from chlordiazepoxide (2). We report herein the synthesis of the oxazolidone-fused benzodiazepine derivative (1), together with the structure determination of the by-product indolenine derivative (4), which was possibly formed as the result of multi-step rearrangement of the initially formed chlordiazepoxide derivative (3). Benzodiazepine compounds are known to undergo a variety of rearrangements giving rise to various heterocyclic compounds.[2] In our earlier studies on oxazolidinobenzodiazepines and other tricyclic benzodiazepines, we also found interesting rearrangements leading to quinoxalines,[3] quinolones,[4a] isoindoles,[4b,4c] and acridanones.[4c] The present work involves rearrangement of the 1,4-benzodiazepine derivative to the indolenine derivative.

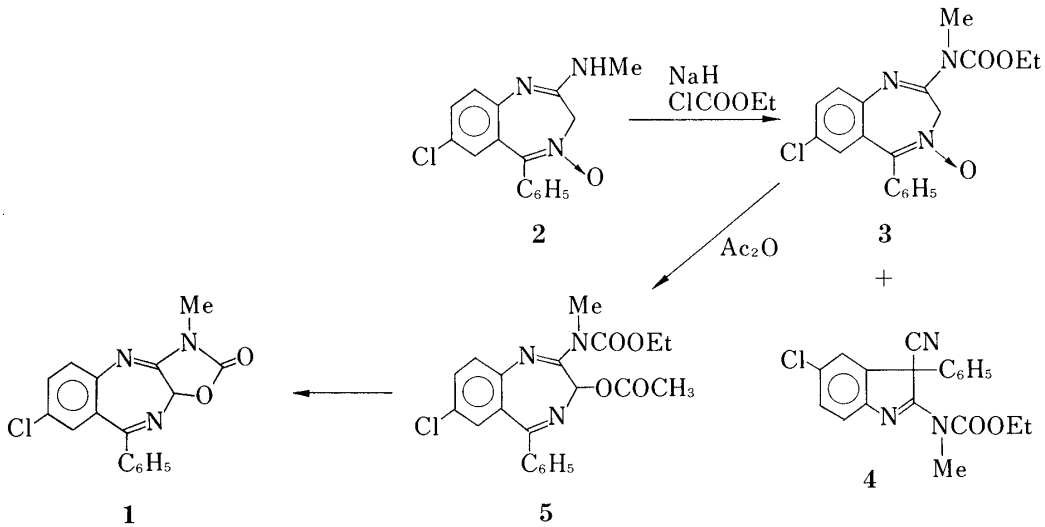

Chart 1

The new ring system in which the oxazolidone ring is fused to 1,4-benzodiazepine was formed in several steps starting from chlordiazepoxide (**2**). Chlordiazepoxide was treated with sodium hydride in N,N-dimethylformamide followed by reaction with ethyl chloroformate to afford two crystalline products (**3** and **4**) in yields of 50% and 4.9%, respectively, with 20% recovery of the starting material (**2**). The major product (**3**) was assigned as the expected benzodiazepine derivative on the basis of analytical and spectroscopic data. In the NMR spectra taken in $CDCl_3$, acetone-d_6 or DMF-d_7 at room temperature, the methylene proton signals were obscure because of coalescence. The methylene protons, however, appeared as a singlet at 5.16 ppm when measured in DMF-d_7 at 132 °C. The minor product (**4**), formulated as $C_{19}H_{16}ClN_3O_2$, showed no methylene group in the nuclear magnetic resonance (NMR) spectrum. The two hydrogen atoms at the C_3-position of chlordiazepoxide had been lost, as is evident in the spectral and analytical data. It was clear that an ethoxycarbonyl group had been introduced on the secondary amine, since the infrared (IR) and NMR spectra showed the disappearance of the N–H hydrogen. The removal of the N-oxide oxygen was indicated by the empirical formula deduced from analytical and mass spectral data. The structure of **4** was eventually determined by X-ray crystallographic analysis. In the IR spectrum there was no indication of the presence of the cyano group which was later shown to be present by X-ray crystallographic analysis. After the full structure of **4** had been unambiguously determined, we found that this type of rearrangement has been reported by Gilman and coworkers[5] in the reaction of the N-methyl derivative of **2** with dimethyl sulfate in the presence of the lithium anion of dimethyl sulfoxide.

The indolenine derivative **4** may have been formed by further reaction of the initially formed carbamate **3** with sodium hydride and an additional molecule of ethyl chloroformate. The N-oxide oxygen may be stripped off with the evolution of carbon dioxide after reaction with ethyl chloroformate, since gas evolution was observed during the reaction. The suggested mechanism for the formation of **4** is depicted in Chart 2 following the lines proposed by Gilman and coworkers, although the starting materials and reagents utilized for the two reactions are different.

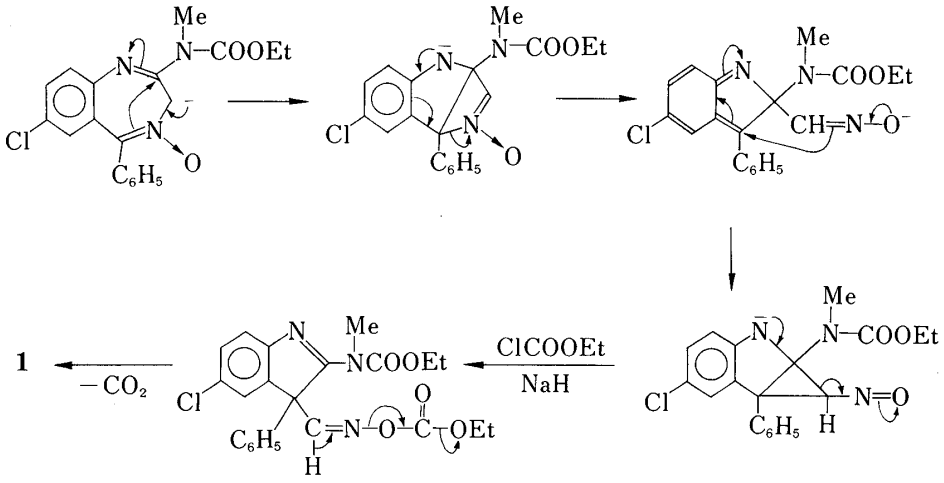

Chart 2

The carbamate derivative **3** was refluxed in acetic anhydride for 5 min to give the 2-acetoxy derivative (**5**). The resulting acetoxy compound was converted into the tricyclic compound **1** by treatment with silica gel.

The tricyclic benzodiazepine (**1**) and the intermediate compound, including the rearrangement product, were tested for central nervous system activities, but proved to be inactive.

Structure Determination of 4 by X-Ray Analysis

The crystals of 4 for X-ray analysis were grown from ethyl alcohol as colorless prisms. The crystal data for this compound are: a=17.0685 (6), b=8.9023 (3), c=23.0803 (9)Å, β= 99.826 (4)Å, space group C2/c, D_c=1.36 g/cm^3, Z=8. Intensities of 2397 independent reflections were collected on a Rigaku four-circle diffractometer with graphite-monochromated Cu-$K\alpha$ radiation, with 2θ up to 128 °.

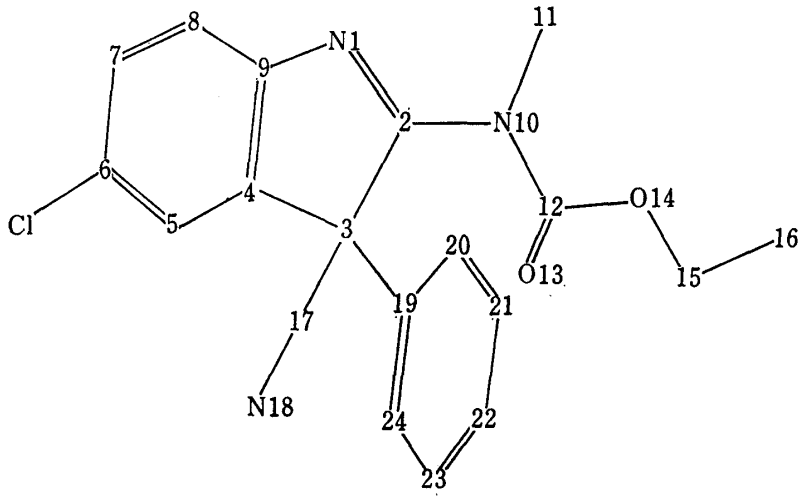

Fig. 1. Atomic Numbering of Compound 4

Unaccompanied numbers indicate C atoms.

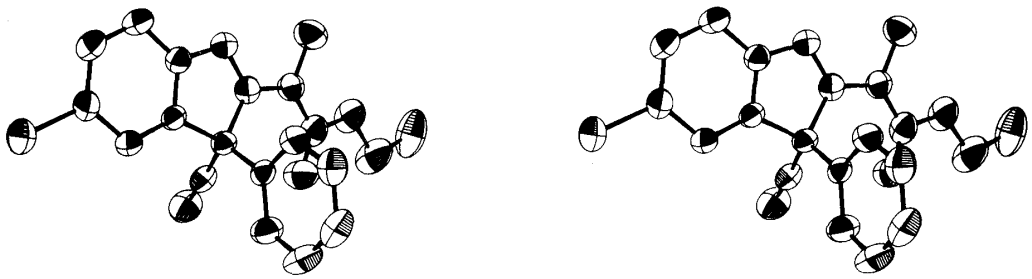

Fig. 2. Stereoview of the Molecule

Thermally vibrating Ellipsoids are drawn at the 50% probability level.

The structure was solved by use of the MULTAN program[6] with 299 normalized structure factors ($E \geq 1.5$). The positions of all 25 non-hydrogen atoms were found from the first E-map and those of the H atoms from a subsequent difference synthesis. The refinement of the structure was performed by block-diagonal least-squares methods with anisotropic temperature factors for non-hydrogen atoms and isotropic factors for H atoms. The function minimized was $W(|F_o|-|F_c|)^2$ where $w=1/\delta^2$ (F) and the final R value was 0.045. The atomic parameters with their estimated standard deviations are listed in Tables I and II. The numbering system and a stereoscopic view of the molecule are shown in Fig. 1 and Fig. 2, respectively. The bond lengths and angles are given in Tables III and IV, respectively.

In the indolenine moiety, the six-membered ring and the five-membered ring are planar to within deviations of 0.008 and 0.028 Å, respectively, and the dihedral angle between the two planes is 2.36 °. The deviation of the N (10) atom from the plane defined by the three adjacent atoms is 0.016 Å.

TABLE I. Final Positional ($\times 10^4$) and Anisotropic Thermal ($\times 10^4$) Parameters with Estimated Standard Deviations in Parentheses Anisotropic

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl	−1097(1)	−659(1)	2963(1)	36(1)	136(1)	36(1)	−19(1)	1(1)	2(1)
N(1)	2131(1)	956(2)	4108(1)	33(1)	113(3)	19(1)	3(1)	3(1)	6(1)
C(2)	2130(1)	2377(3)	4021(1)	31(1)	125(4)	15(1)	−2(2)	3(1)	1(1)
C(3)	1367(1)	2991(2)	3632(1)	30(1)	80(4)	17(1)	1(2)	3(1)	0(1)
C(4)	889(1)	1532(2)	3563(1)	31(1)	80(3)	17(1)	2(2)	7(1)	2(1)
C(5)	122(1)	1254(2)	3285(1)	30(1)	89(4)	19(1)	4(2)	5(1)	1(1)
C(6)	−126(1)	−231(3)	3293(1)	31(1)	111(4)	22(1)	−7(2)	5(1)	0(1)
C(7)	358(2)	−1366(3)	3549(1)	43(1)	89(4)	27(1)	−7(2)	7(1)	2(1)
C(8)	1120(2)	−1069(3)	3823(1)	44(1)	91(4)	25(1)	6(2)	6(1)	8(1)
C(9)	1377(1)	408(3)	3830(1)	31(1)	104(4)	17(1)	2(2)	7(1)	4(1)
N(10)	2800(1)	3207(2)	4237(1)	32(1)	127(3)	22(1)	−7(1)	0(1)	1(1)
C(11)	3506(2)	2366(3)	4523(1)	39(1)	183(5)	33(1)	5(2)	−4(1)	6(2)
C(12)	2817(2)	4764(3)	4210(1)	43(1)	165(5)	20(1)	−20(2)	0(1)	2(2)
O(13)	2280(1)	5527(2)	3969(1)	49(1)	129(3)	41(1)	−15(1)	−10(1)	5(1)
O(14)	3521(1)	5262(2)	4471(1)	47(1)	179(4)	30(1)	−37(1)	−6(1)	3(1)
C(15)	3615(2)	6896(4)	4477(2)	68(2)	199(6)	44(1)	−58(3)	−13(1)	15(2)
C(16)	4430(2)	7214(4)	4747(2)	89(2)	314(8)	32(1)	−93(3)	14(1)	−23(2)
C(17)	926(2)	4110(3)	3925(1)	44(1)	90(4)	20(1)	−7(2)	6(1)	1(1)
N(18)	531(1)	4909(2)	4122(1)	66(1)	130(4)	32(1)	9(2)	18(1)	−8(1)
C(19)	1514(1)	3528(2)	3027(1)	28(1)	85(4)	16(1)	−8(2)	1(1)	1(1)
C(20)	2012(1)	2684(3)	2742(1)	37(1)	123(4)	20(1)	4(2)	5(1)	6(1)
C(21)	2115(2)	3061(3)	2175(1)	41(1)	175(5)	22(1)	−8(2)	10(1)	0(2)
C(22)	1729(2)	4269(3)	1898(1)	55(2)	149(5)	20(1)	−26(2)	8(1)	5(2)
C(23)	1234(2)	5101(3)	2177(1)	65(2)	126(5)	23(1)	0(2)	1(1)	18(2)
C(24)	1126(2)	4746(3)	2748(1)	46(1)	111(4)	24(1)	11(2)	6(1)	8(1)

Thermal parameters are in the form $\exp[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})]$

TABLE II. Final Hydrogen-atom Positional Parameters ($\times 10^3$) and Thermal Parameters

	x	y	z	B(Å^2)
H(C5)	−25(1)	206(2)	306(1)	4.6(0.6)
H(C7)	14(1)	−238(2)	355(1)	6.3(0.6)
H(C8)	150(1)	−186(2)	403(1)	5.2(0.6)
H(C11A)	336(2)	139(3)	462(1)	10.1(0.9)
H(C11B)	379(1)	302(3)	484(1)	7.0(0.7)
H(C11C)	384(1)	219(3)	426(1)	9.0(0.8)
H(C15A)	323(1)	745(2)	469(1)	6.5(0.6)
H(C15B)	350(2)	730(3)	402(1)	8.9(0.8)
H(C16A)	460(2)	662(3)	517(1)	12.5(1.0)
H(C16B)	474(2)	672(3)	449(1)	10.8(0.9)
H(C16C)	448(2)	837(3)	480(1)	10.4(0.9)
H(C20)	229(1)	179(2)	293(1)	5.7(0.6)
H(C21)	249(1)	236(3)	198(1)	7.5(0.7)
H(C22)	179(1)	454(2)	144(1)	6.1(0.6)
H(C23)	92(1)	595(2)	197(1)	6.8(0.7)
H(C24)	78(1)	536(2)	297(1)	4.3(0.5)

Table III. Bond Lengths (Å)

Cl-C(6)	1.744(2)	N(10)-C(11)	1.476(3)
N(1)-C(2)	1.281(3)	N(10)-C(12)	1.388(3)
N(1)-C(9)	1.424(3)	C(12)-O(13)	1.199(3)
C(2)-C(3)	1.550(3)	C(12)-O(14)	1.325(3)
C(2)-N(10)	1.381(3)	O(14)-C(15)	1.464(4)
C(3)-C(4)	1.527(3)	C(15)-C(16)	1.451(4)
C(3)-C(17)	1.480(3)	C(17)-N(18)	1.128(3)
C(3)-C(19)	1.537(3)	C(19)-C(20)	1.382(3)
C(4)-C(5)	1.378(3)	C(19)-C(24)	1.372(3)
C(4)-C(9)	1.378(3)	C(20)-C(21)	1.390(4)
C(5)-C(6)	1.391(3)	C(21)-C(22)	1.363(4)
C(6)-C(7)	1.374(3)	C(22)-C(23)	1.364(4)
C(7)-C(8)	1.371(3)	C(23)-C(24)	1.398(4)
C(8)-C(9)	1.385(3)		
C(5)-H(C5)	1.05 (2)	C(16)-H(C16A)	1.12 (3)
C(7)-H(C7)	0.98 (2)	C(16)-H(C16B)	0.96 (3)
C(8)-H(C8)	1.02 (2)	C(16)-H(C16C)	1.04 (3)
C(11)-H(C11A)	0.95 (3)	C(20)-H(C20)	0.99 (2)
C(11)-H(C11B)	1.00 (2)	C(21)-H(C21)	1.05 (2)
C(11)-H(C11C)	0.92 (2)	C(22)-H(C22)	1.12 (2)
C(15)-H(C15A)	1.02 (2)	C(23)-H(C23)	1.00 (2)
C(15)-H(C15B)	1.10 (3)	C(24)-H(C24)	1.01 (2)

Table IV. Bond Angles (°)

C(2)-N(1)-C(9)	106.9(1)	N(1)-C(9)-C(4)	112.5(2)
N(1)-C(2)-C(3)	114.7(1)	N(1)-C(9)-C(8)	126.2(2)
N(1)-C(2)-N(10)	119.5(2)	C(2)-N(10)-C(12)	122.8(2)
C(3)-C(2)-N(10)	125.6(3)	C(2)-N(10)-C(11)	116.9(2)
C(2)-C(3)-C(4)	98.1(1)	C(11)-N(10)-C(12)	120.3(1)
C(2)-C(3)-C(17)	114.5(1)	N(10)-C(12)-O(14)	109.8(2)
C(2)-C(3)-C(19)	112.6(1)	N(10)-C(12)-O(13)	124.5(3)
C(4)-C(3)-C(17)	108.4(1)	O(13)-C(12)-O(14)	125.7(4)
C(4)-C(3)-C(19)	109.7(1)	C(12)-O(14)-C(15)	115.2(1)
C(17)-C(3)-C(19)	112.4(2)	O(14)-C(15)-C(16)	107.1(2)
C(3)-C(4)-C(9)	107.5(1)	C(3)-C(17)-N(18)	173.9(10)
C(3)-C(4)-C(5)	130.5(3)	C(3)-C(19)-C(24)	122.1(1)
C(5)-C(4)-C(9)	122.0(3)	C(3)-C(19)-C(20)	118.2(2)
C(4)-C(5)-C(6)	115.7(2)	C(20)-C(19)-C(24)	119.5(1)
Cl-C(6)-C(5)	118.2(1)	C(19)-C(20)-C(21)	120.2(2)
Cl-C(6)-C(7)	119.0(2)	C(20)-C(21)-C(22)	120.2(2)
C(5)-C(6)-C(7)	122.8(1)	C(21)-C(22)-C(23)	119.8(1)
C(6)-C(7)-C(8)	120.7(3)	C(22)-C(23)-C(24)	120.9(3)
C(7)-C(8)-C(9)	117.5(2)	C(19)-C(24)-C(23)	119.4(2)
C(4)-C(9)-C(8)	121.3(1)		

Experimental

All melting points are uncorrected. NMR spectra were recorded on a Varian A-60 machine, and signals are given in δ units downfield from tetramethylsilane as an internal standard. IR spectra were measured on a Nihon-Bunko Jasco IR-A or a Perkin-Elmer 225 spectrometer. A Nihon-Denshi JMS-01-SG spectrometer was used to obtain mass spectra.

7-Chloro-2-(N-methylethoxycarbonylamino)-5-phenyl-3H-1,4-benzodiazepine-4-oxide (3) and 5-Chloro-3-cyano-2-(N-methylethoxycarbonylamino)-3-phenyl-3H-indole (4)——A dispersion of NaH in mineral oil (*ca.* 50%, 1.20 g) was added to a stirred solution of chlordiazepoxide (**2**, 6.00 g) in DMF (80 ml) at room temperature and the mixture was stirred until NaH disappeared. The mixture was ice-cooled and ethyl chloroformate (2.28 g) was added. After stirring for 1 h with ice-cooling and standing overnight at room temperature, the reaction mixture was poured into ice-water and extracted with ether. The extract was washed with

water, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from EtOH to give **4** as pale yellow crystals (350 mg), mp 212—213°C. *Anal.* Calcd for $C_{19}H_{16}ClN_3O_2$: C, 64.50; H, 4.56; N, 11.88. Found: C, 64.56; H, 4.67; N, 12.25. MS *m/e*: 353 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1735 (ester). NMR ($CDCl_3$) δ: 3.11 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.59 (3H, s, NCH_3), 4.09 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.1—7.4 (m, aromatic H). The sample utilized for X-ray crystallographic analysis was obtained by recrystallization from EtOH.

The crystalline residue obtained from the mother liquor was chromatographed on a column of silica gel with benzene–MeOH (100: 1) to give **3** (3.75 g) as crystals. Recrystallization from EtOH gave pale yellow needles (2.6 g), mp 152—153°C. *Anal.* Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.55; H, 4.97; N, 11.44. MS *m/e*: 371 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1700 (ester). NMR ($CDCl_3$) δ: 1.36 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.37 (3H, s, NCH_3), 4.38 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.1—7.9 (8H, m, aromatic H). Further elution with benzene–MeOH (100: 5) gave the starting material **2** (1.2 g).

3-Acetoxy-7-chloro-2-(N-methylethoxycarbonylamino)-5-phenyl-3H-1,4-benzodiazepine (**5**)——A solution of the 4-oxide (3, 500 mg) in Ac_2O (10 ml) was refluxed for 5 min. The Ac_2O was removed by distillation *in vacuo* and the residue was recrystallized from EtOH to give colorless crystals (420 mg), mp 142—143°C. *Anal.* Calcd for $C_{21}H_{20}ClN_3O_4$: C, 60.95; H, 4.87; N, 10.15; Cl, 8.57. Found: C, 60.35; H, 4.87; N, 10.36; Cl, 8.67. MS *m/e*: 413 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1710, 1725 (ester). NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.24 (3H, s, $OCOCH_3$), 3.28 (3H, s, NCH_3), 4.28 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.84 (1H, s, methine H), 7.3—7.8 (8H, m, aromatic H).

7-Chloro-3-methyl-9-phenyl-2-oxo-11H-2,3-dihydrooxazolo[5,4-*b*][1,4]benzodiazepine (**1**)——A solution of the 4-oxide (3, 1.0 g) in Ac_2O (20 ml) was refluxed for 10 min, then Ac_2O was distilled off and the residue was chromatographed on a column of silica gel. The eluate with benzene–AcOEt (20: 1) yielded crystals which were recrystallized from benzene to afford **1** as colorless fine crystals (250 mg), mp 206—207°C. *Anal.* Calcd for $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; N, 12.90. Found: C, 62.32; H, 3.79; N, 12.66. MS *m/e*: 325 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1780 (C=O). NMR ($CDCl_3$) δ: 3.24 (3H, s, NCH_3), 5.74 (1H, s, methine H), 7.3—7.8 (8H, m, aromatic H).

References and Notes

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