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Studies on Benzodiazepinooxazoles. V.[1] Reactions of Benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole Derivatives with Acetic Anhydride

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Treatment of benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole derivatives (IIIa and IIId) with acetic anhydride and pyridine gave isoindole compounds (IV, V, VI, IX, X and XI) with ring contraction. A plausible mechanism of the reaction and the physical properties of these products are presented.

Sternbach and his co-workers[3] have reported that 1,4-benzodiazepines rearrange to isoindole derivatives on treatment with acetic anhydride in the presence of pyridine. In the preceding paper,[4] we have reported that benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole derivatives rearrange with ring contraction to give isoindoles by the action of sodium hydride. In this reaction, the compounds having no halogen at *o*-position of 11b-phenyl group gave no isoindole derivatives. In the course of our studies on benzodiazepinooxazole chemistry, we have found that similar rearrangements and ring contractions occur even in benzo[6,7]-1,4-diazepino[5,4-*b*]oxazoles bearing no substituent at *o*-position of 11b-phenyl group with acetic anhydride in the presence of pyridine.

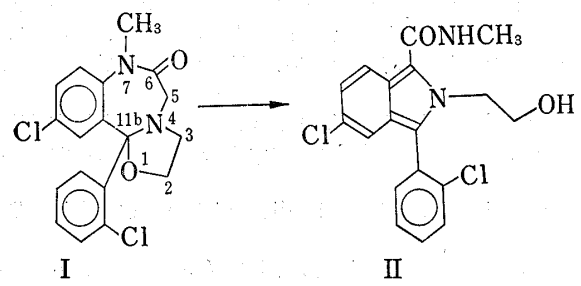

Chart 1

Treatment of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIa) with acetic anhydride-pyridine gave three compounds (IV, V and VI). The structural assignment of these products were made based on the infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra. The UV spectra (Fig. 1) of these products showed typical isoindole absorption pattern.

The first reaction product (IV) ($C_{18}H_{14}ONCl$, 7.3% yield) showed a carbonyl band at 1630 cm^{-1} and typical vinyl bands at 970 and 915 cm^{-1} in the IR spectrum. In the nuclear magnetic double resonance (NMDR) spectrum (Fig. 2) in deuteriochloroform at 100 Mc, the vinyl protons ($>N\text{-}\underset{H}{C}=C<\overset{H}{H}$) appeared at 4.78 ppm (double doublet, J_{AX}=16 Hz, J_{AB}=1 Hz), 5.21 ppm (double doublet, J_{BX}=8 Hz, J_{BA}=1 Hz) and 7.60 ppm (quartet, J=8 Hz). Double irradiation at 5.21 ppm resulted in the change of the peak at 7.60 ppm (quartet) to a doublet (J=16 Hz). Moreover, the peak at 7.60 ppm changed to a doublet (J=8 Hz) when the signal at 4.78 ppm was irradiated. From these spectral data, the structure of IV was assigned to be 1-acetyl-5-chloro-3-phenyl-2-vinylisoindole. The structure of IV was finally determined by its conversion to N-ethyl derivative. Catalytic hydrogenation of IV over Pd-C in ethanol gave dihydro derivative, 1-acetyl-2-ethyl-5-chloro-3-phenylisoindole (VII).

1) Part IV: A. Terada, Y. Yabe, T. Miyadera, and R. Tachikawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 807 (1973).
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
3) R.I. Fryer, B. Brust, J.V. Earley, and L.H. Sternbach, *J. Chem. Soc. (C)*, **1967**, 366.
4) A. Terada, Y. Yabe, T. Miyadera, and R. Tachikawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 742 (1973).

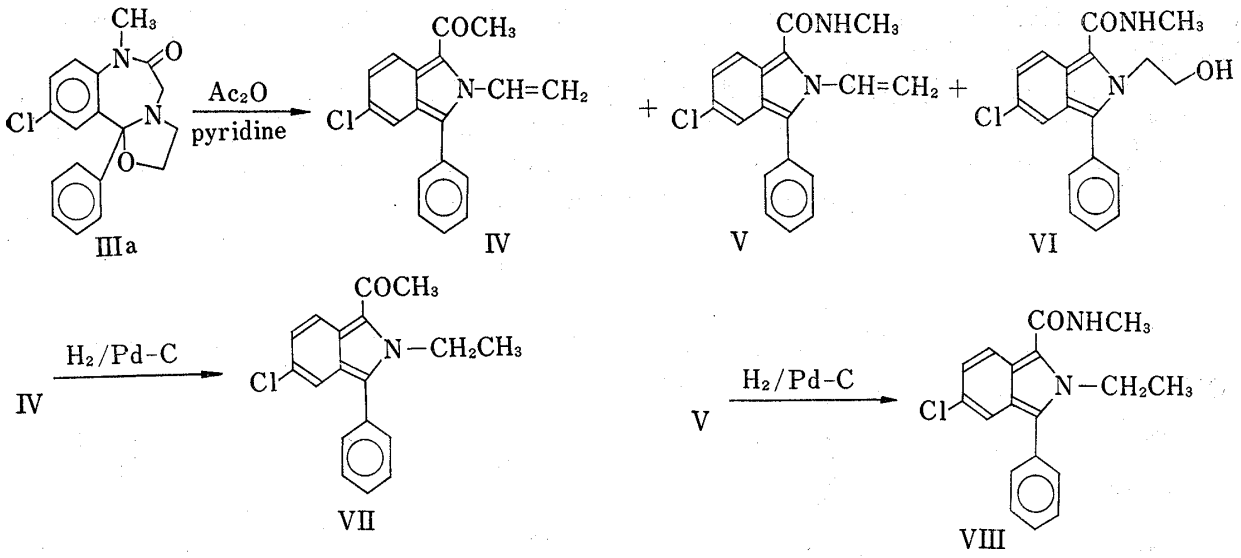

Chart 2

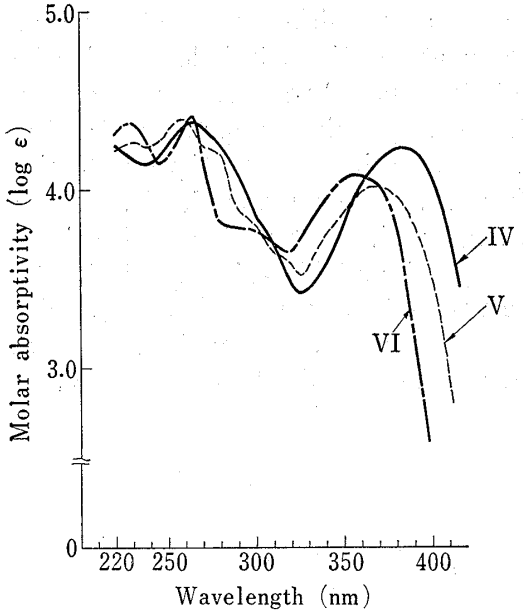

Fig. 1

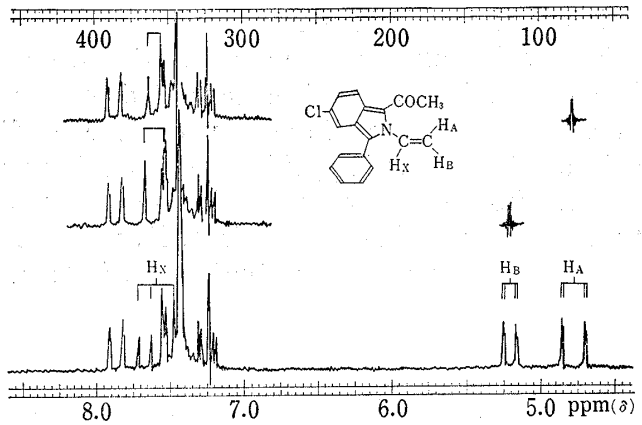

Fig. 2. The NMR Spectrum of IV

The second product (V) ($C_{18}H_{15}ON_2Cl$, 15.8% yield) showed a strong amino absorption band at 3260 cm^{-1}, a secondary amide band at 1640 cm^{-1} and typical vinyl bands at 960 and 906 cm^{-1} in the IR spectrum. The NMR spectrum exhibited a doublet at 3.07 ppm (3H, J=5 Hz) due to the -$NHCH_3$, which changed to a singlet on the addition of deuterium oxide. Other peaks closely resembled that of IV (see Experimental). From these results, it seemed to be reasonable to assume that the structure of V was 5-chloro-N-methyl-3-phenyl-2-vinyl-1-isoindolecarboxamide. In order to confirm this structure, V was reduced catalytically over Pd-C to give 5-chloro-2-ethyl-N-methyl-3-phenyl-1-isoindolecarboxamide (VIII).

The final product (VI) ($C_{18}H_{17}O_2N_2Cl$, 1.9% yield) showed a strong absorption band due to the amino and hydroxyl groups at 3325 cm^{-1} and a secondary amide band at 1625 cm^{-1} in the IR spectrum. The NMR spectrum exhibited a doublet at 3.00 ppm (3H, J=5 Hz, -$NHCH_3$) (which changed to a singlet on the addition of deuterium oxide), a broad singlet at 3.45 ppm (1H, OH), a triplet at 3.70 ppm (2H, J=6 Hz, -N-CH_2-), a triplet at 4.76 ppm (2H, J=6 Hz, -CH_2-O-), an aromatic multiplet centered at 7.58 ppm (8H) and a multiplet

at 8.10 ppm (1H, NH). These results enabled one to assign VI as 5-chloro-2-(2-hydroxyethyl)-N-methyl-3-phenyl-1-isoindolecarboxamide.

On the other hand, the compounds having the methyl group at 2 or 3 position (IIIb or IIIc) did not give the rearrangement products under the same conditions and the starting materials were quantitatively recovered. It is not clear why these substituted compounds (IIIb or IIIc) did not rearrange to isoindole derivatives.

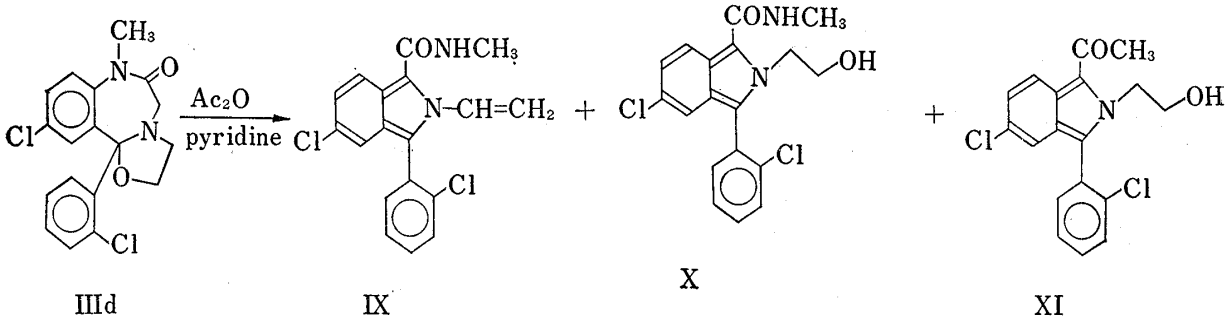

Chart 3

Similarly, the compound (IIId) having a chlorine atom at *o*-position of 11b-phenyl group was allowed to react with acetic anhydride-pyridine to afford three isoindole derivatives (IX, X and XI). The structure of the first two products (IX and X) was determined by comparison of the IR, UV and NMR spectra with those of the corresponding compounds (V and VI) which were obtained in the aforementioned reactions. Considering the reaction mechanism, the compound, IX, would be generated presumably from X. The compound, IX, however, could not be obtained from X under the conditions employed. But prolonged heating of X in acetic anhydride-pyridine afforded O-monoacetyl (XII) and N,O-diacetyl derivatives (XIII), whose structures were determined by the spectral data (see Experimental). Thus it was concluded that the product, X, was not the precursor of IX. From these facts, the compound, VI, which was obtained from IIIa, would also not be the precursor of V.

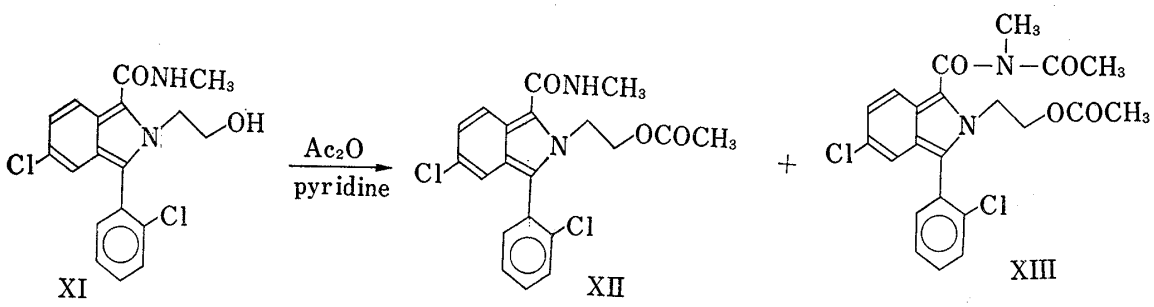

Chart 4

The remaining product (XI) ($C_{18}H_{15}O_2NCl_2$) showed a hydroxyl band at 3360 cm^{-1} and a carbonyl band at 1605 cm^{-1} in the IR spectrum. The UV spectrum revealed characteristic isoindole absorption pattern. The NMR spectrum exhibited a singlet at 2.75 ppm (3H) due to the methyl protons, a broad singlet at 2.92 ppm (1H) for a hydroxyl proton and two kind of multiplets at 3.83 and 4.67 ppm (-N-CH_2-CH_2-O-) in addition to aromatic proton peaks. Thus, XI was assigned to be 1-acetyl-5-chloro-3-(*o*-chlorophenyl)-2-(2-hydroxyethyl)isoindole.

The formation of VI and X can be explained in the same manner as described for the NaH–DMF reaction of 1,4-benzodiazepines.[5] However, some other explanations should be

5) A. Terada, Y. Yabe, T. Miyadera, and R. Tachikawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 742 (1973).

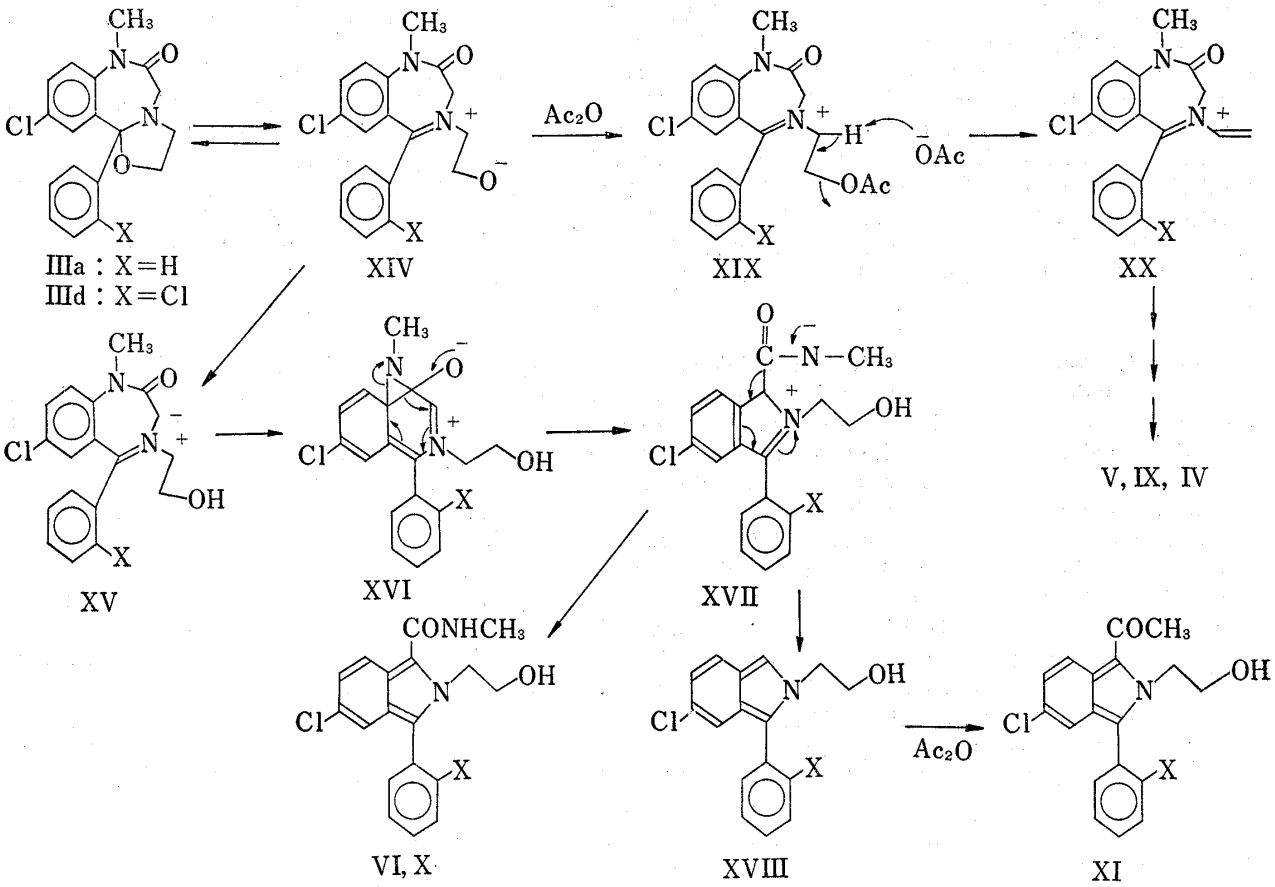

Chart 5

required in order to elucidate the formation of the different compounds (IV, V, IX and XI). The acetyl isoindole (XI) may be formed from the isoindole intermediate (XVII) with possible expulsion of methyl isocyanate. Reasonably the resulting isoindole (XVIII) is acetylated under the reaction conditions. The vinyl products (V, IX and IV) could not result from the hydroxyl compounds (VI, X and XI) under the reaction conditions. Thus, the dehydration to the vinyl group would occur at an earlier stage as depicted in Chart 5. The formation of these vinyl products (V, IX and IV) after the dehydration can be explained in the same manner as that of hydroxyl compounds (VI, X and XI).

Experimental[6]

Reaction of 10-Chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (IIIa) with Acetic Anhydride and Pyridine——A mixture of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIa, 3.28 g), acetic anhydride (10 ml) and pyridine (1.58 g) was heated under reflux for 2 hr, poured into water and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The oily residue was chromatographed on Al_2O_3 (Merck, grade II, 60 g). First fraction: Elution with C_6H_6 and recrystallization from EtOH gave 1-acetyl-5-chloro-3-phenyl-2-vinylisoindole (IV) (0.215 g) as green needles, mp 146—151°. *Anal.* Calcd. for $C_{18}H_{14}ONCl$: C, 73.10; H, 4.77; N, 4.73; Cl, 11.97. Found: C, 72.80; H, 4.86; N, 4.70; Cl, 11.98. IR ν_{max}^{Nujol} cm^{-1}: 1630, 970, 915. UV λ_{max}^{EtOH} mμ (ε): 263.3 (24000), 308 (5000, shoulder), 384 (17000). NMR (δ in $CDCl_3$): 2.72 (3H, singlet, $-COCH_3$), 4.78 (1H, double doublet, $J_{AX}=16$ Hz, $J_{AB}=1$ Hz, C=C–H), 5.21 (1H, double doublet, $J_{BX}=8$ Hz, $J_{BA}=1$ Hz, C=C–H), 7.43 (8H, multiplet, aromatic protons), 7.60 (1H, quartet, $J=8$ Hz, N–CH=C). Second fraction: Elution with C_6H_6 and recrystallization from EtOH afforded 5-chloro-N-methyl-3-phenyl-2-vinyl-1-isoindolecarboxamide (V) (0.490 g) as pale yellow needles,

6) All melting points are uncorrected. NMR spectra were recorded on a Varian A-60 and HA-100 spectrometers.

mp 129—131°. *Anal.* Calcd. for $C_{18}H_{15}ON_2Cl$: C, 69.57; H, 4.87; N, 9.01; Cl, 11.41. Found: C, 69.71; H, 4.94; N, 9.28; Cl, 11.64. IR ν_{max}^{Nujol} cm^{-1}: 3260, 1640, 960, 906. UV λ_{max}^{EtOH} mμ (ε): 230.3 (18800), 259 (25400), 300 (6300, shoulder) 368 (10400). NMR (δ in $CDCl_3$): 3.07 (3H, doublet, $J=5$ Hz, $NHCH_3$), 4.93 (1H, double doublet, $J_{AX}=16$ Hz, $J_{AB}=1$ Hz, C=C–H), 5.22 (1H, double doublet, $J_{BX}=8$ Hz, $J_{BA}=1$ Hz, C=C–H), 5.98 (1H, multiplet, NH), 7.42 (8H, multiplet, aromatic protons), 7.50 (1H, multiplet, N–CH=). Third Fraction: Elution with C_6H_6–AcOEt (1: 1) and recrystallization from C_6H_6 gave 5-chloro-2-(2-hydroxyethyl)-N-methyl-3-phenyl-1-isoindolecarboxamide (VI) (0.063 g) as colorless needles, mp 182—183.5°. *Anal.* Calcd. for $C_{18}H_{17}O_2N_2Cl$: C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.67; H, 5.21; N, 8.35; Cl, 10.61. IR ν_{max}^{Nujol} cm^{-1}: 3325, 1625. UV λ_{max}^{EtOH} mμ (ε): 227.5 (23800), 262.7 (26000), 298 (6000), 357.5 (12000). NMR (δ in d_7-DMF): 3.00 (3H, doublet, $J=5$ Hz, $NHCH_3$), 3.45 (1H, broad singlet, OH), 3.70 (2H, triplet, H=6 Hz, $-CH_2-N-$), 4.76 (2H, triplet, $J=6$ Hz, CH_2-O-), 7.58 (8H, aromatic protons, multiplet), 8.10 (1H, multiplet, NH).

1-Acetyl-2-ethyl-5-chloro-3-phenylisoindole (VII)——A suspension of 5% Pd-C (20 mg) in EtOH (30 ml) was stirred under H_2 atmosphere until no more hydrogen was absorbed. Then IV (100 mg) was added and the mixture stirred under H_2 atmosphere. After one mole of H_2 was absorbed, the catalyst was filtered off and washed with EtOH. The combined filtrate was evapolated under reduced pressure to give a solid. Recrystallization from EtOH afforded VII (80 mg) as pale green needles, mp 111—112°. *Anal.* Calcd. for $C_{18}H_{16}ONCl$: C, 72.61; H, 5.39; N, 4.71; Cl, 11.93. Found: C, 72.83; H, 5.47; N, 4.83; Cl, 11.47.

2-Ethyl-5-chloro-N-methyl-3-phenyl-1-isoindolecarboxamide (VIII)——A suspension of 5% Pd-C (20 mg) in EtOH (30 ml) was stirred under H_2 atmosphere until no more hydrogen was absorbed. Then V (100 mg) was added and a mixture stirred under H_2 atmosphere. After one mole of H_2 was absorbed, the catalyst was filtered off and washed with EtOH. The combined filtrate was evapolated under reduced pressure to afford a solid. Recrystallization from EtOH gave VIII (46 mg) as colorless needles, mp 218°. *Anal.* Calcd. for $C_{18}H_{17}ON_2Cl$: C, 69.12; H, 5.48; N, 8.96; Cl, 11.38. Found: C, 69.46; H, 5.46; N, 9.16; Cl, 11.30.

Reaction of 10-Chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-(*o*-chlorophenyl)benzo[6,7]-1,4-diazepino-[5,4-*b*]oxazol-6-one (III-d) with Acetic Anhydride and Pyridine——A mixture of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-(*o*-chlorophenyl)benzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIId, 3.63 g), acetic anhydride (10 ml) and pyridine (1.58 g) was heated under reflux for 2 hr. After cooling, a reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The combined extracts were washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The oily residue was chromatographed on Al_2O_3 (Merck, grade II, 60 g).

First Fraction: Elution with C_6H_6 and recrystallization from C_6H_6 gave 5-chloro-N-methyl-3-(*o*-chlorophenyl)-2-vinyl-1-isoindolecarboxamide (IX) (210 mg) as colorless needles, mp 142—143°. *Anal.* Calcd. for $C_{18}H_{14}ON_2Cl_2$: C, 62.62; H, 4.29; N, 8.11; Cl, 20.54. Found: C, 62.66; H, 4.24; N, 8.37; Cl, 20.64. IR ν_{max}^{Nujol} cm^{-1}: 3330, 1647, 961, 916. UV λ_{max}^{EtOH} mμ (ε): 230 (23000), 259.3 (25400), 304 (5200, shoulder), 318 (4600), 361 (10900). NMR (δ in $CDCl_3$): 3.04 (3H, doublet, $J=5$ Hz, $NHCH_3$), 4.81 (1H, double doublet, $J_{AX}=15.5$ Hz, $J_{AB}=1$ Hz, C=C–H), 5.07 (1H, double doublet, $J_{BX}=8.5$ Hz, $J_{AB}=1$ Hz, C=C–H), 6.07 (1H, multiplet, NH), 7.40 (7H, multiplet, aromatic protons), 7.50 (1H, multiplet, N–CH=C).

Second Fraction: Elution with C_6H_6–AcOEt (3: 1) and recrystallization from EtOH gave 1-acetyl-5-chloro-3-(*o*-chlorophenyl)-2-(2-hydroxyethyl)isoindole (XI) (61 mg) as colorless crystals, mp 156—160°. *Anal.* Calcd. for $C_{18}H_{15}O_2NCl_2$: C, 62.08; H, 4.34; N, 4.02; Cl, 20.36. Found: C, 61.87; H, 4.38; N, 4.06; Cl, 20.14. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1605. UV λ_{max}^{EtOH} mμ (ε): 237 (14800), 270 (23600), 300 (5000, shoulder), 363 (15900), 376.5 (17700). NMR (δ in $CDCl_3$): 2.75 (3H, singlet, $COCH_3$), 2.92 (1H, broad singlet, OH), 3.83 (2H, multiplet $N-CH_2-$), 4.67 (2H, multiplet, $-CH_2-O$), 7.48 (7H, multiplet, aromatic protons).

Third Fraction: Elution with C_6H_6–AcOEt (1: 1) and recrystallization from EtOH afforded 5-chloro-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (X) (271 mg) as colorless crystals, mp 186—189°. IR ν_{max}^{Nujol} cm^{-1}: 3325, 1643, 1625. UV λ_{max}^{EtOH} mμ (ε): 264.6 (23800), 343.5 (12300), 360 (shoulder). NMR (δ in $CDCl_3$): 3.09 (3H, doublet, $J=7.5$ Hz, $-NH-CH_3$).

5-Chloro-N-methyl-2-(2-acetoxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XII) and 5-Chloro-N-acetyl-N-methyl-2-(2-acetoxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XIII)——A mixture of 5-chloro-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (X) (100 mg), acetic anhydride (1 ml) and pyridine (24 mg) was heated under reflux for 6.5 hr. After cooling, the solvent was evaporated under reduced pressure to give an oily residue. The thin-layer chromatogram of this oil showed two spots at *Rf* 0.37 and 0.20 (silica gel, C_6H_6–AcOEt (7: 3)). The mixture was separated into each component by the preparative TLC.

Rf=0.37: Recrystallization from *n*-heptane gave XIII (32 mg) as pale yellow prisms, mp 123—124.5°. *Anal.* Calcd. for $C_{22}H_{20}O_4N_2Cl_2$: C, 59.07; H, 4.50; N, 6.26; Cl, 15.85. Found: C, 59.01; H, 4.21; N, 6.21; Cl, 15.83. IR ν_{max}^{Nujol} cm^{-1}: 1763, 1695, 1638. NMR (δ in $CDCl_3$): 1.88 (3H, singlet, $-N-COCH_3$), 2.19 (3H, singlet, $-O-COCH_3$), 3.33 (3H, singlet, $-N-CH_3$), 4.32 (2H, multiplet, $-N-CH_2-$), 4.75 (2H, multiplet, $-CH_2-O-$), 7.45 (center, 7H, multiplet, aromatic protons).

Rf=0.20: Recrystallization from EtOH–*n*-hexane afforded XII as colorless needles, mp 161—163°. *Anal.* Calcd. for $C_{20}H_{18}O_3N_2Cl_2$: C, 59.27; H, 4.48; N, 6.91; Cl, 17.50. Found: C, 59.30; H, 4.49; N, 7.00; Cl,

17.65. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1738, 1633, 1620. UV λ_{max}^{EtOH} $m\mu$ (ε): 226 (29600), 263.5 (25600), 295 (4400, plateau), 350 (13300), 360 (12500, plateau). NMR (δ in $CDCl_3$): 1.85 (3H, singlet, $COCH_3$), 3.11 (3H, doublet, $J=6$ Hz, $NHCH_3$), 4.32 (2H, multiplet, N–CH_2–), 4.83 (2H, multiplet, –CH_2–O), 6.08 (1H, multiplet, NH), 7.48 (center, 7H, multiplet, aromatic protons).

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