The Synthesis of Oxazolo- and Oxazino[3,2-*d*][1,4]benzodiazepinones

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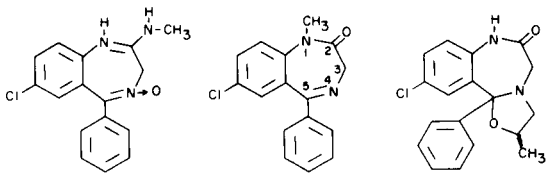
Cyclization of 2′-benzoyl-4′-chloro-2-[(2-hydroxypropyl)amino]acetanilide (**8**) and 2′-benzoyl-4′-chloro-2-[(3-hydroxypropyl)amino]acetanilide (**7**) led to the respective oxazolo (**3**) and oxazino (**5**) analogs of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one. Cyclization of 2′-benzoyl-4′-chloro-2-[2,3-dihydroxypropyl)amino]acetanilide (**9**) could produce either the oxazolo (**4**) or oxazino (**10**) analog. Data is presented to show that cyclization occurred to give the oxazolo (**4**) analog.

Since the initial discovery of chlordiazepoxide, **1**, a potent CNS agent, a considerable number of molecular modifications on the basic benzodiazepine nucleus have been performed in an attempt to expand the usefulness of this class of compounds (2).



1 2 3

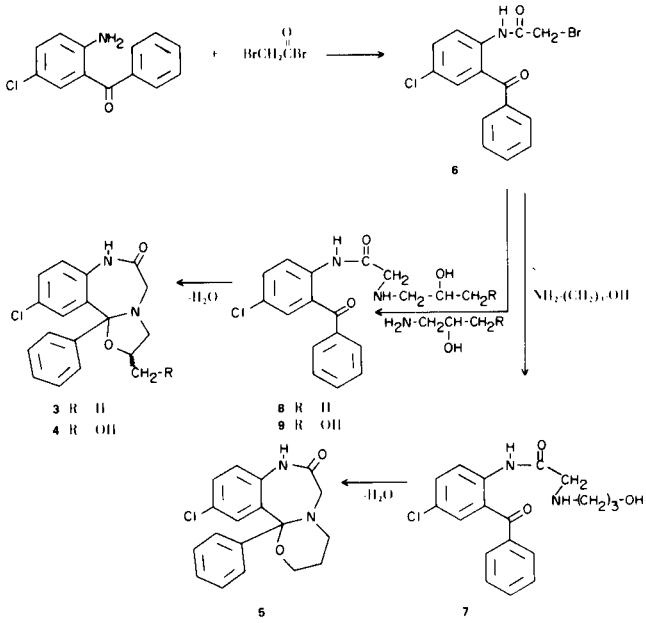
We were interested in determining the effect of modifying the 4,5-double bond in diazepam, **2** an active analog of **1**, by addition of another ring to this system to give the compounds **3**, **4** and **5**. While this work was underway, Takagi reported the biological activity of oxazolazepam (10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyl-oxazolo-[3,2-*d*][1,4]-benzodiazepin-6(5*H*)-one, (**3**) (3a). This compound was reported to have biological activity similar to diazepam, **2**, but much lower toxicity. We wish to report our synthesis and structure determination of these compounds.

Results and Discussion

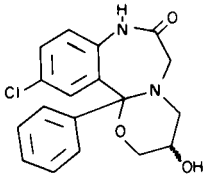
Oxazolazepam (**3**) and the analogs **4** and **5** were synthesized as shown in scheme I.

2-Amino-5-chlorobenzophenone was acylated according to the method (A) of Sternbach to give compound **6** (4). The reaction of **6** with the appropriate amino alcohol gave compounds **7**, **8** and **9** which were cyclized by heating in toluene. The structures of compounds **3**, which was an inseparable mixture of *cis* and *trans* material, and **5** were

SCHEME I



readily deduced from nmr analysis but the structure of compound **4** could not be assured by this procedure since two products are possible, **4** and **10**.

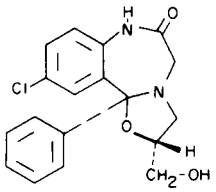


10

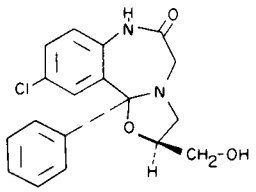
TABLE I

	Relative Abundance %			
	M^+	M^+-Y	M^+-X	M^+-77
Compound **3**	328 (32.2%)		313 (2.6%)	251 (100%)
Compound **4**	344 (10.6%)	326 (1.4%)	313 (7.3%)	267 (100%)
Compound **5**	328 (10.7%)	298 (19.5%)	297 (15.1%)	251 (100%)
Compound **11**	372 (6.3%)	341 (0.1%)	327 (8.5%)	295 (100%)
Compound **12**	358 (6 %)		327 (10 %)	281 (100%)

The product formed by ring closure of compound **9** appeared as a single material by tlc, but the nmr spectrum, like that of compound **3**, was more complicated than might have been expected for a single material. This material also appears to be a mixture of *cis* and *trans* products, compounds **4a** and **4b** respectively. The nature of the nmr spectrum argues in favor of structure **4** over **10** since the



4a



4b

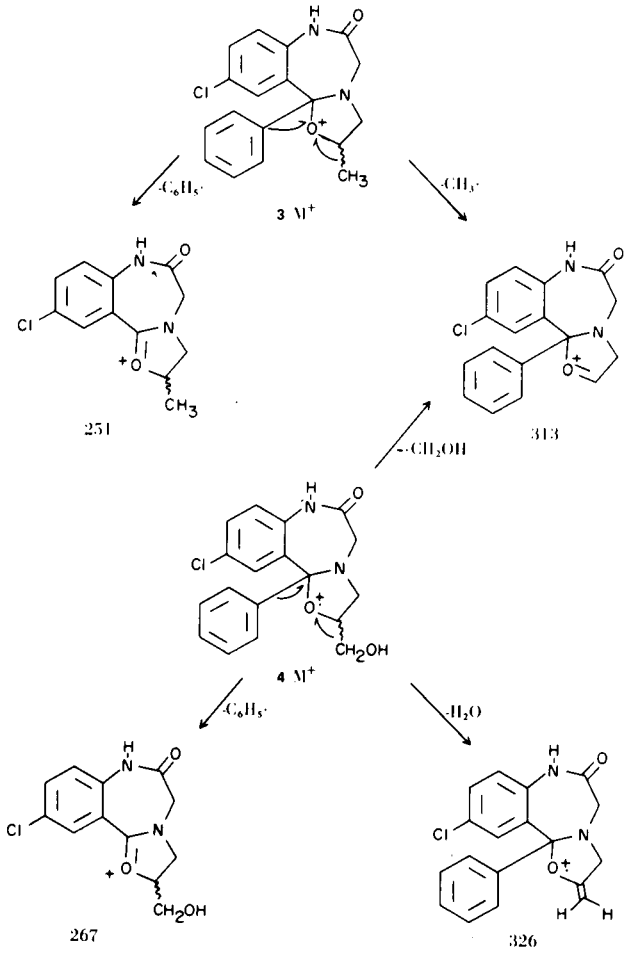
cis and *trans* isomers of **10** should have spectra which are more similar than those of **4a** and **4b**. More conclusive evidence for structure **4** over **10** was obtained from a comparison of the mass spectra of the cyclic products **3**, **4** and **5** (Table I).

The interpretation of the mass spectra of compounds **3** and **4** is shown in scheme II, while that of compound **5** is shown in scheme III. As can be seen, the fragmentation of compound **3** is much different than that of compound **5**. The fragmentation of compound **4** parallels that of **3** in that both give rise to a m/e 313 peak. If compound **9** had cyclized to the six-membered ring, **10**, a loss of 31 units would be difficult while a loss of 30 units, similar to that noted for **5** M^+, would be expected.

Compound **4** was treated with sodium hydride followed by methyl iodide to give compounds **11** and **12**.

Once again **11** was recovered as a mixture of *cis* and *trans* isomers which could not be separated by chromatography or crystallization. Both of these compounds were submitted for mass spectral analysis and showed a fragmentation pattern similar to that of compounds **2** and **4**

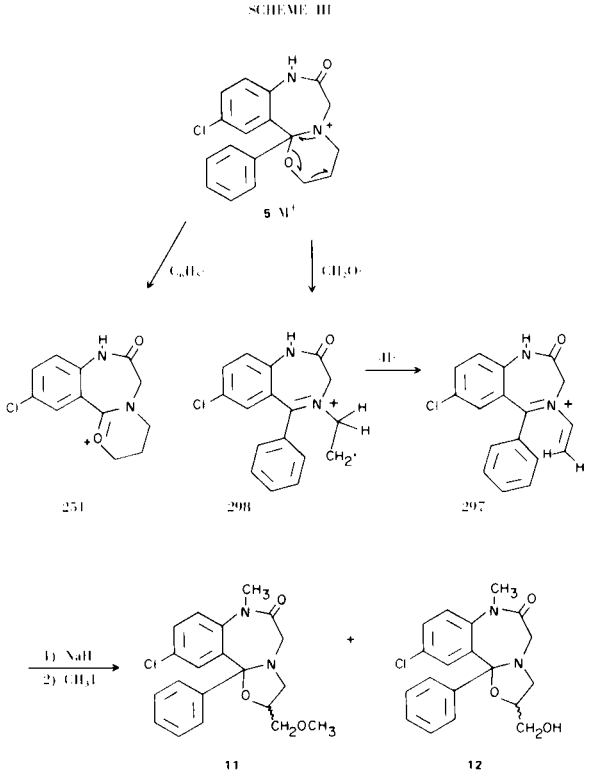
SCHEME II



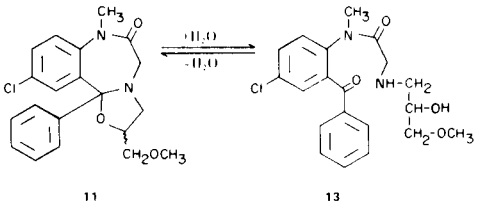
(Table I). This data along with that presented above is highly suggestive that the cyclization product of compound **9** is the oxazolo compound **4**.

Compound **11** was hydrolyzed to compound **13** which was isolated as a single material by chromatography. This

SCHEME III



material was readily characterized by nmr, but upon standing or when subjucted to mass spectral analysis the material recyclized to compound **11**. Thus, this attempt to determine the location of the methoxy failed.



EXPERIMENTAL

The nmr spectra were obtained on a Varian Associates A-60A spectrometer operating at a frequency of 60MHz. The internal standard was tetramethylsilane. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra were determined with a Perkin-Elmer model 421. The spectra were run as nujol mulls. The mass spectra were recorded on an ATLAS CH-4 mass spectrometer incorporating a TO-4 ion source. T.l.c. was performed using Silica Gel GF plates.

2′-Benzoyl-4′-chloro-2-[(2-hydroxypropyl)amino]acetanilide (**8**).

A mixture of 13.5 g. (0.038 mole) of 2-bromoacetamido-5-chlorobenzophenone (4) in 60 ml. of 1-amino-2-propanol (Aldrich Chem. Co.) was stirred at room temperature for 2 hours. The reaction mixture was dumped into a slurry of crushed ice-water and extracted with ether. The ether layer was washed with water, brine and dried (magnesium sulfate). Removal of the solvent gave 12.8 g. of a yellow oil which by nmr appeared to be the desired product. A 3 g. sample was converted to its hydrochloride salt which after two recrystallizations from ethanol-ether gave 2.7 g. of product, m.p. 191.5-192.5°. Data for the analytical sample follow: nmr (deuteriochloroform) δ 11.67 (broad, 1, HNCO), 8.67 (d, 1, J = 9Hz, 6′H), 7.3-7.9 (m, 7, aromatic), 3.93 (m, 1, W ½24Hz, CH-OH), 3.42 (s, 2, NCH_2CO), 3.1-2.5 (m, 4, N-CH_2-C, exchangeables), 1.13 (d, 3, J = 6Hz, $CHCH_3$); ir (mull), 1690 (N-C=O); 1665 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_3 \cdot HCl$: C, 56.40; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 56.55; H, 5.32; N, 7.41; Cl, 18.70.

10-Chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*]-[1,4]benzodiazepin-6(5*H*)-one (**3**).

A solution of 9.8 g. (0.028 mole) of crude 2′-benzoyl-4′-chloro-2-[(2-hydroxypropyl)amino]acetanilide in 250 ml. of dry toluene and 50 mg. of *p*-toluenesulfonic acid was heated under reflux in a nitrogen atmosphere for 45 hours. The water was removed by running the solvent through 4A molecular sieve. Removal of the solvent gave 10.4 g. of a gummy solid which was recrystallized from ethyl acetate to give 2.1 g. of product. An additional 800 mg. of product was recovered from the mother liquor. The mother liquor was concentrated and chromatographed on 500 g. of silica gel using 1:1 ethyl acetate:cyclohexane as eluting solvent. Fractions No. 10-19 (80 ml. each) contained 700 mg. of 2-amino-5-chlorobenzophenone, fractions no. 20-28 contained 800 mg. of product and fractions no. 51-54 (80 ml. each) using methanol as eluting solvent contained 2.45 g. of starting material. The combined product fractions were recrystallized from chloroform (hydrocarbon stabilized) to give 3.0 g. of product, m.p. 185°. From the mother liquor an additional 800 mg. of product was recovered. Data for the analytical sample follow: nmr (deuteriochloroform) δ 8.60 (broad, 1, amide), 8.30 (broad, 1, amide), 7.81 (d, 1, J = 2.5Hz, 8H), 7.1-7.5 (m, 13, aromatic), 6.85 (d, 1, 11H), 6.80 (d, 1, 11H), 4.20 (m, 2, CH_2-O), 3.5-2.3 (m, 4, methylenes), 1.35 (d, 3, J = 6Hz, CH_3C), 1.25 (d, 3, J = 6Hz, CH_3C); ir (mull), 1690 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.62; H, 5.30; N, 8.39; Cl, 11.07.

2′-Benzoyl-4′-chloro-2-[(2,3-dihydroxypropyl)amino]acetanilide (**9**).

To a solution of 3.54 g. (0.01 mole) of 2-bromoacetamido-5-chlorobenzophenone in 25 ml. of DMF was added 2.73 g. (0.03 mole) of 1-amino-2,3-dihydroxypropane with stirring under a nitrogen atmosphere. Within 15 minutes only a trace of starting material remained. The reaction mixture was concentrated, treated with water and extracted with chloroform. The organic layer was washed with water and brine and concentrated. The yellow solid was chromatographed on 400 g. of silica gel using 10% methanol: chloroform as eluting solvent. The product was recovered and recrystallized from benzene to give 2.25 g., m.p. 105-107°. Data for the analytical sample follows: nmr (deuteriochloroform) δ 11.67 (broad, 1, amide), 8.70 (d, 1, J = 10Hz, 6′H), 7.4-7.9 (m, 7, aromatic), 3.83 (m, 1, CH-O), 3.62 (m, 2, CH_2-O), 3.45 (s, 2, O ‖ C-CH_2-N), 3.0-3.5 (broad, 3, exchangeable), 2.76 (d, 2, J = 5Hz, N-CH_2-); ir (mull), 1690 (N-C=O), 1635 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_4$: C, 59.59; H, 5.28; N, 7.72; Cl, 9.77. Found: C, 59.49; H, 4.94; N, 7.43; Cl, 9.75.

10-Chloro-2,3,7,11b-tetrahydro-2-(hydroxymethyl)-11b-phenyl-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (**4**).

A solution of 10 g. (0.0275 mole) of 2′-benzoyl-4′-chloro-2-[(2,3-dihydroxypropyl)amino]acetanilide, 50 mg. of *p*-toluene-

sulfonic acid and 250 ml. of dry toluene was heated under reflux in a nitrogen atmosphere for 48 hours. The water was removed with 4A molecular sieve. Removal of the solvent resulted in recovery of 9.0 g. of a thick oil which was taken up in ethyl acetate and upon cooling gave 4.5 g. of product. A second recrystallization from ethyl acetate gave 2.5 g., m.p. 162-165°. Data for the analytical sample follows: nmr (deuteriochloroform) δ 9.68 (broad, 1, amide), 7.0-7.6 (m, 8, aromatic), 3.8-4.9 (broad, 3), 3.1-3.8 (unresolved multiplets, 5); ir (mull), 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; N, 8.13; Cl, 10.28. Found: C, 62.76; H, 4.80; N, 7.77; Cl, 10.30.

2'-Benzoyl-4'-chloro-2[(3-hydroxypropyl)amino]acetanilide Hydrochloride (**7**).

To 6 ml. of 3-amino-1-propanol in 20 ml. of dimethylformamide in an ice bath was added dropwise with stirring 2.12 g. of 2-bromoacetamido-5-chlorobenzophenone in 20 ml. of dimethylformamide. After 2 hours at room temperature tlc (10% methanol-benzene) showed no starting material. The solution was concentrated at high vacuum to remove solvents, water added and the mixture extracted with ether three times. The ether extract was washed with saturated sodium chloride, dried and hydrogen chloride introduced. The crystals which separated were recrystallized from isopropyl alcohol to give 1.45 g. (2 crops) melting at 193-198°. Data for the analytical sample follows: nmr (d_6-DMSO) δ 7.4-7.9 (m, 8, aromatic), 3.72 (s, 2, $COCH_2$), 3.33-3.6 (m, 2, CH_2-O), 2.68-3.0 (m, 2, CH_2N), 1.5-2.0 (m, 2, C-CH_2-C).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_3 \cdot HCl$: C, 56.40; H, 5.26; Cl, 18.50; N, 7.31. Found: C, 56.37; H, 5.27; Cl, 18.57; N, 7.00.

11-Chloro-3,4,8,12b-tetrahydro-12b-phenyl-2*H*-[1,3]-oxazino[3,2-*d*]-[1,4]benzodiazepin-7(6*H*)-one (**5**).

A solution of 3.4 g. of 2'-benzoyl-4'-chloro-2[(3-hydroxypropyl)-amino]acetanilide and 100 mg. of *p*-toluenesulfonic acid in 150 ml. of toluene was heated under reflux for 22 hours using a Dean-Stark water separator. At that time most of the starting material was gone as shown by tlc (ethyl acetate). The solution was concentrated to dryness under reduced pressure and the product crystallized from ethyl acetate; yield, 1.53 g., m.p. 213-216°. Data for the analytical sample follows: nmr (d_6-DMSO) δ 10.05 (s, 1, amide), 7.1-7.5 (m, 8, aromatic), 3.67-4.05 (m, 2, $COCH_2N$), 3.3-3.5 (m, 2, CH_2O), 2.8-3.18 (m, 2, CH_2-N), 1.5-1.9 (m, 2, C-CH_2-C).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$ (M.W. 328.80): C, 65.75; H, 5.21; Cl, 10.78. Found: C, 66.02; H, 5.33; Cl, 10.89.

10-Chloro-2,3,7-11b-tetrahydro-2-(methoxymethyl)-7-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (**11**).

To a solution of 3.33 g. (0.0096 mole) of 10-chloro-7,11b-dihydro-2-(hydroxymethyl)-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one in 100 ml. of DMF under a nitrogen atmosphere was added 0.576 g. (0.024 mole) of 57% sodium hydride. The reaction mixture was stirred at 25° for 4 hours. To the reaction mixture was added 7.1 g. (0.05 mole) of methyl iodide and stirring was continued for 1.5 hours. The reaction mixture was concentrated *in vacuo*, the residue was treated with water and extracted with ether. The ether extract was washed with brine and dried (magnesium sulfate). Removal of the solvent gave 4.4 g. of a solid which was chromatographed on 400 g. of silica gel (Brinkmann) using 5% methanol:95% chloroform as eluting solvent. The first material off of the column was product which was recrystallized from cyclohexane to give 1.26 g., m.p. 131-133°. Data for the analytical sample follows: nmr (deuteriochloroform), mixture of *cis* and *trans* isomers δ 7.98 (d, 1, J = 2.5Hz, H-11), 7.67 (d, 1, J = 2.5Hz, H-11), 7-7.6 (m, 14, aromatic), 4.1-4.6 (m, 2, O-CH_2-), 3.42 (s, 3, O-CH_3), 2.57 (s, 3, N-CH_3), 3.25 (s, 3, OCH_3), 2.59 (s, 3, N-CH_3), 2.8-3.7 (m, 12, -CH_2-); ir (mull), 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{20}H_{21}ClN_2O_3$: C, 64.42; H, 5.68; Cl, 9.51; N, 7.52. Found: C, 64.30; H, 5.82; Cl, 9.55; N, 7.52.

The second solid off of the column was recrystallized from ethyl acetate, m.p. 193-196°. The mass spectrum showed the presence of only one methyl, m/e 358, compound **12**.

2'-Benzoyl-4'-chloro-2-[(2-hydroxy-3-methoxypropyl)amino]-acetanilide (**13**).

A sample of 0.5 g. of 10-chloro-2,3,7,11b-tetrahydro-2-(methoxymethyl)-7-methyl-11b-phenyloxazolo[3,2-*d*][1,4]-benzodiazepin-6(5*H*)-one (**11**) was treated with 50 ml. of 10% hydrochloric acid with stirring under a nitrogen atmosphere for 5 hours. The reaction mixture was made basic with aqueous sodium hydroxide and extracted with ether. The organic extract was dried (magnesium sulfate). Removal of the solvent gave a residue which was chromatographed on silica gel (Brinkmann). The first sample off the column was starting material. The second material was open chain product which was present as an oil; nmr (deuteriochloroform), δ 7.0-7.9 (m, 8, aromatic), 3.5-3.8 (m, 1, HC-OH), 3.35 (s, 6, OCH_3, N-CH_3), 3.04 (s, 2, CH_2-O), 2.83 (s, 2, exchangeables), 3.18 (broad s, 2, CH_2-C=O), 2.4-2.65 (broad, 2, CH_2-N). A sample of the oil was submitted for mass spectrum: m/e 372, 327, 295 (same as starting material). Upon standing the oil solidified to give the 10-chloro-2,3,7,11b-tetrahydro-2-(methoxymethyl)-7-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (**11**), m.p. 130-135°.

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