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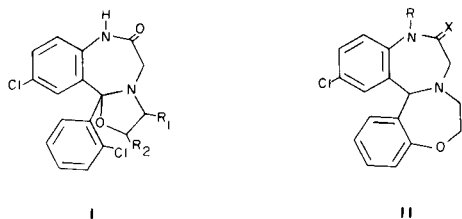
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The novel 1,4-benzodiazepino[4,5-*d*][1,4]benzoxazepine ring system has been constructed *via* preformed benzoxazepine intermediates. Several derivatives have been prepared as potential anxiolytic agents.

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Several oxazolobenzodiazepines (I) have exhibited significant pharmacological profiles as potential anticonvulsant/anxiolytic agents with improved potency over diazepam (1-3). In the interest of developing novel psychotropic agents of therapeutic potential, we have undertaken the synthesis of the isomeric 1,4-benzodiazepino[4,5-*d*][1,4]benzoxazepines (II).



This report outlines an approach to this novel benzodiazepine system by cyclization of functionalized benzoxazepine intermediates rather than utilization of preformed benzodiazepine precursors.

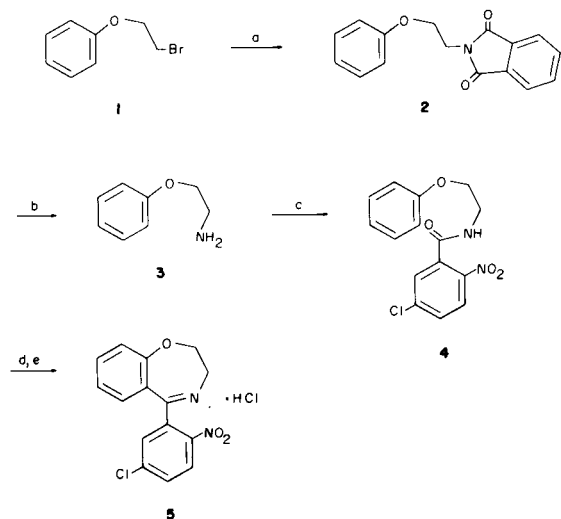
The benzoxazepine nucleus was constructed *via* a Bischler-Napieralski cyclization route (4) as illustrated in Scheme I. Condensation of β -bromophenetole (1) with potassium phthalimide in warm dimethylformamide provided phthalimide 2 in 87% yield. Hydrazinolysis generated amino derivative 3 which was readily acylated with 5-chloro-2-nitrobenzoyl chloride to give amide 4 in

67% overall yield. Cyclodehydration of substituted *N*-(2-phenoxyethyl)benzamides to the corresponding benzoxazepines has been subject of several reports (5,6). Refluxing amide 4 with a mixture of phosphorous oxychloride and phosphorous pentoxide in xylene followed by conversion to the hydrochloride provided benzoxazepine 5 in 44% yield.

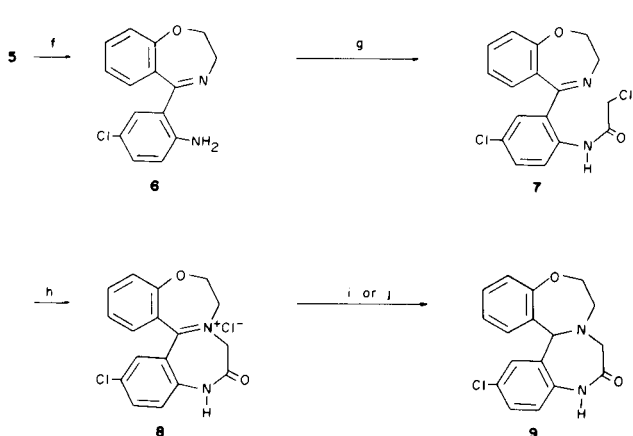
Reagents: a. potassium phthalimide, DMF; b. $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$; c. 5-chloro-2-nitrobenzoyl chloride; d. $\text{POCl}_3 \cdot \text{P}_2\text{O}_5$, xylene; e. HCl (g).

Elaboration of nitrobenzoxazepine 5 to the desired benzodiazepine ring system is outlined in Scheme II. Reduction of a number of substituted dihydrobenzoxazepines to their tetrahydro derivatives has been reported to occur with hydrogen using standard catalysts and with sodium borohydride (7). In our hands, the free base of compound 5 gave a complex mixture of products under these conditions. Apparently, the presence of the *ortho*-nitro group complicates the situation (8). However, selective reduction of the nitro substituent with tin(II) chloride in an acetic-hydrochloric acid mixture (9) provided amino derivative 6. Acylation with chloroacetic anhydride (10) gave chloroacetanilide 7. Cyclization in refluxing 1-propanol yielded iminium salt 8. Hydrogenation with 1% platinum on carbon or facile reduction with sodium borohydride presented the 1,4-benzodiazepino[4,5-*d*][1,4]benzoxazepine skeleton 9.

Scheme I

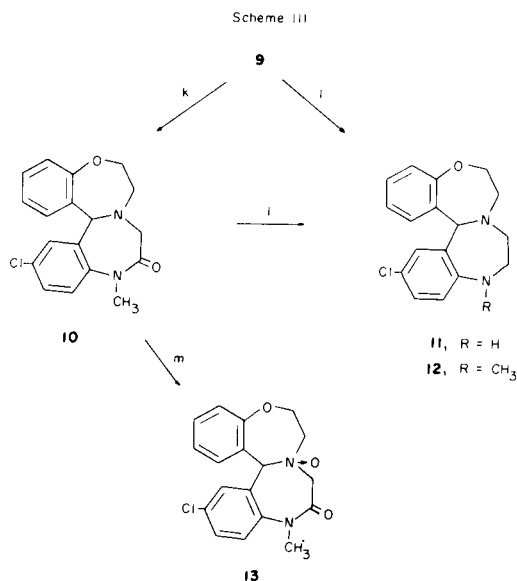


Scheme II



Reagents: f. $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, HCl, HOAc; g. chloroacetic anhydride, K_2CO_3 , CH_2Cl_2 ; h. *n*-PrOH, Δ ; i. H_2 , 1% Pt/C, CH_3OH ; j. NaBH_4 , CH_3OH .

Modification of the unsubstituted benzodiazepinone **9** provided several interesting derivatives. Alkylation using sodium hydride and dimethyl sulfate in dimethylformamide gave methyl analog **10**. Borane reduction of amides **9** and **10** yielded the corresponding benzodiazepines **11** and **12**. Oxidation with *meta*-chloroperbenzoic acid (**11**) resulted in tertiary amine oxide **13**.



Reagents: k. NaH, $(\text{CH}_3)_2\text{SO}_4$, DMF; l. BH_3/THF ; m. MCPBA, CH_2Cl_2 .

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727 or a Pye Unicam SP3-200 spectrophotometer. Nuclear magnetic resonance spectra were taken at 60 MHz on either a JEOL C-60HL or a JEOL FX-60 spectrometer, and chemical shifts are given relative to internal tetramethylsilane. Mass spectra were obtained from a Finnigan Model 4000 spectrometer interfaced to a Finnigan 9610 gas chromatograph and equipped with an INCOS data system. Elemental analysis was performed by Micro-Tech Laboratories, Skokie, Illinois. Thin layer chromatograms were run on silica gel PF-254 plates and column chromatography was performed using silica gel 60 (E. Merck, AC) or absorption alumina (Fisher Scientific).

N-(2-Phenoxyethyl)phthalimide (**2**).

A mixture of β -bromophenetole (**1**) (94.8 g, 0.47 mole), potassium phthalimide (104.7 g, 0.56 mole) and 400 ml of anhydrous dimethylformamide was warmed at 85° for one hour. After cooling, chloroform was added and the resulting mixture was washed with 0.2*N* sodium hydroxide and water, dried (sodium sulfate), and concentrated *in vacuo*. The solid residue was triturated with ether and collected by filtration to give 109 g (87%) of colorless crystals, mp $126\text{--}128^\circ$. Recrystallization from ethyl acetate/ether gave an analytical sample, mp $127\text{--}129^\circ$; ir (chloroform): 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 4.18 (t, 4, CH_2), 6.70-8.00 (m, 9, aromatic H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.81; H, 4.75; N, 5.03.

N-(2-Phenoxyethyl)-5-chloro-2-nitrobenzamide (**4**).

A mixture of **2** (96.7 g, 0.36 mole), hydrazine hydrate (22.7 ml, 0.38 mole) and 1500 ml of methanol was refluxed for 2 hours. The cooled mix-

ture was filtered and the filtrate was concentrated *in vacuo*. The combined solids were suspended in ether and shaken with 40% potassium hydroxide (**12**). The aqueous was extracted with ether and the combined organics were dried (potassium carbonate) and concentrated *in vacuo* to give 39.5 g of a light yellow oil (**3**).

A solution of 5-chloro-2-nitrobenzoyl chloride (11.0 g, 0.05 mole) in 15 ml of dioxane was added dropwise to a mixture of sodium hydroxide (2.0 g, 0.05 mole) in 25 ml of water and **3** (7.9 g, 0.06 mole) in 10 ml of dioxane with ice bath cooling. After stirring at room temperature overnight, the mixture was diluted with water and extracted with dichloromethane. The organic extract was washed with water, dried (sodium sulfate) and concentrated *in vacuo*. The residue was recrystallized from toluene giving 12.7 g (80%) of pale yellow needles, mp $126\text{--}128^\circ$; ir (chloroform): 3480 (NH), 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.88 (t, 2, N-CH_2), 4.15 (t, 2, O-CH_2), 6.40 (bs, 1, NH), 6.70-7.70 (m, 7, aromatic H), 8.01 (d, 1, aromatic H *ortho* to NO_2).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_4$: C, 56.17; H, 4.08; N, 8.74. Found: C, 56.50; H, 4.16; N, 8.54.

5-(5'-Chloro-2'-nitrophenyl)-2,3-dihydro-1,4-benzoxazepine (**5**).

To a mechanically stirred mixture of **4** (45 g, 0.14 mole) and phosphorous oxychloride (125 ml, 1.40 moles) in one liter of xylene at reflux was added phosphorus pentoxide (100 g, 0.90 mole) in five portions at 15 minute intervals. This mixture was refluxed for 4.5 hours, cooled and poured into ice water. (The organic layer was separated and yielded 9 g recovered **4**.) The aqueous was made basic with concentrated ammonia and extracted with dichloromethane. The extracts were washed with water, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was taken up in dichloromethane/toluene and treated with hydrogen chloride (**g**) to yield 27 g of a tan solid. Recrystallization of 6 g from ethanol gave 3.7 g (44%) of yellow crystals, mp $236\text{--}239^\circ$ dec; ir (potassium bromide): 1670 cm^{-1} (C=N); nmr (trifluoroacetic acid): 4.50 (m, 2, N-CH_2), 4.98 (m, 2, O-CH_2), 7.00-8.10 (m, 6, aromatic H), 8.53 (d, 1, aromatic H *ortho* to NO_2).

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}_3\cdot\text{HCl}$: C, 53.11; H, 3.57; N, 8.26. Found: C, 53.09; H, 3.61; N, 8.30.

5-(2'-Amino-5'-chlorophenyl)-2,3-dihydro-1,4-benzoxazepine (**6**).

A warm solution of **5** (21.4 g, 0.06 mole) in 250 ml of glacial acetic acid was added dropwise to a mixture of tin(II) chloride dihydrate (113.6 g, 0.5 mole) in 300 ml of concentrated hydrochloric acid and 65 ml of glacial acetic acid and stirred at room temperature overnight. This mixture was poured into 10% sodium hydroxide/ice water and extracted with dichloromethane. The organic extract was washed with water and brine, dried (magnesium sulfate), and concentrated *in vacuo*. Filtration chromatography through 350 g silica gel with 1% methanol/chloroform gave 10 g of a light brown solid, mp $107\text{--}109^\circ$. Recrystallization from cyclohexane gave 7.5 g (44%) of a tan solid, mp $108\text{--}110^\circ$; ir (chloroform): 3440 cm^{-1} (NH_2); nmr (deuteriochloroform): δ 3.74 (t, 2, N-CH_2), 4.60 (t, 2, O-CH_2), 6.17 (bs, 2, NH_2), 6.50-7.60 (m, 7, aromatic H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}$: C, 66.06; H, 4.80. Found: C, 66.26; H, 4.81.

5-(2'-Chloroacetamido-5'-chlorophenyl)-2,3-dihydro-1,4-benzoxazepine (**7**).

A solution of chloroacetic anhydride (37.0 g, 0.22 mole) in 300 ml of dichloromethane was added dropwise to a mixture of anhydrous potassium carbonate (60.2 g, 0.44 mole) and **6** (25.8 g, 0.10 mole) in one liter of dichloromethane with a cold water bath present. Stirring was continued at room temperature for 30 minutes and water was added to dissolve the inorganic material and hydrolyze the unreacted anhydride. The organic material was washed with water, dried (magnesium sulfate) and stirred with and decanted from 25 g silica gel. Concentration *in vacuo* gave a yellow solid that was recrystallized at room temperature from dichloromethane/hexane to give 19.2 g (58%) of pale yellow crystals that decomposed slowly above 130° without melting; ir (chloroform): 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.90 (t, 2, N-CH_2), 4.28 (s, 2, CH_2Cl), 4.75 (t, 2, O-CH_2), 7.10-7.90 (m, 6, aromatic H), 8.85 (d, 1, aromatic H *or*-

tho to NHC=O), 13.65 (bs, 1, NH); ms: M^+ m/e 348.

Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_2$: C, 58.45; H, 4.04. Found: C, 58.84; H, 3.94.

14-Chloro-6,7,9,11-tetrahydro[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepin-10-one Chloride (**8**).

A solution of **7** (8.6 g, 25 mmoles) in 500 ml of 1-propanol was refluxed for 1.5 hours. Concentration *in vacuo* gave an orange solid that was recrystallized twice from methanol/ether to yield 5.7 g (65%) of a yellow solid that decomposed above 232°; ir (potassium bromide): 1700 (C=O); 1660 cm^{-1} (C=N); nmr (methanol- d_4): δ 4.30-5.90 (m, 6, CH_2), 7.20-8.40 (m, 7, aromatic H); ms: [(M-HCl)H] $^+$ m/e 313.

Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_2$: C, 58.45; H, 4.04. Found: C, 57.79; H, 4.25 (13).

14-Chloro-6,7,11-15b-tetrahydro[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepin-10(9*H*)-one Hydrochloride (**9**-HCl).

A solution of **8** (5.4 g, 15 mmoles) in 300 ml of methanol with 0.27 g of 1% platinum on carbon was hydrogenated in a Parr apparatus at 15 psi until the uptake of hydrogen subsided after 2.5 hours. Filtration and concentration *in vacuo* gave 5.1 g of light yellow solid that was recrystallized from methanol/ether to give 1.7 g (31%) of white needles, mp 246-249° dec; ir (potassium bromide): 1690 cm^{-1} (C=O); nmr (DMSO- d_6): δ 3.10-4.00 (m, 6, CH_2), 6.03 (s, 1, CH), 6.90-7.20 (m, 7, aromatic H), 8.80 (bs, 1, NH), 10.80 (s, 1, NH); ms: (MH) $^+$ m/e 315.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2 \cdot HCl$: C, 58.13; H, 4.59; N, 7.98. Found: C, 58.43; H, 4.67; N, 7.93.

14-Chloro-6,7,11,15b-tetrahydro[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepin-10(9*H*)-one (**9**).

To a solution of **8** (8.8 g, 25 mmoles) in 200 ml of methanol at ice bath temperature was added powdered sodium borohydride (1.0 g, 26 mmoles) in small portions. Stirring was continued for 10 minutes and the resulting mixture was diluted with dichloromethane. The organic extract was washed with aqueous sodium carbonate and water, dried (sodium sulfate), and concentrated *in vacuo* to yield 7.0 g (88%) of a yellow solid that decomposed slowly above 88°. This compound was identical with the free base obtained from **9**-HCl by ir, nmr and tlc and could be used in subsequent steps without further purification.

14-Chloro-6,7,11,15b-tetrahydro-11-methyl[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepin-10(9*H*)-one Hydrochloride (**10**-HCl).

A solution of **9** (10.0 g, 32 mmoles) in 40 ml of anhydrous dimethylformamide was added to sodium hydride, prepared by washing 50% oil dispersion (1.8 g, 37 mmoles) with pentane, with ice bath cooling. After stirring for 20 minutes, a solution of dimethyl sulfate (3.2 ml, 34 mmoles) in 10 ml of dimethylformamide was added dropwise and stirred for 3 hours. The mixture was poured into 5% sodium carbonate and extracted with dichloromethane. The organics were washed with water, dried (magnesium sulfate) and concentrated *in vacuo* to give 9.5 g of an orange oily solid. A hydrochloride was obtained from **7** of this residue and recrystallized from ethanol to give 4.5 g (53%) of pale yellow crystals that decomposed with melting above 165°; ir (potassium bromide): 1670 cm^{-1} (C=O); nmr (trifluoroacetic acid): δ 3.50-5.00 (m, 9, CH_2 , CH_3), 6.25 (s, 1, CH), 7.20-8.00 (m, 7, aromatic H); ms: M^+ m/e 328.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_2 \cdot HCl$: C, 59.19; H, 4.97. Found: C, 59.40; H, 5.35.

14-Chloro-6,7,9,10,11,15b-hexahydro[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepine (**11**).

A mixture of **9** (6.0 g, 17 mmoles) in 100 ml of tetrahydrofuran was stirred mechanically under nitrogen while adding 1.0 M borane/THF (69.6 ml, 69.6 mmoles). This mixture was refluxed for 3 hours, quenched with 50 ml 6*N* hydrochloric acid and refluxed for one hour. The cooled mixture was made basic with 5% sodium hydroxide and extracted with dichloromethane. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was recrystallized from dichloromethane/hexane to give 2.1 g (40%) of a white solid, mp 212-214°; ir (potassium bromide): 3330 cm^{-1} (NH); nmr (DMSO- d_6): δ

3.00 (m, 6, N- CH_2), 4.00 (m, 2, O- CH_2), 5.25 (s, 1, CH), 5.68 (bs, 1, NH), 6.50-7.40 (m, 7, aromatic H); ms: (MH) $^+$ m/e 301.

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.87; H, 5.69; N, 9.32. Found: C, 67.82; H, 5.63; N, 9.56.

14-Chloro-6,7,9,10,11,15b-hexahydro-11-methyl[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepine (**12**).

To a solution of **10** (8.6 g, 26 mmoles) in 220 ml of tetrahydrofuran under nitrogen was added 1.02 M borane/THF (90 ml, 92 mmoles) and the resulting mixture was refluxed for 3 hours. After cooling, 80 ml of 6*N* hydrochloric acid was added carefully and stirred at room temperature overnight. Workup as for **11** gave 2.5 g (30%) of pale yellow crystals, mp 171.5-173°; nmr (deuteriochloroform): δ 2.70-3.30 (m, 9, N- CH_2 , N- CH_3), 4.10 (m, 2, O- CH_2), 5.45 (s, 1, CH), 6.80-7.30 (m, 7, aromatic H); ms: M^+ m/e 314.

Anal. Calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08. Found: C, 68.27; H, 5.99.

14-Chloro-6,7,11,15b-tetrahydro-11-methyl[1,4]benzodiazepino[4,5-*d*][1,4]benzoxazepin-10(9*H*)-one 8-Oxide (**13**).

A solution of 85% *meta*-chlorobenzoic acid (2.65 g, 13 mmoles) in 65 ml dichloromethane was added dropwise to a solution of **10** (4.3 g, 13 mmoles) in 90 ml dichloromethane at ice bath temperature. After one hour, the reaction solution was poured onto a column of 160 g alumina and eluted with dichloromethane followed by 3% methanol/dichloromethane to give a yellow solid. Recrystallization from methanol/ether gave 3.0 g (67%) of off-white crystals, mp 210-212°; ir (potassium bromide): 1675 cm^{-1} (C=O); nmr (DMSO- d_6): δ 3.35 (m, 2, N- CH_2), 3.50 (s, 3, N- CH_3), 3.70-4.10 (m, 4, O- CH_2 , N- CH_2 -C=O), 5.43 (s, 1, CH), 7.10-7.80 (m, 7, aromatic H); ms: (MH) $^+$ m/e 345.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; N, 8.13. Found: C, 62.56; H, 5.07; N, 8.07.

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REFERENCES AND NOTES

- (1) T. Kamioka, H. Takagi, S. Kobayashi and Y. Suzuki, *Arznieim.-Forsch.*, **22**, 884 (1972).
- (2) T. Kamioka, I. Nakayama and H. Takagi, *Jpn. J. Pharmacol.*, **23**, Suppl. 65, Abstract 99 (1973).
- (3) For an excellent review on anxiolytics see: S. Fielding and H. Lal, "Industrial Pharmacology", Vol 3, Futura Publishing Co, Inc, Mount Kisco, NY, 1979.
- (4) Benzoxazepines have also been generated from substituted benzophenones: H. A. Luts, *J. Pharm. Sci.*, **58**, 1460 (1969); R. T. Standridge, U. S. Patent 4,125,538 (1978); *Chem. Abstr.*, **90**, 72246r (1979).
- (5a) A. Waefelaer, German Offen. 2,100,654 (1971); *Chem. Abstr.*, **75**, 129856m (1971); (b) A. Waefelaer, J. Pecher, A. Dubois and P. Poulter, *Bull. Soc. Chim. Belg.*, **85**, 787 (1976).
- (6) T. Hirohashi, T. Izumi, H. Yamamoto, U. S. Patent 3,676,460 (1972); German Offen. 2,014,223 (1970); *Chem. Abstr.*, **73**, 190697m (1970).
- (7) A. Waefelaer, J. Pecher, A. Dubois and P. Poulter, *Bull. Soc. Chim. Belg.*, **85**, 898 (1976).
- (8) Interaction of the *ortho*-nitro substituent in the hydrogenation of *ortho*-nitrobenzonitrile has been documented: H. Moll, H. Musso, H. Schröder, *Angew. Chem., Int. Ed. Engl.*, **2**, 212 (1963).
- (9) E. F. Elslager, J. Davoll, P. Jacob, A. M. Johnson, J. Johnson and L. M. Werbel, *J. Med. Chem.*, **21**, 639 (1978).
- (10) H. H. Ong and E. L. May, *J. Org. Chem.*, **37**, 732 (1972).
- (11) J. C. Craig and K. K. Purushothaman, *ibid.*, **35**, 1721 (1970).
- (12) H. Mosher, *J. Am. Chem. Soc.*, **68**, 1565 (1946).
- (13) Satisfactory elemental analysis could not be obtained due to the unstable and hygroscopic nature of this compound.