Synthesis of 1,3,4,14b-Tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepines [1]

Avelina Ong-Lee, Leo Sylvester and Jan W. F. Wasley*

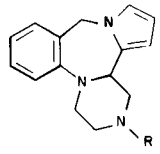
Research and Development Department, Pharmaceuticals Division,
CIBA-GEIGY Corporation, Summit, New Jersey 07901

Received April 1, 1983

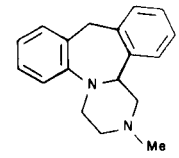
1,3,4,14b-Tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines (**1a-e**) were synthesized to investigate their potential CNS activity. The key step in the synthesis was the formation of the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**13**) by reduction and concomitant cyclization of the nitroketone (**11**). Biological evaluation of **1a-e** revealed interesting properties for **1b** (CGS 7525A) [2].

J. Heterocyclic Chem., **20**, 1565 (1983).

As part of a program to investigate novel tri- and tetracyclic ring systems containing a fused pyrrole moiety as potential psychotropic agents, we undertook the synthesis of a series of 1,3,4,14b-tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepines (**1**). Mianserin (**2**), a clinically effective antidepressant, has a lower incidence of anticholinergic side effects than the tricyclic antidepressant drugs such as amitryptyline [3]. Our goal was to prepare novel CNS agents with a therapeutic profile similar to mianserin.



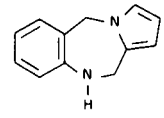
1



2

1a, R = H
1b, R = Me
1c, R = CO_2Et
1d, R = CO_2Me
1e, R = Me, N-oxide

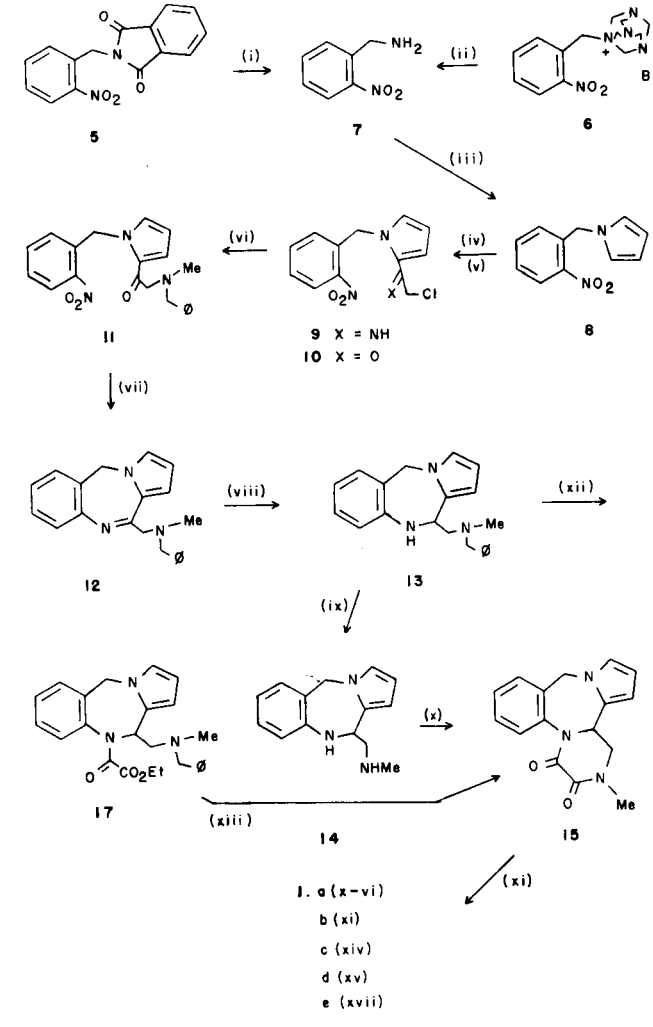
Although 1,3,4,14b-tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepine is a novel heterocycle, pyrrolo[2,1-*c*][1,4]benzodiazepine (**3**) has been reported [4,5] by workers evaluating **3** and related compounds as potential antitumor agents based on their structural similarity to anthramycin.



3

The title compounds were synthesized as indicated (Scheme 1). Reaction of *o*-nitrobenzyl chloride (**4**) with the potassium salt of phthalimide in DMF was followed by hydrazinolysis of **5** in ethanol to afford *o*-nitrobenzylamine (**7**) in an overall yield of 50%. A more economical procedure was the bromination of *o*-nitrotoluene either by bromine or by *N*-bromosuccinimide in carbon tetrachloride followed by treatment of the crude reaction mixture

SCHEME I



Scheme 1

(i) N_2H_4, EtOH, heat (ii) aq. HCl, EtOH (iii) 2,5-diMeO THF, HAc, heat (iv) $ClCH_2CN$, HCl (g), Et_2O (v) H_2O, heat (vi) $HN(Me)CH_2\varnothing$, EtOH, heat (vii) H_2, PtO_2, EtAc (viii) H_2, PtO_2, EtAc, HAc (ix) H_2, Pd-C, HAc, 3 atm., 40°C (x) $(CO_2Et)_2$, 180° (xi) B_2H_6, THF (xii) EtO_2C-COCl, Et_3N, Toluene (xiii) H_2, Pd-C, EtOH, HAc (xiv) Cl-CO_2Et (xv) Cl-CO_2Me (xvi) 20% KOH (xvii) *m*-CPBA, CH_2Cl_2.

with hexamethylene-tetramine (HMTA) to yield the quaternary bromide **6**. This crystalline intermediate represented a convenient form in which to store the incipient and unstable *o*-nitrobenzylamine (**7**), which was prepared from **6** by treatment with aqueous hydrochloric acid to yield the hydrochloride salt of **7** from which the free base could be readily liberated just prior to use. When **7** was condensed with 2,5-dimethoxy tetrahydrofuran by heating the reagents in refluxing glacial acetic acid, *i.e.*, normal pyrrole forming conditions [6], only small amounts of the desired 1-(*o*-nitrobenzyl)pyrrole (**8**) were obtained. A modification of this procedure was developed in which the 2,5-dimethoxy tetrahydrofuran and the acetic acid reagents were combined and preheated to 95° and a solution of the *o*-nitrobenzylamine (**7**), in a small volume of acetic acid was added rapidly to the reaction mixture. The reaction under these conditions was completed within 5 minutes and the isolated yields of **8** were 85-90%. A modification of the Houben-Hoesch reaction [7] was used to obtain **9** using **8** and chloroacetonitrile in ethereal solution and dry hydrogen chloride. Subsequently, it was found more advantageous to use tetrahydrofuran as the solvent [8]. The hydrochloride salt of the imine **9** was obtained in 90% yield but was contaminated with approximately 10% of the isomer in which attack had occurred at the β-position of the pyrrole ring. This finding is consistent with that previously observed in the preparation of pyrrole-2-carboxaldehydes by the Vilsmeier-Haack reaction [9]. However, this undesired side-product was readily removed by recrystallization of **9** from ethanol [8]. The imine hydrochloride **9** was converted to the corresponding chloromethyl-1-(*o*-nitrobenzyl)-2-pyrryl ketone (**10**) by suspending the salt in water and heating the suspension for 1 hour at 80°. The α-chloroketone **10** readily reacted with *N*-methylbenzylamine in refluxing ethanol to produce [(benzyl)(methyl)amino]methyl 1-(*o*-nitrobenzyl)-2-pyrryl ketone (**11**) in 80% yield. Hydrogenation of the nitro ketone **11** proved to be quite specific as to the requirements of catalyst and solvent. The optimal conditions for this hydrogenation were the use of platinum oxide as catalyst and ethyl acetate as solvent, and the hydrogenation was carried out at atmospheric pressure and room temperature. The nitro ketone **11** was subjected to the above conditions until 3 equivalents of hydrogen had been absorbed. The amino ketone cyclized spontaneously to the imine **12** which was not isolated. At this point, a small amount of acetic acid was added to the hydrogenation mixture and continued hydrogenation at room temperature and atmospheric pressure resulted in the absorption of an additional equivalent of hydrogen and the formation of 11-{[(benzyl)(methyl)amino]methyl}-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**13**) in 75% yield. The tricycle **13** was resubjected to hydrogenation conditions using palladium-on-carbon (5%) as catalyst and glacial acetic acid as solvent. The reaction was conducted in a Parr apparatus (40°, 3 atmospheres). These conditions resulted in the smooth debenzylation of **13** to yield 11-(methylaminomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**14**). A Riebsomer reaction [10] of the diamine **14** with diethyl oxalate at 180° provided 1,14b-dihydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepin-3,4-dione (**15**) in 80% yield.

An improved procedure was later developed in which the tricycle **13** was acylated with ethyl oxalyl chloride in toluene at 20° using triethylamine as the base to yield the amide **17** in 90% yield. When the amide **17** was subjected to the debenzylation conditions of hydrogenation in ethanol using 5% palladium-on-carbon as catalyst (40° and 3 atmospheres) **17** smoothly cyclized to give the piperazine dione **15** in 60% yield.

A variety of reducing agents were used in attempts to reduce the piperazine dione **15** to the amine **1b**. It was found that this reduction was most readily accomplished by either alane or borane in tetrahydrofuran, producing 1,3,4,14b-tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo-[2,1-*c*][1,4]benzodiazepine (**1b**) in 63% yield. Compound **1b** was characterized as its monomaleate salt (CGS 7525A). Conversion of **1b** to 1,3,4,14b-tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1a**) was accomplished by treatment of **1b** with ethyl or methyl chloroformate in toluene to yield the carbamates **1c** and **1d** respectively, followed by hydrolysis with 20% aqueous potassium hydroxide to give **1a** in 63% yield. Treatment of **1b** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride afforded 1,3,4,14b-tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine 2-oxide (**1e**) in 89% yield following chromatography on neutral alumina; the *N*-oxide **1e** was characterized as its monomaleate salt.

Biological evaluation in a variety of receptor binding assays, behavioral and electrophysiological tests showed **1b** (CGS 7525A, maleate salt) to possess selective alpha-2 adrenoreceptor antagonist properties and preliminary results have been reported [2]. A discussion of the detailed structure activity relationships for the series will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The ^{1}H nmr spectra were obtained on a Hitachi Perkin Elmer R-600 or Bruker 360 spectrometers in the solvent indicated. Chemical shifts are reported in ppm from TMS as an internal reference and are given in δ units. Mass spectra were recorded on a AEI MS 902 mass spectrometer. The ir spectra were recorded on a Perkin Elmer 137 spectrometer. Elemental analyses were performed by the Analytical Services Group, CIBA-GEIGY Pharmaceuticals Division, Summit, NJ.

o-Nitrobenzylphthalimide (**5**).

A mixture of *N*-potassium phthalimide (54 g, 0.29 mole), *o*-nitrobenzyl chloride (50 g, 0.29 mole) and *N,N*-dimethylformamide (120 ml) was heated at reflux temperature for 3 hours. The reaction mixture was allowed to cool to room temperature and poured into ice-water (900 ml) with stirring. After 30 minutes the crude product **5** was collected by filtration as an off-white solid, (70 g, 85% yield), mp 190-209° lit [11] 217-218°; nmr (DMSO-d_6): 7.5-8.2 (m, 8H, aromatic), 5.2 (s, 2H, methylenes); ir (Nujol): 1770, 1705, 1530 cm^{-1}.

o-Nitrobenzylamine (**7**).

A mixture of *o*-nitrobenzylphthalimide (**5**) (70 g, 0.248 mole), hydrazine hydrate (14.6 g, 0.248 mole) and ethanol (600 ml) was heated at reflux temperature for 4 hours. To the reaction mixture was added concentrated hydrochloric acid (50 ml). After 30 minutes, the reaction mixture was cooled to room temperature and *o*-nitrobenzylamine (**7**) was collected as its hydrochloride salt which was isolated as colorless needles (27 g, 58%) mp 236-240° lit [11] 248°; nmr (DMSO-d_6): 7.7-9 (m, 7H, 4 aromatic, 3 exchangeables), 4.4 (s, 2H, methylenes); ir (Nujol): 2600-2800 cm^{-1}, broad salt bands.

Anal. Calcd. for $C_7H_8N_2O_2 \cdot HCl$: C, 43.68; H, 4.71; N, 14.55. Found: C, 44.06; H, 4.78; N, 14.69.

(1:1)-Quaternary Ammonium Salt from Hexamethylene Tetramine and *o*-Nitrobenzyl Bromide (**6**).

o-Nitrotoluene (69 g, 0.5 mole) was dissolved in carbon tetrachloride (500 ml) and irradiated wtih an ultraviolet enriched 300 W floodlamp placed about 2 cm from the wall of the reaction flask. The solution was stirred mechanically and heated at reflux temperature. To the refluxing solution bromine (40 g, 0.25 mole) in carbon tetrachloride (50 ml) was added dropwise over 4 hours. On completion of the addition, the reaction mixture was maintained at reflux temperature until evolution of hydrogen bromide ceased. The reaction mixture was then cooled to room temperature and shaken with 10% aqueous sodium sulfite solution (250 ml), followed by brine (250 ml). The solution was then dried (sodium sulfate) and assayed by gc using a temperature profile of 180°/3'/25°-minute/-300° and a 12% UC-W 98 (Chromosorb W-80/100) stationary phase. The gc analysis indicated that the reaction mixture contained 4% of *o*-nitrotoluene, 52% of the desired *o*-nitrobenzyl bromide and 41% of *o*-nitro-α,α-dibromomethylbenzene. After concentration of the reaction mixture to approximately 300 ml hexamethylene tetramine (32.2 g, 0.23 mole) was added and the reaction stirred overnight at room temperature. The quaternary bromide **6** crystallized and was collected by filtration (77 g, 83%). An analytical sample was obtained by recrystallization from ethanol, mp 140-150° dec; nmr (DMSO-d_6): 7.6-8.2 (m, 4H, aromatic), 5.1 (s, 6H, methines), 4.4 (s, 18H, methylenes).

Anal. Calcd. for $C_{13}H_{18}BrN_5O_2$: C, 43.83; H, 5.09; N, 19.66. Found: C, 53.70; H, 4.88; N, 20.04.

o-Nitrobenzylamine (**7**).

The hexamethylene tetramine salt **6** (144 g, 0.4 mole) was suspended in ethanol (350 ml) at room temperature and stirred mechanically. To this heavy suspension was added 12*N* hydrochloric acid (168 ml, 2.02 mole) over a period of 2 minutes. The reaction mixture rapidly changed from a yellow suspension to an amber solution and a 5° exotherm was noted. After approximately 10 minutes a precipitate began to form and a very heavy suspension developed which was allowed to stir overnight at room temperature. The suspension was cooled (5°) in ice-water bath and the solids were collected by filtration and dried *in vacuo* at 60° overnight. The crude *o*-nitrobenzylamine hydrochloride (130 g, 100%) was contaminated with some ammonium chloride and had mp 243° lit [11] 248°. The free base was generated in the usual manner and obtained as a yellow orange oil (43 g, 70%) and was used in the next step without further purification or characterization.

1-(*o*-Nitrobenzyl)pyrrole (**8**).

A stirred solution of 2,5-dimethoxytetrahydrofuran (7.55 g, 0.057 mole) in glacial acetic acid (25 ml) was heated to 95°. To this solution *o*-nitrobenzylamine (**7**) (8.0 g, 0.05 mole) was added rapidly over a period of 2 minutes. The reaction mixture rapidly changed from colorless to orange, and after heating at reflux temperature for 5 minutes, it had become black. The solvent was then evaporated under reduced pressure and the residue distilled under vacuum to yield the pyrrole **8** as a pale yellow oil (9.1 g, 86%) bp 108-112° at 0.05 mm. After standing (prolonged) at room temperature, the product crystallized as yellow crystals, mp 38-40°; nmr (deuteriochloroform): 7.2-8.1 (m, 4H, aromatic), 6.6-6.8 (t, 2H, pyrrole), 6.1-6.3 (t, 2H, pyrrole), 5.5 (s, 2H, methylene); ir (chloroform): 1530, 1350 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.22; H, 5.08; N, 13.84.

Chloromethyl 1-(*o*-Nitrobenzyl)-2-pyrryl Ketone (**10**).

Through a solution of 1-(*o*-nitrobenzyl)pyrrole (**8**) (34 g, 0.17 mole) and chloroacetonitrile (12.9 g, 0.17 mole) in diethyl ether (100 ml) dry hydrogen chloride gas was bubbled for 3 hours. During this time the reaction mixture was stirred mechanically and maintained at a temperature of approximately 10° by means of an ice-bath. The hydrogen chloride saturated reaction mixture was stirred overnight at room temperature and the precipitated chloromethyl 1-(*o*-nitrobenzyl)-2-pyrryl ketimine hydrochloride (**9**) (34 g, 64%) was collected by filtration as a yellow solid, mp 210-212°. A suspension of the imine **9** (34 g, 0.11 mole) in water (350 ml) was stirred for 1 hour at 80°. The reaction was allowed to cool to room temperature and the ketone **10** (25 g, 83%) was collected an off-white solid, mp 106-110°. An analytical sample was obtained by recrystallization from ethanol, mp 112-114°; nmr (deuteriochloroform): 7.1-8.2 (m, 5H, pyrrole, 4 aromatic), 6.3-6.6 (m, 2H, pyrrole), 5.8 (s, 2H, benzylic methylene), 4.5 (s, 2H, α-halomethylene); ir (chloroform): 1657, 1530, 1348, 1092, 1060, 979 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3$: C, 56.01; H, 3.95; N, 10.05. Found: C, 56.34; H, 4.08; N, 10.22.

{[(Benzyl)(methyl)amino]methyl}-1-(*o*-nitrobenzyl)-2-pyrryl Ketone (**11**).

To a suspension of chloromethyl 1-(*o*-nitrobenzyl)-2-pyrryl ketone (**10**) (51 g, 0.18 mole) in toluene (250 ml) was added *N*-methylbenzylamine (24.4 g, 0.2 mole) and triethylamine (20 g, 0.2 mole). The reaction mixture was heated with stirring at 95° for 6 hours and then allowed to stir overnight at room temperature and diluted with water (250 ml). The organic phase was washed with brine, dried (magnesium sulfate) and the solvent evaporated under reduced pressure. The residue was crystallized from ethanol (200 ml) to give **11** (58 g, 87%). An analytical sample was obtained by recrystallization from ethanol, mp 103-105°; nmr (deuteriochloroform): 8.05-8.27 (m, 1H, aromatic), 86.92-7.5 (m, 9H, 8 aromatic, 1 pyrrole), 6.2-6.59 (m, 2H, pyrrole), 5.96 (s, 2H, benzylic methylene), 3.55 (s, 4H, methylenes), 2.25 (s, 3H, methyl); ir (chloroform): 1637, 1513 cm^{-1}.

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.45; H, 6.08; N, 11.30.

11-{[(Benzyl)(methyl)amino]methyl}-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine (**13**).

A solution of {[(benzyl)(methyl)amino]methyl}-1-(*o*-nitrobenzyl)-2-pyrryl ketone (**11**) (50 g, 0.14 mole) in ethyl acetate (1 *l*) was hydrogenated at room temperature and atmospheric pressure using platinum oxide (5 g) as catalyst. Uptake of hydrogen ceased after 3.5 hours (formation of imine **12**). Acetic acid (50 ml) was then added to the reaction mixture and the hydrogenation continued for an additional 1.5 hours, by which time the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent evaporated under reduced pressure to yield a brown semi-solid. This residue was extracted with ethyl acetate (2 × 500 ml) and the combined extracts were washed with (i) saturated sodium bicarbonate solution (2 × 500 ml) and (ii) water (2 × 500 ml). The ethyl acetate extracts were then dried (sodium sulfate) and the sol-

vent evaporated under reduced pressure to yield the tricycle **13** as a tan solid (31.3 g, 72%) after trituration with diethyl ether (100 ml). An analytical sample was obtained by recrystallation from ethanol, mp 151-152°; nmr (deuteriochloroform): 6.42-7.5 (m, 10H, aromatic, 1 pyrrole), 5.82-6.13 (m, 2H, pyrrole), 5.57 (d, J = 16, 1H, methylene bridge), 4.83-5.25 (m, 2H, methine + 1 exchangeable), 4.64 (d, J = 16, 1H, methylene bridge), 3.78 (d, J = 13, 1H, benzylic methylene), 3.44 (d, J = 13, 1H, benzylic methylene), 2.95 (m, 2H, methylene), 2.3 (s, 3H, methyl); ir (Nujol): 3314 (NH), 1594, 748 (1,2 disubs$_9$phenyl) 740, 692 cm^{-1} (mono subs phenyl); ms: m/e 317 (M^+), 183 (M-134), 134 (M-183).

Anal. Calcd. for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.23; H, 7.14; N, 13.24.

11-(Methylaminomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**14**).

A mixture of **13** (500 mg, 0.0015 mole) ethanol (35 ml) and acetic acid (5 ml) was hydrogenated over 5% palladium-on-carbon (250 mg) for 7 hours (40°, 3 atmospheres). The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (100 ml). The methylene chloride extract was dried (magnesium sulfate) and the solvent evaporated under reduced pressure to yield **14** (400 mg, 92%). This material was characterized as the acetate salt of **14**, mp 130-133°; nmr (deuteriochloroform): 6.5-7.6 (m, 8H, aromatic, 1 pyrrole, 4 aromatic, 3 exchangeables), 5.83-6.08 (m, 2H, pyrrole), 5.33 (d, J = 15.5, 1H, benzylic methylene), 4.99 (t, J = 7, 1H, methine), 4.77 (d, J = 1.5, 1H, benzylic methylene), 3.18 (d, J = 7, 2H, methylene), 2.55 (s, 3H, methyl), 1.98 (s, 3H, methyl of acetate); ir (chloroform): 3314 (NH) 2700-2100 (salt) 1755, 1706 (COOH) cm^{-1}; ms: m/e 227 (M^+), 183 (M-44).

Anal. Calcd. for $C_{14}H_{17}N_3 \cdot CH_3CO_2H$: C, 66.87; H, 7.37; N, 14.64. Found: C, 66.89; H, 7.03; N, 14.63.

Ethyl 11-{[(Benzyl)(methyl)amino]methyl}-10,11-dihydro-α-oxo-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10-acetate (**16**).

To a mixture of 11-{[(benzyl)(methyl)amino]methyl}-10,11-dihydro-2*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**13**) (10 g, 0.032 mole) and triethylamine (3.2 g, 0.032 mole) in tetrahydrofuran (500 ml) was added a solution of ethyl oxalyl chloride (4.3 g, 0.032 mole) in tetrahydrofuran (50 ml). The addition was carried out dropwise over a 15 minute period and the temperature of the reaction mixture was maintained below 25°. The reaction was stirred overnight at ambient temperature. The solvent was evaporated to small volume under reduced pressure and the residue was extracted with methylene chloride (2 × 150 ml). The combined methylene chloride extracts were washed with brine (2 × 150 ml), dried (magnesium sulfate) and the solvent evaporated under reduced pressure to yield a dark oil which crystallized upon standing. Recrystallization of this material from isopropanol yielded the amide **17** (11.5 g, 90%) mp 100-102°; nmr (magnesium sulfate): 7.0-7.5 (m, 9H, aromatic), 6.22-6.7 (m, 2H, pyrrole), 5.9-6.17 (m, 2H, 1 pyrrole, 1 methine), 5.48 (d, J = 14.5, 1H, benzylic methylene), 4.67 (d, J = 14.5, 1H, benzylic methylene), 4.01 (q, J = 7, 2H, methylene of ethyl), 3.81 (d, J = 13, 1H, benzylic methylene), 4.01 (q, J = 7, 2H, methylene of ethyl), 3.81 (d, J = 13, 1H, benzylic methylene), 3.27 (d, J = 13, 1H, benzylic methylene), 2.4 (m, 2H, methylene), 2.19 (s, 3H, methyl), 1.0 (t, 3H, J = 7, methyl of ethyl); ir (Nujol): 1739 (CO_2Et), 1667 (amide cm^{-1}; ms: m/e 417 (M^+), 344 (M-73), 283 (M-134), 182 (M-235), 134 (M-283).

Anal. Calcd. for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 72.31; H, 6.48; N, 10.07.

1,14b-Dihydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-3,4-dione (**15**).

Method a.

A mixture of 11-(methylaminomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin (**14**) (10.3 g, 0.04 mole) and diethyl oxalate (7.95 g, 0.05 mole) was slowly heated to 140° during 45 minutes an to 180° during 15 minutes, at which temperature it was maintained for 30 minutes. On cooling to room temperature, the reaction mixture was diluted with benzene (25 ml) and chromatographed on silica gel using methanol-chloroform (1:2) as eluent. Evaporation of the solvent under reduced pressure yielded the dilactam **15** (2.5 g, 25%). An analytical sample was obtained by recrystallization from ethanol, mp 178-179°; nmr (deuteriochloroform): 7.16-7.5 (m, 4H, aromatic), 6.62 (t, J = 2.5, 1H, pyrrole), 5.9-6.1 (m, 2H, pyrrole), 5.2 (d, J = 14.5, 1H, bridge methylene), 5.13 (t, J = 5.5, 1H, methine), 4.63 (d, J = 14.5, 1H, bridge methylene), 3.75-4.0 (m, 2H, methylene), 3.07 (s, 3H, methyl); ir (Nujol) 1685, 1672 (amide CO) cm^{-1}; ms: m/e 281 (M^+), 253 (M-28), 182 (M-99).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.05; H, 5.45; N, 14.68.

Method b.

A mixture of ethyl-11-{[(benzyl)(methyl)amino]methyl}-10,11-dihydro-α-oxo-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10-acetate (**17**) (18 g, 0.045 mole), ethanol (300 ml) and acetic acid (75 ml) was hydrogenated in a Parr apparatus (40°, 3 atmospheres) for 1.5 hours using 5% palladium-on-carbon as catalyst. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue was extracted with ethyl acetate (2 × 150 ml), washed with (i) saturated sodium bicarbonate solution (2 × 150 ml) and (ii) water (2 × 150 ml), dried (sodium sulfate) and the solvent evaporated under reduced pressure to yield the dilactam **15** as a viscous oil (11.6 g, 96%) which crystallized upon standing. An analytical sample was obtained by recrystallization from ethanol, mp 178-179° identical in all respects to the sample described in method a (*vide supra*).

1,3,4,14b-Tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*][1,4]benzodiazepine (**1b**).

To the suspension of 1,14b-dihydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepin-3,4-dione (**15**) (14.1 g, 0.05 mole) in tetrahydrofuran (460 ml) 1-molar diborane solution in tetrahydrofuran (200 ml = 0.01 mole) was added while stirring and cooling in ice. The mixture was heated at reflux temperature for 1 hour, cooled to room temperature and removed by evaporation under reduced pressure and the residue was dissolved in methylene chloride (150 ml). The methylene chloride solution was washed with dilute aqueous sodium carbonate solution (100 ml), dried (magnesium sulfate) and evaporated to dryness under reduced pressure. The residue was dissolved in diethyl ether (200 ml), treated with charcoal, filtered and the solvent evaporated under reduced pressure to give the amine **1b** as an amber oil. This material was dissolved in methanol (100 ml) and the solution was added to a solution of maleic acid (3.76 g, 1 equivalent) in methanol (100 ml). The mixture was again treated with charcoal and the solvent reduced in volume under reduced pressure to 50 ml. Diethyl ether was then added dropwise until turbid and the monomaleate salt of **1b** crystallized on standing (8 g, 63%). An analytical sample was obtained by recrystallization from methanol-diethyl ether, mp 180-183°; nmr (deuteriochloroform + DMSO-d_6): 6.92-7.4 (m, 4H, aromatic), 6.7 (t, J = 2, 1H, pyrrole), 6.25 (s, 2H, olefinic protons) (maleic acid), 5.93 (d, J = 2, 2H, pyrrole), 5.46 (d, J = 13.5, 1H, bridge methylene), 4.42-4.8 (m, 1H, methine), 4.6 (d, J = 13.5, 1H, bridge methylene), 3.0-3.8 (m, 6H, methylenes), 2.887 (s, 3H, methyl); ir (Nujol): 2700-2100 (salt), 1705 (COOH) cm^{-1}; ms: m/e 253 (M^+), 238 (M-15), 209 (M-44), 182 (M-71).

Anal. Calcd. for $C_{16}H_{19}N_3 \cdot C_4H_4O_4$: C, 65.02; H, 6.28; N, 11.38. Found: C, 64.95; H, 6.26; N, 11.18.

1,3,4,14b-Tetrahydro-2-carbethoxy-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1c**).

To a solution of 1,3,4,14b-tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1b**) (1.9 g, 0.0075 mole) in benzene (50 ml) was added ethyl chloroformate (2.14 g, 0.02 mole). The reaction mixture was heated at reflux temperature for 3 days, diluted with diethyl ether (200 ml) and washed with 1*N* hydrochloric acid (100 ml) and with both aqueous sodium chloride solution (100 ml) and saturated sodium bicarbonate solution (100 ml). The organic phase was separated, dried (magnesium sulfate) and the solvent removed by evaporation under reduced

pressure to give the carbamate **1c** (1.2 g, 50%) as an amber glass. An analytical sample was obtained by crystallization from ethanol, mp 82-83°; nmr (deuteriochloroform): 6.8-7.45 (m, 4H, aromatic), 6.6 (t, J = 2, 1H, pyrrole), 6.0 (d, J = 2, 2H, pyrrole), 5.47 (d, J = 13, 1H, bridge methylene), 4.54 (d, J = 13, 1H, bridge methylene), 3.81-4.36 (m, 5H, methylene, 1 methine), 2.7-3.5 (m, 4H, methylene), 1.3 (t, J = 7, 3H, methine of ethyl); ir (Nujol): 1710 (CO) cm^{-1}; ms: m/e 311 (M^+), 238 (M-73), 209 (M-102), 182 (M-129).

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.57; H, 6.45; N, 13.30.

By an analogous procedure 1,3,4,14b-tetrahydro-2-carbomethoxy-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1d**) was prepared. An analytical sample was obtained by crystallization from methanol, mp 128-131°; nmr (deuteriochloroform): 6.8-7.45 (m, 4H, aromatic), 6.61 (t, J = 2, 1H, pyrrole), 6.0 (d, J = 2, 2H, pyrrole), 5.48 (d, J = 13, 1H, bridge methylene), 4.56 (d, J = 13, 1H, bridge methylene), 3.95-4.35 (m, 3H, methylene + methine), 3.78 (s, 3H, methyl), 2.95-3.5 (m, 4H, methylene); ir (Nujol): 1710 (CO) cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.14. Found: C, 68.34; H, 6.59; N, 13.82.

1,3,4,14b-Tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1a**).

A mixture of 1,3,4,14b-tetrahydro-2-carbethoxy-10*H*-pyrazino[1,2-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepine (930 mg, 0.003 mole), ethanol (40 ml) and 20% aqueous potassium hydroxide (20 ml) was heated at reflux temperature for 32 days. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (150 ml) and washed with water (2 × 150 ml). The organic phase was dried (magnesium sulfate) and the solvent evaporated under reduced pressure. The residue was dissolved in diethyl ether (100 ml) and a solution of maleic acid (0.55 g, 0.005 mole) in isopropanol (10 ml) was added. The maleate salt of **1a** was collected (270 mg, 25%) and recrystallized from ethanol, mp 174-175°; nmr (DMSO-d_6): 6.66-7.41 (m, 5H, aromatic, pyrrole), 6.1 (s, 2H, maleic olefinic protons), 5.9 (d, J = 2, 2H, pyrrole), 5.39 (d, J = 13, 1H, bridge methylene), 4.82 (d, J = 13, 1H, bridge methylene), 4.25-4.64 (m, 1H, methine), 3.0-3.7 (m, 6H, methylenes); ir (Nujol): 2700-2100 (salt) 1714 (CO_2H), 1575 (CO_2^-) cm^{-1}; ms: m/e 239 (M^+), 209 (M-30, 182 (M-57).

Anal. Calcd. for $C_{15}H_{17}N_3 \cdot C_4H_4O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.33; H, 5.73; N, 11.91.

1,3,4,14b-Tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]-benzodiazepine 2-Oxide (**1e**).

To a stirred solution of 1,3,4,14b-tetrahydro-2-methyl-10*H*-pyrazino-[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1b**) (11.7 g, 0.046 mmole) in methylene chloride (100 ml) was added a solution of 85% *m*-chloroperbenzoic acid (9.4 g, 0.046 mole) in methylene chloride (120 ml). The reaction was stirred at room temperature for 5 hours, then the mixture was passed through an alumina column (basic, 300 g) and eluted initially with methylene chloride, followed by methylene chloride-methanol (9:1). Removal of the solvent under pressure gave the *N*-oxide **1e** (11.1 g, 89%) mp 199-201°; **1e** was characterized as its monomaleate salt. An analytical sample was obtained by recrystallization from 2-propanol, mp 177-178°; nmr (DMSO-d_6): 6.96-7.5 (m, 4H, aromatic), 6.88 (t, J = 2, 1H, 1H, pyrrole), 6.15 (s, 2H, olefinic protons of maleate), 5.95 (d, J = 2, 2H, pyrrole), 5.42 (d, J = 13, 1H, bridge methylene), 4.84-5.0 (m, 1H, methine), 4.84 (d, J = 13, 1H, bridge methylene), 3.56 (s, 3H, methyl), 3.3-4.3 (6H, methylenes); ir (Nujol): 2700-2100 (salt bands), 1704 (COOH), 1884 (COO^-) cm^{-1}; ms: m/e 269 (M^+), 252 (M-17), 209 (M-60), 182 (M-87).

Anal. Calcd. for $C_{16}H_{19}N_3O \cdot C_4H_4O_4$: C, 62.32; H, 6.02; N, 10.90. Found: C, 62.40; H, 6.16; N, 10.88.

Acknowledgement.

We thank Dr. H. W. Gschwend for his encouragement and support of this work. We thank the Staff of the CIBA-GEIGY Analytical Services Group, Summit, particularly Ms. R. H. Behnke for the nmr spectra, Ms. N. Cahoon and Mr. M. Hatolski for ir spectra and Ms. B. Warren for mass spectra and Mr. G. Robertson and Mr. R. Oeckinghaus for microanalytical data. We are also thankful to Dr. S. Boyer for valuable discussions and support. We are grateful to Mrs. D. Alves and Ms. D. Drew for preparing the typescript.

REFERENCES AND NOTES

[1] These compounds are the subject of U. S. Patent 4,316,900 (1982); *Chem. Abstr.*, **92**, 6566k (1980).

[2] J. M. Liebman, R. A. Lovell, A. Braunwalder, G. Stone, P. Bernard, B. Barbaz, J. Welch, H. Kim, J. W. F. Wasley and R. D. Robson, *Life Sci.*, **32**, 355 (1983).

[3a] R. N. Brogden, R. C. Neal, T. M. Speight and G. S. Avery, *Drugs*, **16**, 273 (1978); [b] A. P. Zis and F. K. Goodwin, *Arch. Gen. Psychiatry*, **36**, 1097 (1979); [c] G. B. Cassano, L. Conti, L. Dell'Osso, G. Massimetti, "Advances in Biochemical Psychopharmacology", Vol **32**, E. Costa and G. Racagni, eds, Raven Press, New York, NY (1982) pp 125-239; [d] R. J. Branconnier, J. O. Cole, S. Ghazvinian and S. Rosenthal, *ibid.*, pp 195-212.

[4] G. DeMartino, S. Massa and G. Valitutti, *Il Farmaco, Ed. Sci.*, **29**, 579 (1974).

[5a] M. Scalzo, S. Massa, G. DeMartino, R. Giuliano and M. Artico, *ibid.*, **29**, 459 (1974); [b] G. DeMartino, R. Giuliano, S. Massa, G. C. Poretta, M. Artico, E. Dolfini and L. Morasca, *ibid.*, **27**, 972 (1972).

[6a] A. D. Josey and E. L. Jenner, *J. Org. Chem*, **27**, 2466 (1962). [b] A. D. Josey, *Org. Synth.*, **47**, 81 (1967); [c] N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952); [d] N. Elming and N. Clauson-Kaas, *ibid.*, **6**, 817 (1952).

[7a] L. N. Ferguson, *Chem. Rev.*, **38**, 227 (1946); [b] C. G. Raisen, *J. Chem. Soc.*, 3319 (1949).

[8] E. A. Roskin, deceased, unpublished observation.

[9a] R. M. Silverstein, E. E. Ryskiewicz, C. Willard and B. C. Koehler, *J. Org. Chem.*, **20**, 668 (1955); [b] W. C. Anthony, *ibid.*, **25**, 2049 (1960).

[10] J. L. Riebsomer, *ibid.*, **15**, 68 (1950).

[11] H. Fischer, *Ber.*, **55**, 2390 (1922).

[12] H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).