SYNTHESIS OF 3,6-DISUBSTITUTED β-CARBOLINES WHICH POSSESS EITHER BENZODIAZEPINE ANTAGONIST OR AGONIST ACTIVITY

Timothy J. Hagen, Filadelfo Guzman, Christopher Schultz, and
James M. Cook*
Department of Chemistry
University of Wisconsin-Milwaukee
Milwaukee, Wisconsin 53201, U.S.A.

Phil Skolnick
NIAMDD
Bethesda, Maryland 20892, U.S.A.

Harlan E. Shannon
NIDA Addiction Center
Post Office Box 5180
Baltimore, Maryland 21224, U.S.A.

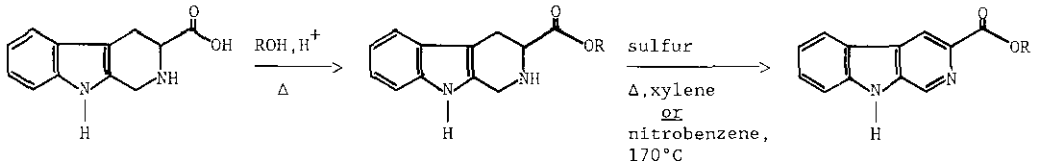
Abstract — A series of 3-substituted and 3,6-disubstituted β-carbolines have been synthesized. These compounds have been screened *in vitro* in order to determine the size of substituents which benzodiazepine receptors will tolerate at positions -3 and -6 of the β-carboline nucleus. It has been found that the receptor will tolerate ester alkyl groups at position-3 as large as cyclohexyl **1g** but not as large as adamantyl **5d**. Moreover, N-aryl substituents as large as naphthobenzylamino **8b** can be introduced at position-6 without significant loss of receptor binding affinity.

Numerous β-carboline-3-carboxylates have been shown to be antagonists of the benzodiazepines. For example, the ethyl ester (BCCE) antagonized the anticonvulsant effects of diazepam,[1,2] the anticonflict activity of lorazepam and diazepam,[3,4] and the ataxic effects of diazepam as demonstrated in the horizontal wire test.[2,5] Similar benzodiazepine antagonist properties have been demonstrated for the propyl ester (PCC) and the methyl carboxamide, FG-7142.[3,4,6,7] BCCE also blocks the effects of benzodiazepines, measured electrophysiologically,[5] as well as blocking the decrease in levels of cerebral cyclic GMP caused by benzodiazepines.[8] The t-butyl

ester (BCCt), in fact, has been shown to reverse midazolam-ethanol induced CNS depression suggesting these effects may be mediated through the benzodiazepine receptor.[9] However, β-carbolines such as BCCE and the methyl ester, BCCM, are not simply antagonists of the benzodiazepines. Rather, they appear to be inverse agonists[10] since they produce effects which are opposite to those of the benzodiazepines. In this regard BCCE has been shown to potentiate the convulsant effects of pentylenetetrazole in rodents[1,2] and baboons[11], as well as demonstrating convulsant activity in all species tested thus far.[6,7,12] The propyl ester, however, appears to be the exception in that it is not a proconvulsant in baboons.[7] The ester derivatives of β-carboline-3-carboxylic acid such as 1b and 1c have limited use in vivo because they are readily hydrolyzed by esterase enzymes and, therefore, possess very short half-lives (5-10 min) in plasma in most animal species.[13,14]

Because of the lability of these ester functions, it was decided to prepare a series of 3-substituted β-carbolines which would not be readily degraded in vivo. The esters of β-carboline-3-carboxylic acid 1a were prepared either by Fischer esterification or via the reaction of the corresponding acid chloride with the lithium alkoxide of the appropriate alcohol. Esters 1b-d and 1f-1h (see Scheme I and Table 1) were prepared by heating 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid 2 with the corresponding alcohol in the presence of anhydrous hydrogen chloride to provide the tetrahydro esters represented by 3. This process

Scheme I



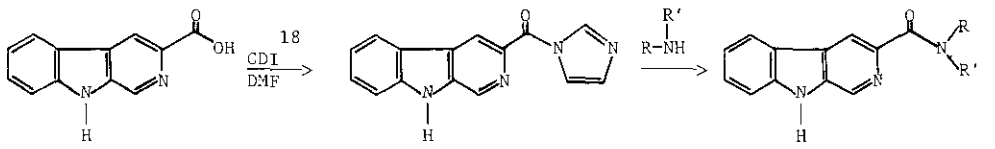
2 3

1a, R=H
1b, R=CH_3
1c, R=CH_2CH_3
1d, R=$CH_2CH_2CH_3$
1e, R=$C(CH_3)_3$
1f, R=C_5H_9
1g, R=C_6H_{11}
1h, R=$CH_2C(CH_3)_3$

was followed by oxidation to generate the fully aromatic β-carbolines 1. The dehydrogenation was carried out by heating 2 in the presence of sulfur either in refluxing mixed xylenes or in nitrobenzene at 170°C.[15] The t-butyl ester 1e could not be synthesized in this manner, but could be obtained via the reaction of the acid chloride of 1a with lithium t-butoxide. The 3-hydroxymethyl-β-carboline 4 (3 HMC) was prepared by reduction of BCCE 1b with lithium borohydride (see reference 17 for details).

The amide analogs of β-carboline-3-carboxylic acid 1a were synthesized either from BCCM 1b or from the parent acid 1a. The parent amide (see Table 1) was synthesized by bubbling anhydrous ammonia for 2 days through a solution of 1b dissolved in methanol. The solvent was removed and the crude material was purified by column chromatography. The 3-hydroxyethylamide derivative 5c was prepared by heating BCCM (1b) in ethanolamine for 2.5 h at 160°C. The bulky adamantylamide 5d and the corresponding N-methyl, N-butylamide 5e were synthesized by treating 1a with 1,1-carbonyldiimidazole (CDI) in dry DMF to form the imidazole derivative 6,

Scheme II



1a

6

5a, R=R'=H
5b, R=H, R'=CH_2CH_3
5c, R=H, R'=CH_2CH_2OH
5d, R=H, R'= 
5e, R=CH_3, R'=$CH_2CH_2CH_2CH_3$

as illustrated in Scheme II. This synthetic intermediate 6 could be isolated by dilution of the reaction mixture with water followed by filtration of the solid which results. Treatment of 6 with the corresponding amines provided the amides 5d and 5e, according to the procedure of Lippke[18], in very good yield.

Examination of the data in Table 1 clearly illustrates that the t-butyl ester (BCCt) 1e (K_i = 10 nM) binds to benzodiazepine receptors in vitro[17] with an affinity very close to that of BCCM 1b or BCCE 1c. When the size of the alkyl group was increased to neopentyl 1h; however, the binding affinity dramatically decreased to 750 nM. This observation is significant for insertion of one methylene group between the ester oxygen and the t-butyl group decreases the binding affinity by a factor of 75 [10 nM (1e) vs 750 nM (1h)]. Other esters at position-3 which are intermediate in steric bulk such as the cyclopentyl 1f (K_i = 50nM) and the cyclohexyl 1g (K_i = 48nM) derivatives can become pseudoplanar and bind very tightly to the benzodiazepine receptor in comparison to the neopentyl ester. In agreement with our previous "planarity hypothesis",[17] it is believed the receptor site possesses a narrow cleft which will not tolerate bulky ester groups such as that contained in 1h, but will accept derivatives in which the hydrocarbon portion of the ester can approach planarity; derivatives 1f and 1g are just such compounds.

A parallel trend is observed in the series of β-carbolines which carry amide substituents at position-3. As depicted in Table 1, the primary amide 5a binds tightly to the receptor with a K_i = 68 nM, while the ethyl and 2-hydroxyethyl substituted amides bind with less affinity (K_i = 200[18] and 210 nM, respectively). When very large alkyl groups, such as adamantyl or N-methyl,N-butyl are attached to the amide at position-3, the binding constants for the corresponding compounds 5d and 5e decrease dramatically to one micromolar (1000 nM), respectively.

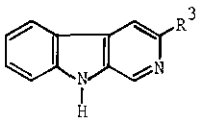


Table 1: In vitro binding of β-carboline-3-carboxylates to the benzodiazepine receptor(s).

No.	R^3	K_i (nM)
1b	CO_2CH_3	5
1c	$CO_2C_2H_5$	5
1d	$CO_2C_3H_7$	3
1e	$CO_2C(CH_3)_3$	10
1f	$CO_2C_5H_9$	50
1g	$CO_2C_6H_{11}$	48
1h	$CO_2CH_2C(CH_3)_3$	750
5a	$CONH_2$	68
5b	$CONHC_2H_5$	200[18]
5c	$CONHC_2H_4OH$	210
5d	CONH-ADAMANTYL	1000
5e	$CON(CH_3)(C_4H_9)$	1000
4	CH_2OH	1470
1a	CO_2H	25,000

In addition to the synthesis of molecules to accurately probe the topography of benzodiazepine receptors, the impetus for the preparation of 3-substituted esters which bear larger substituents stems from the selectivity observed in vivo for the n-propyl ester 1d and the t-butyl ester (BCCt) 1e.[16] It has been shown recently that BCCt is a selective antagonist of the effects of diazepam.[16] It has also been proposed that Bz_1 receptors mediate two of the effects of benzodiazepines (possibly anxiolytic and anticonvulsant) whereas Bz_2 receptors are responsible for the other two actions commonly observed for these drugs[19,20] termed ataxic and sedative-hypnotic. In this regard, BCCt 1e does not antagonize the ataxic effects of diazepam;

however, 1e does antagonize the anticonvulsant properties of diazepam.[16] BCCt therefore appears in vivo to be a selective Bz antagonist. It should be reemphasized that 1b and 1c lose 80% of their activity in rat plasma in ten min. due to hydrolysis by esterase enzymes,[13,14] whereas, BCCt (1d) maintains more than 50% of its activity after ninety min.[16] The other ester analogs reported here, such as 1f and 1g are easier to prepare than BCCt (1d) and are as stable. Since 1f and 1g bind tightly to the receptor in vitro and are readily available, they can now be tested in vivo for selective Bz receptor-mediated actions.

The 6,7-dimethoxy-4-ethyl-3-ethoxycarbonyl-β-carboline, DMCM and the 6-benzyloxy-4-methoxymethyl-3-ethoxycarbonyl-β carboline, ZK 93423, differ significantly in their in vivo activity. DMCM is a potent inverse agonist (convulsant), while ZK 93423 elicits a pharmacological profile (agonist) very similar to that of diazepam.[21,22] These interesting results demonstrate the importance of the effect of substitution at position-6 of the β-carboline nucleus on in vivo activity. With these results as leads, a wide variety of 6-substituted 3-methoxycarbonyl-β-carbolines have been prepared. The in vitro binding data of these compounds are depicted in Table 2. Examination of the K_i values for the compounds

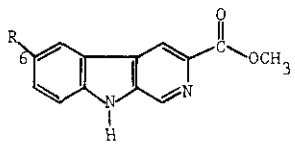


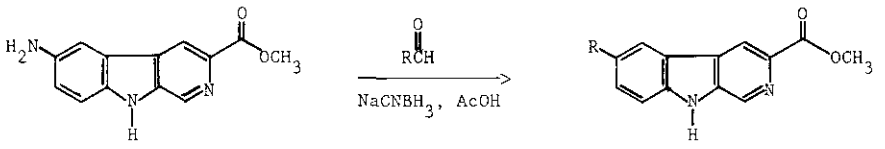
Table 2: In vitro binding of 6-substituted 3-methoxycarbonyl-β-carbolines to the benzodiazepine receptor(s).

No.	R	K_i (nM)
7a	Cl	5[23]
7b	Br	5[23]
7c	OH	5[23]
7d	NH_2	10
7e	$NHCOCH_3$	10
8a	$NHCH_2C_6H_5$	10
8b	NH-(1-NAPTHOBENZYL)	48
8c	NH-(2-NAPTHOBENZYL)	38
8d	$NH(C_6H_{11})$	10
9	$N(CH_2C_6H_5)_2$	210
10	diazepam (control)	5
11	chlorodiazepoxide (control)	250

depicted in Table 2 indicates that the benzodiazepine receptor site can tolerate large groups at position-6 of the β-carboline nucleus without significant loss of binding affinity. The 6-chloro, 6-bromo, 6-hydroxyl and 6-fluoro (K_i = 2 nM)[23] derivatives 7a-7c bind to the receptor with K_i values of 5 nM or less, moreover, the parent 6-amino-3-methoxycarbonyl-β-carboline 7d (K_i = 10 nM) binds tightly to the receptor. In addition, the 6-benzylamino 8a (K_i = 10 nM), 6-(1-naphthobenzyl)amino 8b (K_i = 48 nM), 6-(2-naphthobenzyl)amino 8c (K_i = 38 nM) and 6-cyclohexylamino 8d (K_i = 10 nM) analogs all bind to the receptor with potent affinities. The 6-N,N-dibenzylamino derivative 9 (K_i = 210 nM) binds to the receptor with much less affinity than 8a-8d; however, 9 still binds to the receptor tighter than the clinically used Librium® (chlorodiazepoxide 11). Data reported for 8a-8d indicate that the benzodiazepine receptor can tolerate much larger substituents at position-6 than originally anticipated. It is felt the alkyl and aryl substituents at position 6- of the β-carboline fit into a large lipophilic pocket which is different from the cleft described above into which the ester alkyl (C-3) groups must fit.

The methods employed to synthesize analogs 8a-8d and 9 are outlined below. Treatment of BCCM 1b with a mixture of concentrated nitric acid/fuming nitric acid[24] at 0°C provided 6-

Scheme III



7d

R
8a, $NHCH_2C_6H_5$
8b, NH-(1-napthobenzyl)
8c, NH-(2-napthobenzyl)
8d, NH-cyclohexyl
8e, $N(CH_2C_6H_5)_2$

nitro-3-methoxycarbonyl-β-carboline in good yield. Catalytic reduction (5%, Pd/C, H_2) of 6-nitro BCCM in methanol gave *6-amino-3-methoxycarbonyl-β-carboline* 7d. *It is important* to point out that the BCCM employed in this process must be pure for the presence of sulfur impurities (see Scheme I) will poison the palladium catalyst resulting in incomplete reduction. Reaction of the 6-amino-β-carboline 7d with the appropriate aldehyde or ketone, followed by treatment of the resulting imine with sodium cyanoborohydride[25], in the presence of acetic acid, gave the 6-arylbenzylamino and 6-alkylamino derivatives 8 and 9 in good yields.

The 6-benzylamino substituent of 8a does serve as a bioisostere for the benzyloxy portion portion of ZK 93423. However, 8a lacks a substituent at position-4 and the ethyl ester has

been replaced by a methyl ester function. Preliminary results with 8a in vivo in rats indicate that 8a has both anticonvulsant and sedative properties[26], somewhat analogous to the agonist activity exhibited by ZK 93423[21].

The observation that substituents at position-3 of β-carbolines can result in selective antagonist action (BCCt), coupled with the ability of the substitutents at position-6 to alter activity of β-carbolines from antagonist (BCCM 1b, BCCE, 1c DMCM, etc.) to agonist (ZK 93423 and 8d) is intriguing. In regard to the affinity of ligands for Bz receptors, the data from the present work seem to indicate that at least two lipophilic pockets on the benzodiazepine receptor are important for the binding of β-carboline ligands. One of these appears to become narrower and interacts with substituents at C-3, while substituents at C-6 fit into a lipophilic pocket which is larger. Experiments to further define the topography and the pharmacophore for benzodiazepine receptors are in progress in our laboratory. In addition, further work detailing the in vivo activity of N-substituted 6-amino-β-carbolines is underway and will be reported in due course.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker 250 MHz NMR spectrometer. IR spectra were taken on a Beckmann Acculab-1 instrument, while mass spectral data were obtained on a Hewlett Packard 5855 GC-mass spectrometer. Microanalysis were performed on an F and M Scientific Corp. model 185 carbon, hydrogen and nitrogen analyzer. High resolution mass spectra were run at the National Institutes of Health on an A.E.I. MS902 mass spectrometer.

3-Cyclohexyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3g).

The ester 3g was obtained via a Fischer esterification procedure. The 3-carboxy-1,2,3,4-tetrahydro-β-carboline 2 (6 gms, 28.6 mmol) was added to an anhydrous solution of cyclohexanol which had been saturated with hydrogen chloride gas. The solution was heated to 112°C and held at this temperature until the theoretical amount of water was collected in a Dean-Stark trap. The solution was cooled and filtered. The solvent was removed under reduced pressure and the residual oil was dissolved in cold (0°C) aqueous acid (1 N HCl, 100 ml). The filter cake which remained was suspended in cold (0°C) aqueous acid (0.1 N HCl) and filtered. The aqueous layers were combined and extracted with ethyl acetate (3 x 50 ml). The aqueous solution was brought to pH 8 with NH_4OH solution (2%). The turbid solution which resulted was extracted with CH_2Cl_2 (2 x 100 ml). The organic fractions were combined and dried (Na_2SO_4) after which the solvent was removed under reduced pressure to yield the ester as a solid 3 (2.62 gms, 30%): mp 143-

147°C; IR (KBr) 3250, 3160, 2930, 2855, 1730, 1450, 1350, 1340, 1330, 1270, 1240, 1190, 1150, 1110 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ8.30-7.90 (s, br, 1H), 7.60-6.80; (m, br, 3H), 5.00-4.60 (m, br, 1H), 4.10-3.40 (m, br, 3H), 3.20-2.60 (d, br, 2H), 2.30-1.00 (m, br, 10H); mass spectrum (CI, CH_4), m/z 299 (M+1).

3-Cyclohexyloxycarbonyl-β-carboline (1g).

The 3-cyclohexyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline 3g (1.5 g, 5.0 mmol) was added to nitrobenzene (50 ml) and elemental sulfur (0.4 gm, 12.5 mmol) was added to the mixture. The solution was gradually heated to 170°C and held at this temperature until no further starting material was observed by tlc (silica gel, 15:85, methanol-ethylacetate). After two h, the solvent was removed under reduced pressure to yield an oily residue which was subsequently purified by chromatography (silica gel, benzene-isopropyl alcohol, gradient elution) to provide 1g (0.46 g, 31%): mp 269-271 °C (dec); IR (KBr), 3250, 2980, 2910, 1700, 1400; ^1H NMR (Me_2SO-d_6) δ12.04 (s, 1H), 8.97 (s, 1H), 8.88 (s, 1H), 8.38-8.41 (d, 1H), 7.58-7.67 (m, 2H), 7.27-7.33 (t, 1H), 4.96 (m, 1H), 1.78-1.99 (s, br, 2H), 1.75-1.76 (s, 2H), 1.34-1.58 (m, 6H); mass spectrum (CI, CH_4), m/z 295 (M+1).

3-tert-butoxycarbonyl-β-carboline (1e).

The β-carboline-3-carboxylic acid 1a was converted into the corresponding acid chloride by suspending the acid (1a, 4.0 g, 17.6 mmol) in freshly distilled thionyl chloride (45 ml) and dry DMF (4 ml). The suspension was gently refluxed for one h. The thionyl chloride and the DMF were then removed, with heating, under reduced pressure and the mixture flash evaporated (2 x 50 ml) with dry benzene under reduced pressure. The dark brown residue was reacted in situ with the lithium alkoxide of tert-butyl alcohol (200 ml t-butyl alcohol, 100 ml of 1.6 N n-butyllithium). After the dropwise addition of the alkoxide into the acid chloride was completed, the mixture was stirred overnight. The work-up included removal of the solvent by evaporation under reduced pressure. The oily residue was dumped into aqueous buffer (pH = 8, NaH_2PO_4, NaOH), followed by extraction with ethylacetate (4 x 100 ml). The organic layers were combined, dried (Na_2SO_4) and the solvent removed under reduced pressure to yield a brown oil. The oil was chromatographed rapidly (silica gel, benzene, 15% CH_3OH/ethyl acetate; gradient elution) to provide an oil. The oil was allowed to stand overnight under nitrogen and furnished the ester as a solid (1e). The ester was recrystallized repeatedly from ethylacetate to provide an analytically pure sample (1e) (0.35 g); mp 219°C (dec); IR (KBr) 3260, 2970, 1710 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ9.75 (s, 1H), 9.60 (s, 1H), 9.05-9.20 (d, 1H), 7.60-8.30 (m, 3H), 2.80 (s, 9H); mass spectrum (CI,CH_4), m/z 269 (M+1).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.68; H, 5.97; N, 10.44. Found: C, 71.61; H, 5.72; N, 10.64.

6-Benzylamino-3-methoxycarbonyl-β-carboline (8a).

The 6-amino-3-methoxycarbonyl-β-carboline 7d (500 mg, 2.1 mmol) and benzaldehyde (245 mg, 2.3 mmol) were added to freshly distilled dry methanol (50 ml). This mixture was stirred for 30 min at room temperature. Sodium cyanoborohydride (520 mg) was then added and the pH adjusted to 7 with glacial acetic acid (6 drops). The reaction mixture was stirred for 8 h at which time no starting meterial remained by tlc (silica gel; ethylacetate:methanol, 85:15).

To this reaction mixture, hydrogen chloride was added (1 ml, 37%) and the solution stirred for 20 minutes at 0°C. The solvent was then reduced in vacuo to provide an oil. The oil was then transferred to a sepratory funnel and the material brought to pH 9 with aqueous NH_4OH (10%). The aqueous layer was extracted with ethylacetate (2 x 50 ml) and CH_2Cl_2 (4 x 50 ml). The organic layers were combined and dried (Na_2SO_4), the solvent was removed under reduced pressure to give a red oil (710 mg). The oil was dissolved in CH_2Cl_2, the solution cooled to 0°C and anhydrous hydrogen chloride bubbled through the mixture to yield (8a) as a dihydrochloride salt (650 mg, 77%): mp 274-275°C.

The free base 8a was prepared by treating a solution of the dihydrochloride salt with aqueous $NaHCO_3$ (saturated) followed by extraction of the solution with $CHCl_3$ (3 x 30 ml). The organic layer was dried (Na_2SO_4) and removed under reduced pressure to yield a solid which was recrystallized from ethylacetate to give (8a): mp 205-206°C, IR(KBr) 3380, 3080, 2420, 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.62 (s, 1H), 8.81 (s, 1H), 8.70 (s, 1H), 7.46-7.05 (m, 8H), 6.11 (br, s, 1H), 4.33 (s, 2H), 3.87 (s, 3H); mass spectrum (CI, CH_4), m/z 332 (M+1, 100).
Anal. Calcd. for $C_{20}N_3O_2H_{17}$ x .25 H_2O: C, 71.52; H, 5.25; N, 12.51. Found: C, 71.61, H, 5.29, N, 12.23.

3-(Imidazole)carbonyl-β-carboline (6).

The β-carboline-3-carboxylic acid 1a (1.16 g, 5.5 mmol) was suspended in dry DMF (50 ml) at room temperature and 1,1 carbonyldiimidazole (1.70 g, 10.5 mmol) was added. A clear brown solution resulted. After stirring for 2 hrs, the reaction mixture was poured onto ice water (750 g) and the resulting precipitate filtered and dried to yield 6 (1.07 g, 75%): mp 296-298°C (dec.); IR (KBr) 3150, 1675 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ12.28 (s, 1H), 9.09 (s, 1H), 9.04 (s, 1H) 8.90 (s, 1H) 8.41 (m, 1H), 8.02 (s, 1H), 7.67 (s, 1H), 7.33 (m, 1H), 7.11 (s, 1H), 7.01 (s, 1H); mass spectrum (EI) m/z 262 (M+, 42), 195 (58), 167 (100).
High resolution mass spectrum calculated for $C_{15}H_{10}N_4O$: 262.0854. Found: 262.0831.
This intermediate 6 was then converted to the amides 5d and 5e by the method of Lippke [18].

3-(2-Ethoxy)carboxamide-β-carboline (5c).

The 3-ethoxycarbonyl-β-carboline 1c (2.05 g, 8.5 mmol) was suspended in ethanolamine (30 ml) and the solution brought to reflux for 2.5 h. The solvent was removed under reduced pressure to yield the amide 5c, which was recrystallized (ethylacetate-methanol, 5:1) to yield pure 5c 1.89 g (87%): mp 211.5-212.5°C; IR (KBr)1650 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ11.99 (s, 1H)m 8.92 (d, 1H), 8.71 (s, 1H), 8.43 (s, 1H), 7.63 (m, 1H), 7.31 (m, 1H), 4.85 (s, br, 1H), 3.68 (m, 3H), 3.48 (m, 3H); mass spectrum (CI,CH_4), m/z 256 (M+1, 100).

Anal. Calcd for $C_{14}N_3O_2H_{13}$: C, 67.59; H, 5.67; N, 9.86. Found: C, 67.72; H, 5.68; N. 9.92.

ACKNOWLEDGEMENT

This work was generously supported by a grant from NIMH (MH 36644). The authors wish to thank Frank Laib for the mass spectra and Greg Kubiak for stimulating discussions. The assistance of Katherine Banna in the preparation of this manuscript is gratefully acknowledged.

REFERENCES

1. S. S. Tenen and J. D. Hirsch, Nature, 1980, 288, 609.
2. N. R. Oakley and B. J. Jones, Eur. J. Pharmacol., 1980, 68, 381.
3. E. N. Petersen, G. Paschelke, W. Kehr, M. Nielsen and C. Braestrup, Eur. J. Pharamcol., 1982, 82, 217.
4. M. G. Corda, W. D. Blaker, W. B. Mendelson, A. Guidett and E. Costa, Proc. Natl. Acad. Sci., 1983, 80, 2072.
5. R. A. O'Brien, W. Schlosser, N. M. Spirt, S. Franco, W. D. Horst, P. Polc and E. D. Bonett Life Sci., 1981, 29, 75.
6. B. J. Jones and N. R. Oakley, Br. J. Pharmacol., 1981, 74, 884P.
7. A. Valin, R. H. Dodd, D. R. Liston, P. Potier and J. Rossier, Eur. J. Pharmacol., 1982, 85, 93.
8. B. K. Koe and L. A. Lebel, Eur. J. Pharmacol., 1983, 90, 97.
9. P. N. Van Gorder, W. E. Hoffmann, V. Baughman, R. F. Albrecht, D. J. Miletich, F. Guzman and J. M. Cook, Anesth. Analog., 1985 64, 129.
10. P. Polc, E. P. Bonett, R. Schattner and W. Haefely, Nauyn-Schmiedeberg's Arch. Pharmacol., 1982, 321, 260.
11. C. Cepda, T. Tanaka, R. Besselievere, P. Potier, R. Naquet and J. Rossier, Neurosci. Lett., 1981, 24, 53.
12. C. Braestrup, R. Schiechen, G. Neef, M. Nielsen and E. N. Petersen, Science, 1982, 216, 1241.

12. C. Braestrup, R. Schiechen, G. Neef, M. Nielsen and E. N. Petersen, Science, 1982, 216, 1241.

13. M. M. Schweri, J. V. Martin, W. B. Mendelson, J. E. Barrett, S. M. Paul and P. Skolnick, Life Sci., 1983, 33, 1505.

14. K. J. Fehske and W. E. Muller, Br. Res., 1982, 238, 268.

15. F. Guzman, M. Cain, P. Larschied, T. Hagen, J. M. Cook, M. Schweri, P. Skolnick and S. M. Paul, J. Med. Chem., 1984, 27, 564.

16. H. E. Shannon, F. Guzman and J. M. Cook, Life Sci., 1984, 35, 2227.

17. M. Cain, R. Weber, F. Guzman, J. M. Cook, S. A. Barker, K. C. Rice and P. Skolnick, J. Med. Chem., 1982, 25, 1081.

18. K. P. Lippke, W. E. Muller and W. G. Schunack, J. Pharm. Sci., 1985, 74, 676.

19. C. A. Klepner, A. S. Lippa, D. I. Benson, M. C. Sano and B. Beer, Pharmacol. Biochem. Behav., 1979, 11, 457.

20. a) B. Dubnick, A. S. Lippa, C. A. Klepner, J. Coupet, E. N. Greenblatt and B. Beer, Pharmacol. Biochem. Behav., 1983, 18, 311; b) H. A. Robertson, Prog. Neuropsychopharmacol. Biol. Psychiatry, 1983, 7, 637; c) H. A. Robertson, M. Riives, D. A. Blank, and M. R. Peterson, Br. Res., 1984, 291, 388; d) K. W. Gee and H. I. Yamamura, Adv. Biochem. Psychopharmacol., 1983, 38, 1.

21. D. N. Stephans, G. T. Shearman, and W. Kehr, Psychopharmacology, 1984, 83, 233.

22. C. Braestrup and M. Nielsen, J. Neurochem., 1981, 37, 333.

23. F. Guzman, M.S. Thesis, University of Wisconsin-Milwaukee, 1985; F. Guzman and J. M. Cook, unpublished results.

24. G. Neef, U. Eder, A. Huth, D. Rahtz, R. Schmiechen and D. Seidelmann, Heterocycles, 1983, 20, 1295.

25. R. F. Borch, M. D. Bernstein and H. Dupont Durst, J. Amer. Chem. Soc., 1971, 93, 2897.

26. T. Hagen, H. Shannon and J. M. Cook, unpublished results.

Received, 9th June, 1986