stainless-steel bomb at 100 °C for 3 h. The resulting reaction solution was evaporated to dryness, and the dried residue was recrystallized from C_6H_5: yield 5.3 g (44%).

Method V. Ethyl 6-Amino-4-[[3-(*N*-methyl-*N*-phenylamino)-2-oxopropyl]amino]-5-nitro-2-pyridinecarbamate Oxime. A solution of 1 (10.3 g, 39.5 mmol), 1-amino-3-(*N*-methyl-*N*-phenylamino)propanone oxime (7.77 g, 40.2 mmol), and triethylamine (4.27 g, 42.2 mmol) in EtOH (200 mL) was heated under N_2 at 75 °C for 24 h. After the reaction mixture was cooled, the yellow solid was collected by filtration, washed with cold EtOH, and dried in vacuo over P_2O_5 at 65 °C: yield 13.8 g.

Method VI. Ethyl 6-Amino-5-nitro-4-[(2-oxo-2-phenylethyl)amino]-2-pyridinecarbamate. A solution of ethyl 6-amino-5-nitro-4-[(2-oxo-2-phenylethyl)amino]-2-pyridinecarbamate oxime (4.72 g, 12.6 mmol) in a 1:1 mixture of 1 N HCl–dioxane (170 mL) was heated with stirring at 60 °C for 2 h. The yellow solid that deposited from the chilled solution was collected by filtration and recrystallized from a 1:1 mixture of H_2O–dioxane (1 L): yield 3.13 g.

Method VII. Ethyl 6-Amino-4-[[3-(*N*-methyl-*N*-phenylamino)-2-oxopropyl]amino]-5-nitro-2-pyridinecarbamate. Crystalline orthophosphoric acid (3.08 g, 31.5 mmol) was added to a stirred solution of ethyl 6-amino-4-[[2-hydroxy-3-(*N*-methyl-*N*-phenylamino)propyl]amino]-5-nitro-2-pyridinecarbamate (3.18 g, 7.87 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (4.86 g, 23.6 mmol) in dry Me_2SO (40 mL). The mildly exothermic reaction was kept below 25 °C by water-bath cooling. After 2.5 h, the deposit of dicyclohexylurea was filtered off and washed with Me_2SO (25 mL). The filtrate was cooled in an ice bath and diluted slowly with H_2O (100 mL) to precipitate the product as a bright yellow solid, which was washed thoroughly with H_2O and dried in vacuo over P_2O_5: yield 2.89 g.

Recrystallization of the crude product from several common organic solvents was unsuccessful. In hot EtOH, the product underwent rapid degradation to a chromatographically complex red gum. Mass spectral analysis showed a prominent molecular ion at M^+ 241, which corresponds to ethyl 4,6-diamino-5-nitro-2-pyridinecarbamate.

Method VIII. Ethyl 6-Amino-4-[[3-[*N*-(4-chlorophenyl)-*N*-methylamino]-2-hydroxypropyl]amino]-5-nitro-2-pyridinecarbamate. A solution of 1 (10.0 g), 1-amino-3-[*N*-(4-chlorophenyl)-*N*-methylamino]-2-propanol (8.25 g), and triethylamine (10.7 mL) in MeOH (120 mL) was heated at 60 °C for 18 h and evaporated to dryness in vacuo. The dark residue was washed with Et_2O (1.5 L) to give a yellow solid. This solid was washed with H_2O (50 mL) and recrystallized twice from a mixture of ethanol and hexane: yield 4.92 g. Similar treatment of the residue obtained from the ether wash from above gave a slightly impure sample of product: yield 5.89 g (35%); mp 175 °C. The total yield was 64%.

Method IX. Ethyl 5-Amino-1,2-dihydro-3-[[(*N*-methyl-*N*-phenylamino]methyl]pyrido[3,4-*b*]pyrazine-7-carbamate. A suspension of the oxime of ethyl 6-amino-4-[[3-(*N*-methyl-*N*-phenylamino)-2-oxopropyl]amino]-5-nitro-2-pyridinecarbamate (30.0 g, 71.9 mmol) and Raney nickel (60 g, weighed wet, washed with EtOH) in EtOH (3000 mL) was hydrogenated at room temperature and atmospheric pressure with vigorous stirring. At the end of 12 h, the hydrogen (7048 mL) absorbed corresponded to 134% of the theoretical for 3 molar equiv of the nitropyridine and 101% of the theoretical for 4 molar equiv. The resulting mixture was heated nearly to boiling under an atmosphere of N_2, and the catalyst was removed by filtration and washed with boiling EtOH (5 × 200 mL). The combined filtrate and wash were concentrated to about 1000 mL in vacuo and cooled in an ice bath to deposit the product as a pale yellow crystalline solid: yield 16.7 g.

Method X. Ethyl 5-Amino-1,2-dihydro-3-phenylpyrido-[3,4-*b*]pyrazine-7-carbamate. A solution of ethyl 6-amino-5-nitro-4-[(2-oxo-2-phenylethyl)amino]pyridine-2-carbamate dioxanate (10:7) (3.10 g, 7.25 mmol) in EtOH (4 L) was hydrogenated in the presence of Raney nickel (9 g, weighed wet, washed with EtOH) at atmospheric pressure with intermittent warming with a water bath. After 6 h the catalyst was removed by filtration, and the filtrate was concentrated in vacuo (<40 °C) to $^1/_{16}$ volume. The solid that deposited from the chilled mixture was collected by filtration and dried in vacuo over P_2O_5: yield 1.82 g. From the filtrate a second crop was obtained: yield 0.17 g. The total yield was 1.99 g.

Acknowledgment. This investigation was supported by Grant CA-25311 awarded by the National Cancer Institute, National Institute of Health. The authors are indebted to Dr. W. R. Laster for the screening of data, to B. J. Bowdon for mitotic indexes, to D. J. Adamson for the inhibition data on the proliferation of cells, and to Dr. W. C. Coburn, Jr., and other members of the Molecular Spectroscopy Section of Southern Research Institute who performed most of the microanalytical and spectral determinations.

Quinazolines and 1,4-Benzodiazepines. 90.[1] Structure–Activity Relationship between Substituted 2-Amino-*N*-(2-benzoyl-4-chlorophenyl)acetamides and 1,4-Benzodiazepinones

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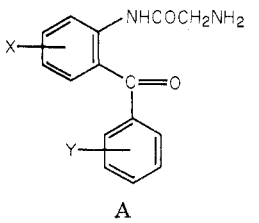
The syntheses of 2-amino-*N*-(2-benzoyl-4-chlorophenyl)acetamides are reported. The pharmacological properties of these compounds were compared with data obtained from the corresponding cyclized products [5-(2,6-dichlorophenyl)-1,4-benzodiazepin-2-ones]. Evidence is presented which suggests that the central nervous system activity observed for 1,4-benzodiazepines is inherent only in the closed seven-membered ring and is not due to the ring-opened form.

One of the procedures extensively employed during the course of our studies on the synthesis of 1,4-benzodiazepin-2-one derivatives involved the preparation and cyclization of aminoacetanilides of type "A".[2] These intermediates could be isolated either as the free base or as the hydrochloride salt.[3] It was noted empirically that the substituent in the ortho position of the benzoyl group seemed to have an effect on the ease of the ring closure.



A

Biological evaluation of the "open amines" showed that their pharmacological profiles were qualitatively the same

† Deceased July 8, 1981.

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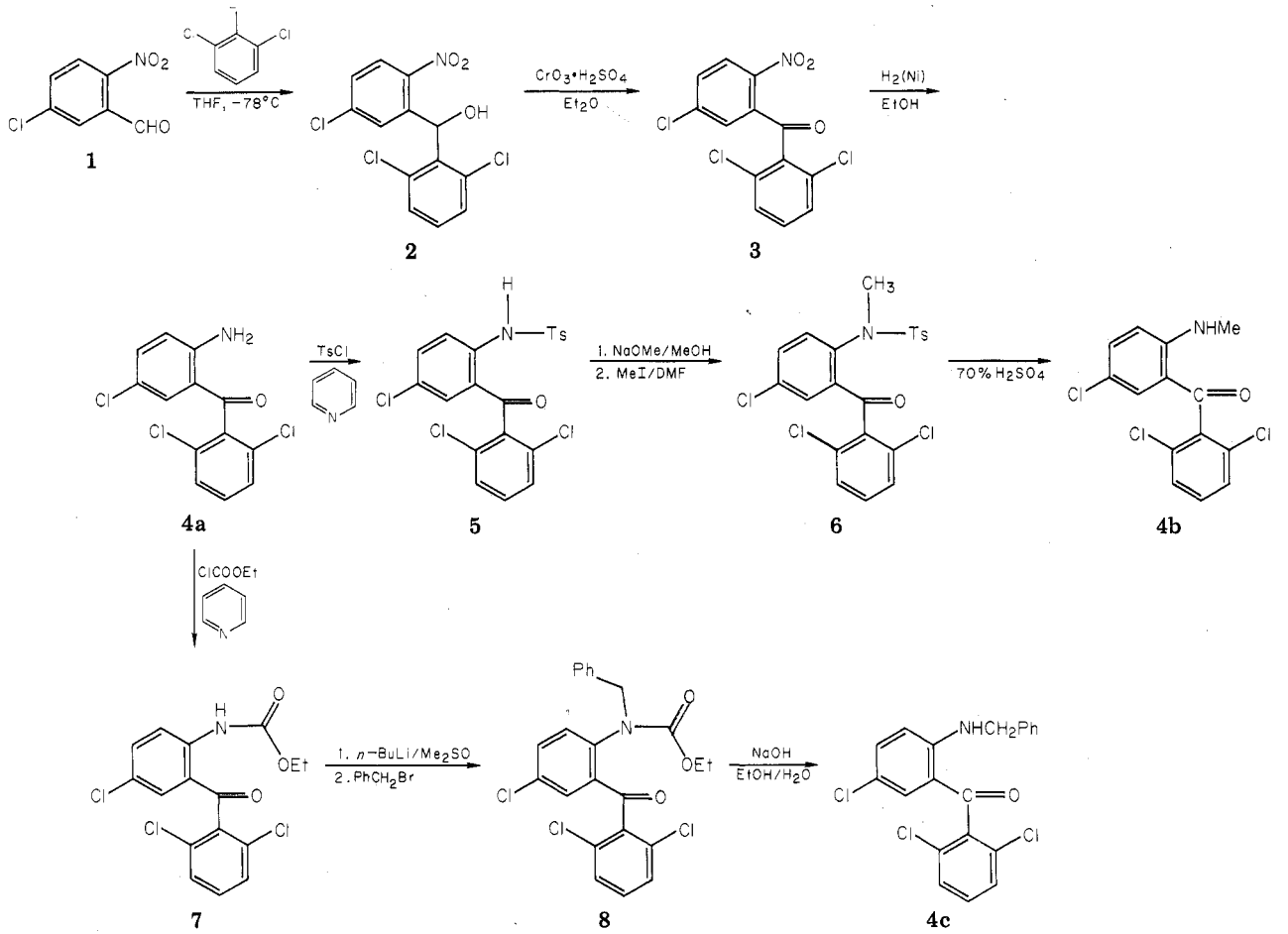
Scheme I



and quantitatively similar to those of the corresponding cyclized benzodiazepinones.[4] Although it has been established that benzodiazepines are biologically active when administered either orally, intravenously, or intramuscularly, there has been no evidence to mitigate against the ring-open form as being the active moiety that is responsible for the action of benzodiazepines at the benzodiazepine receptor. With the recent advent of the receptor-binding assays,[5] we have reexamined both the ring-opened and ring-closed forms of some of these benzodiazepinones[2] where such related pairs of compounds have been synthesized, and we have found relatively small differences in the binding affinities for these compounds.

We now report evidence that supports the hypothesis that it is the benzodiazepinone which is responsible for the biological activity and not the corresponding open aminoacetamides.

Chemistry. While carrying out the synthesis of 5-(2,6-disubstituted-phenyl)benzodiazepine derivatives,[6] we observed that ring closure of 2-amino-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]acetamide (**10a**; Scheme II) could not be effected by any of the normal methods.[2] Presumably, ring closure is prevented by strong hydrogen bonding between the amide hydrogen and the ketone[7] and also by the steric environment of the ketone. Formation of the *N*-methyl- and *N*-benzylacetamides **10b** and **10c**, respectively (Scheme II), effectively removed the problem of hydrogen bonding, and cyclization of these intermediates to the corresponding benzodiazepines **13b** and **13c** could be effected by the use of pivalic acid in refluxing toluene. The 1-H benzodiazepine **13a** was prepared by debenzylating **13c** in 98% sulfuric acid at 100 °C.

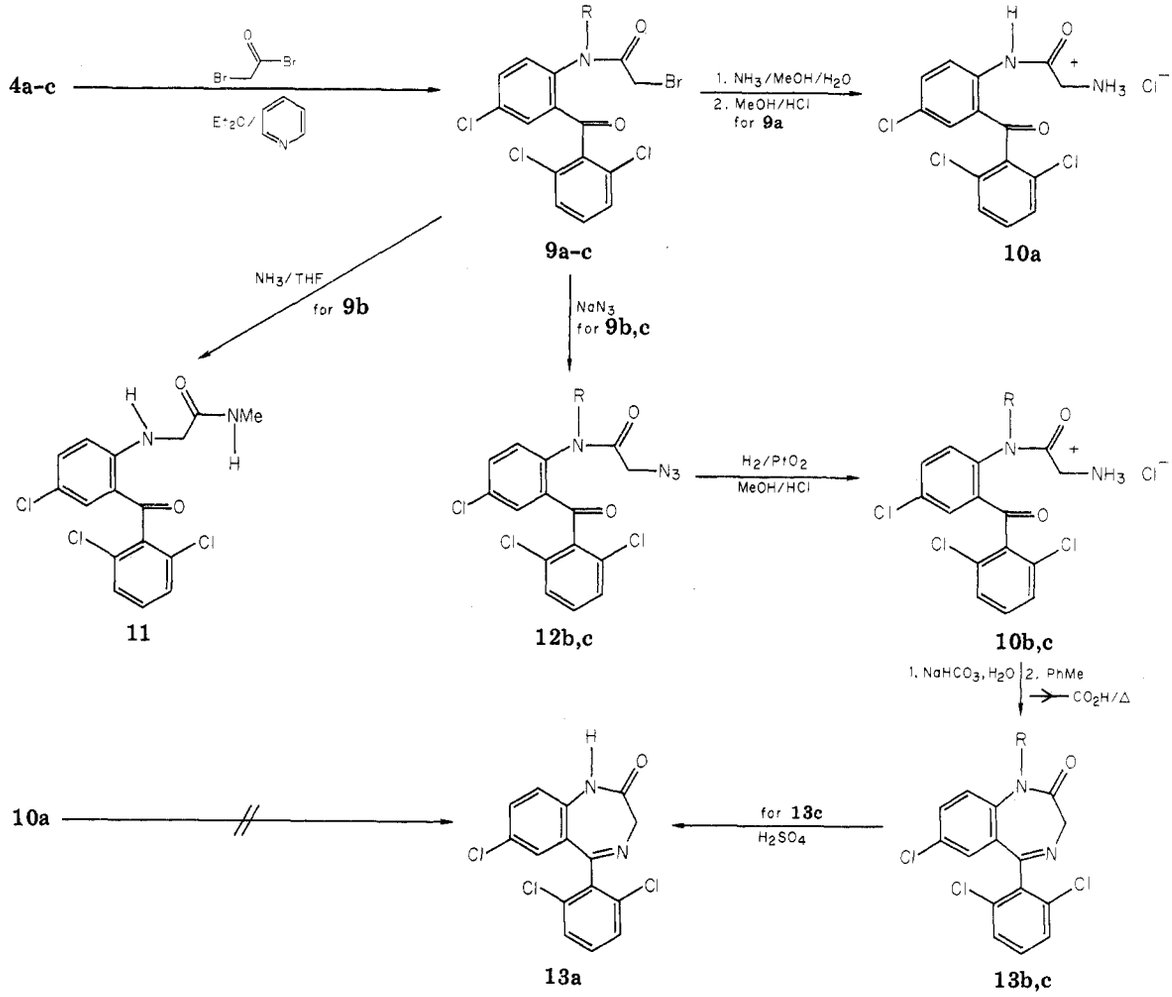
The acetamides **10a–c** were prepared from the iminobenzophenones **4a–c**, which in turn were synthesized as outlined in Scheme I. The addition of 2-nitro-5-chlorobenzaldehyde (**1**) to lithio-2,6-dichlorobenzene, prepared from *m*-dichlorobenzene and *n*-butyllithium at −78 °C, gave the benzhydrol **2**. Without isolation, **2** was oxidized with Jones reagent to the nitrobenzophenone **3**. Hydrogenation of **3** using Raney nickel as catalyst gave **4a**.

The *N*-methylaminobenzophenone **4b** was prepared in a three-step procedure from **4a**. Treatment of **4a** with tosyl chloride in pyridine gave the sulfonamide **5**, which was methylated with methyl iodide in DMF using sodium methoxide as base to give **6**. Removal of the tosyl group by heating **6** in 70% sulfuric acid yielded **4b**.

Since the benzyl group would also be labile to the conditions utilized for the hydrolysis of the sulfonamido group, an alternate procedure was used to prepare the *N*-benzylaminobenzophenone **4c**. Treatment of **4a** with ethyl chloroformate in ether using pyridine as base gave the

(1) Paper 89: J. V. Earley, R. Ian Fryer, R. Y. Ning, *J. Pharm. Sci.*, **68**, 845 (1979).
(2) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
(3) Long-term storage of these intermediates resulted in eventual ring closure to the corresponding 1,4-benzodiazepin-2-ones.
(4) L. O. Randall, unpublished work.
(5) H. Möhler and T. Okada, *Life Sci.*, **20**, 2101 (1977).
(6) R. Ian Fryer, L. H. Sternbach, and J. V. Earley, U.S. Patent 3 523 939, Aug 11, 1970.
(7) M. E. Derieg, R. Schweininger, and R. Ian Fryer, *J. Org. Chem.*, **34**, 179 (1969).

Scheme II[a]



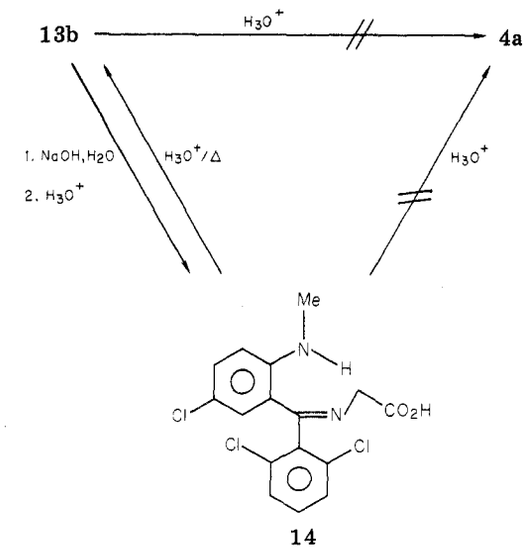
[a] a, R = H; b, R = Me; c, R = $CH_2C_6H_5$.

carbamate **7**. Benzylation of **7** with benzyl bromide in Me_2SO using dimsyllithium as base yielded **8**, which was hydrolyzed with sodium hydroxide in aqueous ethanol to **4c**.

Reaction of **4a–c** with bromoacetyl bromide in ether, using pyridine as base, gave the 2-bromoacetamides **9a–c**, respectively (Scheme II). Treatment of **9a** with methanolic ammonia, followed by methanolic hydrogen chloride, gave the 2-aminoacetamide hydrochloride **10a** directly. Reaction of **9b** with ammonia, however, resulted exclusively in the formation of the Smiles rearrangement product **11**.[8] To circumvent the Smiles rearrangement, the acetamides **9a,b** were treated with sodium azide in Me_2SO, and the resulting azides **12b,c** were hydrogenated, using platinum oxide as catalyst in the presence of hydrogen chloride,[9] to give the aminoacetamide hydrochlorides **10b,c** respectively.

Due to the steric effects of the 2,6-dichloro substituents, the benzodiazepines **13** exhibited remarkable stability to hydrolysis. Thus, unlike other benzodiazepinones, hydrolysis of the lactam **13b**, using 3 N NaOH, gave, after mild treatment of the salt with acid, compound **14**. Attempts to hydrolyze **14** to the ketone with acid resulted only in recyclization to **13b** (Scheme III).

Scheme III



Results and Discussion

Because the 2-aminoacetamide **10a** could not be cyclized and the 2-aminoacetamide **10b** was cyclized only with difficulty and since, in addition, the Schiff's bases **13a** and **13b** are extremely resistant to hydrolysis, it was felt that a biological evaluation of these four compounds would indicate whether the ring-opened or the ring-closed form

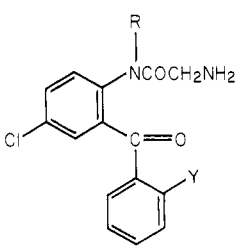
(8) N. W. Gilman, P. Levitan, and L. H. Sternbach, *J. Org. Chem.*, **38**, 373 (1973).
(9) J. B. Peterson and K. H. Lakowitz, *Acta Chem. Scand.*, **23**, 971 (1969).

Table I. Antimetrazole Activity and [^{3}H]Diazepam Binding Assay Results for Acetamides and 1,4-Benzodiazepines

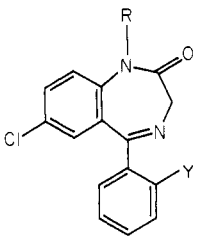
acetanilides hydrochlorides	antimetrazole[a] ED_{50}, mg/kg ip	[^{3}H]diazepam[b] binding assay: IC_{50}, nM	1,4-benzodiazepine	antimetrazole[a] ED_{50}, mg/kg ip	[^{3}H]diazepam[b] binding assay: IC_{50}, nM
15	1.0	9.9	**17**	1.2	8.1
16	3.8	4.8	**18**	0.26	2.8
10a	>400	1000	**13a**	6.0	5.5
10b	>200[c]	930	**13b**	18.9	7.0

[a] Antimetrazole test was carried out on 50–54 day old, CF1 male mice using a modification of the method of Everett and Richards.[12] The ED_{50} was calculated as the dose that would prevent convulsions in 50% of the mice tested after administration of 70 mg/kg of metrazole by the iv route. Groups of 10 mice (active compounds) and 3 mice (inactive compounds) at a minimum of three dose levels were used. Results are reported as 95% fiducial limits. [b] The conditions of Möhler and Okada[5] were used for this assay procedure. [c] Approximate LD_{50} = 245 mg/kg ip.

of benzodiazepines was responsible for the observed CNS activity. As a control, the closely related "less hindered" 2-aminoacetamides **15** and **16**[2] and their corresponding



15, R = CH_3; Y = H
16, R = H; Y = Cl



17, R = CH_3; Y = H
18, R = H; Y = Cl

cyclized benzodiazepine counterparts **17**[2] and **18**[2] were also evaluated in the same biological tests. All of the acetamides were tested as their hydrochloride salts.[11]

It has been reported that for 1,4-benzodiazepines there is a good correlation between the results obtained in the antimetrazole (antipentylenetetrazole) test and the relative anxiolytic potency of these compounds in humans.[10] It was therefore decided to evaluate the acetamide hydrochlorides and the corresponding benzodiazepines in this test procedure as well as in the more recent in vitro [^{3}H]diazepam binding assay.

From an examination of the data presented in Table I, it is evident that the open compound **15** is equipotent to the cyclized benzodiazepinone **17**. A slight indication that it is the benzodiazepine and not the acetamide that is responsible for the observed CNS activity is seen by an examination of the data for the second pair of controls. Compound **16** is slightly less active in both tests than compound **18**. While inhibition of ring closure by either hydrogen bonding or steric factors (discussed above) might be responsible for the lower activity observed for **16** when compared to **18**, the differences are small and the argument is not unequivocal. For example, using the same biological data, it is also tenable that the acetamide is active per se and, as a class of compounds, the acetanilides are more poorly absorbed, are more subject to hydrolysis, or are simply less potent. Such a hypothesis, however, is not tenable based on the biological test data for the hindered acetamides **10a** and **10b**. These compounds were devoid of CNS activity, while the corresponding benzodiazepinones **13a** and **13b** again show good activity as CNS agents.

These results indicate that the geometry imparted by the seven-membered ring structure is probably essential for receptor binding and, furthermore, that if the aminoacetanilides are present in either an in vitro or an in vivo system, cyclization must occur in order for binding to take place.

Experimental Section

Chemistry. Melting points are uncorrected. NMR spectra were recorded on a Varian T-60 or HA-100 instrument and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively.

(2,6-Dichlorophenyl)(5-chloro-2-nitrophenyl)methanone (3). A solution of *n*-butyllithium (20 mL, 43.4 mmol) and 1,3-dichlorobenzene (6.7 g, 45.5 mmol) in THF (100 mL) was stirred at −78 °C for 20 min. In one portion, 5-chloro-2-nitrobenzaldehyde (4.0 g, 21.9 mmol) was added, and stirring at −78 °C was continued for 1 h. Acetic acid (2 mL, 34 mmol) was added, and the mixture was warmed to room temperature. The THF was removed in vacuo, and the residue was dissolved in Et_2O (200 mL). Jones reagent (20 mL, 53.4 mmol) was added dropwise to the Et_2O solution at 0 °C, which was then stirred at room temperature for 12 h. The excess oxidant was removed by the addition of saturated aqueous $NaHSO_3$ solution until the orange color was discharged. The mixture was filtered through Celite, and the filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to dryness. The residue was triturated with Et_2O and petroleum ether to give 5.2 g of **3** as a tan solid. Recrystallization from a mixture of $CHCl_3$ and hexane gave 4.8 g (67%) of **3** as white prisms: mp 179–181 °C; IR ($CHCl_3$) 1700 (C=O), 1550 and 1352 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 3, aromatic H), 7.4–7.8 (m, 3, aromatic H); mass spectrum, *m/e* 327 (M^+). Anal. ($C_{13}H_6Cl_3NO_3$) C, H, N.

(2,6-Dichlorophenyl)(2-amino-5-chlorophenyl)methanone (4a). A mixture of **3** (11.6 g, 35.4 mmol), Raney nickel[13] (2 g), and EtOH (300 mL) was hydrogenated at atmospheric pressure for 8 h. The nickel was removed by filtration, and the EtOH was removed in vacuo. The residue was triturated with Et_2O to give 6.5 g (mp 147–149 °C, 62%) of **4a** as a yellow solid. Recrystallization from a mixture of Et_2O and hexane gave **4a** as yellow prisms: mp 150–151 °C; IR ($CHCl_3$) 3500 and 3350 (NH_2), 1645 (C=O) cm^{-1}. Anal. ($C_{13}H_8Cl_3NO$) C, H, N.

***N*-[4-Chloro-2-(2,6-dichlorobenzoyl)phenyl]-4-methylbenzenesulfonamide (5).** A mixture of **4a** (6.5 g, 22 mmol), and TosCl (8.2 g, 44 mmol) in pyridine (120 mL) was refluxed for 80 min. The mixture was cooled and concentrated in vacuo. The residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in

(10) S. Garatini, E. Mussini and L.O. Randall, Eds., "The Benzodiazepines", Monograph of the Mario Negri Institute for Pharmacological Research, Raven Press, New York, 1973, p 37.

(11) For the [^{3}H]diazepam binding assay, solutions of the acetamides in aqueous pH 7.4 buffer were prepared. Under these conditions, the free base of ring-opened compounds would be present. In the case of compound **15**, the half-life of this form would be expected to be approximaely 73 s at pH 7 [*Experientia*, **33**, 1492 (1977)]. This suggests that at pH 7.4, which is required for the [^{3}H]diazepam binding assay, compound **15** would be in the ring-closed form, compound **17**, during the assay.

(12) G. M. Everett and R. K. Richards, *J. Pharm. Exp. Ther.*, 81, 402 (1944).

(13) A high activity grade Raney Nickel similar to type 28 was used.

vacuo to give 8.5 g (mp 137–139 °C, 88%) of **5** as a tan solid. Recrystallization from a mixture of $CHCl_3$ and hexane gave **5** as white needles: mp 139–140 °C; IR ($CHCl_3$) 3200 (NH), 1660 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.32 (s, 3, CH_3), 7.1–7.8 (m, 10, aromatic H, and NH); mass spectrum, *m/e* 453 (M^+). Anal. ($C_{20}H_{14}Cl_3NO_3S$) C, H, N.

***N*-[4-Chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-methyl-4-methylbenzenesulfonamide (6).** A solution of **5** (8.7 g, 19 mmol) and sodium methoxide (1.9 g, 35 mmol) in MeOH (250 mL) was stirred at room temperature for 1 h. The MeOH was removed in vacuo, and the residue was dissolved in DMF (150 mL). Methyl iodide (10 mL, 160 mmol) was added to the DMF solution and stirred for 4 h. The mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 8.7 g (97%) of **6** as a colorless solid. Recrystallization from a mixture of Et_2O and CH_2Cl_2 gave 8.3 g of **6** as a colorless solid: mp 174–175 °C; IR ($CHCl_3$) 1680 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 2.95 (s, 3, N-CH_3), 7.1–7.7 (m, 10, aromatic H). Anal. ($C_{21}H_{16}Cl_3NO_3S$) C, H, N.

[5-Chloro-2-(methylamino)phenyl](2,6-dichlorophenyl)methanone (4b). A solution of **6** (6.8 g, 14.4 mmol) in 70% aqueous sulfuric acid (60 mL) was heated to 100 °C for 2 h. The solution was cooled and poured over ice. The resulting precipitate was collected by filtration and recrystallized from a mixture of Et_2O and petroleum ether to give 4.1 g (91%) of **4b** as yellow prisms: mp 199–201 °C; IR ($CHCl_3$) 1635 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.97 (d, J = 5 Hz, 1, CH_3), 6.69 (d, J = 8 Hz, 1, aromatic H), 7.0–7.4 (m, 5, aromatic H), 8.88 (br s, 1, NH); mass spectrum, *m/e* 313 (M^+). Anal. ($C_{14}H_{10}Cl_3NO$) C, H, N.

Ethyl *N*-[4-Chloro-2-(2,6-dichlorobenzoyl)phenyl]carbamate (7). A mixture of **4a** (14.3 g, 47.6 mmol), pyridine (25 mL, 0.3 mol), ethyl chloroformate (14 mL, 0.17 mol), Et_2O (200 mL), and CH_2Cl_2 (200 mL) was stirred at room temperature for 60 min. The mixture was washed with water, 5% aqueous $CuSO_4$, and water. The Et_2O solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 15.0 g (mp 149–151 °C, 84%) of **7** as a tan solid. Recrystallization from Et_2O gave **7** as cream-colored needles: mp 150–151 °C; IR ($CHCl_3$) 3290 (NH), 1733 and 1518 (carbamate C=O), 1658 (ketone C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3, CH_3), 4.26 (q, J = 7 Hz, 2, CH_2), 7.2–7.6 (m, 5, aromatic H), 8.58 (d, J = 8 Hz, 1, aromatic H), 10.89 (br s, 1, NH); mass spectrum, *m/e* 371 (M^+). Anal. ($C_{16}H_{12}Cl_3NO_3$) C, H, N.

Ethyl *N*-[4-Chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-(phenylmethyl)carbamate (8). A mixture of *n*-butyllithium in hexane (6.5 mL, 2.17 M, 14 mmol), **7** (5.5 g, 14.7 mmol), and benzyl bromide (2.0 mL, 16.8 mmol) in Me_2SO (30 mL) was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with Et_2O. The Et_2O solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 6.2 g (91%) of a tan solid. Recrystallization from a mixture of Et_2O and petroleum ether gave **8** as colorless prisms: mp 126–127 °C; IR ($CHCl_3$) 1703 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.15 (t, J = 7 Hz, 3, CH_3), 4.15 (q, J = 7 Hz, 2, CH_2), 5.31 (d, 1) and 6.79 (d, 1) (AB system, J = 13 Hz, CH_2-Ph), 6.9–7.6 (m, 11, aromatic H); mass spectrum, *m/e* 461 (M^+). Anal. ($C_{23}H_{18}Cl_3NO_3$) C, H, N.

[5-Chloro-2-[(phenylmethyl)amino]phenyl](2,6-dichlorophenyl)methanone (4c). A mixture of **8** (16.2 g, 35 mmol) and NaOH (25 g, 0.62 mol) in 95% EtOH (500 mL) was refluxed for 72 h. The mixture was cooled, acidified with concentrated hydrochloric acid, diluted with water, and extracted with Et_2O. The Et_2O solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 15 g of a yellow oil. Purification by column chromatography (SiO_2, 300 g; CH_2Cl_2) gave 9.6 g (70%) of **4c** as a yellow solid. Recrystallization from a mixture of Et_2O and petroleum ether gave **4c** as yellow prisms: mp 106–107 °C; IR ($CHCl_3$) 3335 (NH), 1635 and 1626 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.51 (d, J = 6 Hz, 2, $PhCH_2$), 6.66 (d, J = 8 Hz, 1, aromatic H), 7.1–7.5 (m, 10, aromatic H), 9.35 (br s, 1, NH); mass spectrum, *m/e* 389 (M^+). Anal. ($C_{20}H_{14}Cl_3NO$) C, H, N.

2-Bromo-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]acetamide (9a). A solution of **4a** (10 g, 33 mmol) and bromoacetyl bromide (18.4 g, 91 mmol) in Et_2O (250 mL) was stirred at room temperature for 10 min. The Et_2O solution was washed with water, dilute aqueous NaOH, and water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 12 g of a pale yellow oil. The oil was crystallized from a mixture of Et_2O and petroleum ether to give 9.7 g (70%) of **9a** as a colorless solid. Recrystallization from a mixture of Et_2O and petroleum ether gave **9a** as colorless prisms: mp 128–129 °C; IR ($CHCl_3$) 3250 (NH), 1690 (amide C=O), 1660 (ketone C=O) cm^{-1}. Anal. ($C_{15}H_9BrCl_3NO_2$) C, H.

2-Amino-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]acetamide Hydrochloride Hemihydrate (10a). A solution of **9a** (9.7 g, 23 mmol), Et_2O (100 mL), and 15% methanolic ammonia (100 mL) was stirred at room temperature for 12 h. The solvents were removed in vacuo. The residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 6.5 g (80%) of the free base of **10a** as a pale yellow solid. Recrystallization from a mixture of CH_2Cl_2 and petroleum ether gave the free base as colorless prisms: mp 183–184 °C; IR ($CHCl_3$) 3250 (NH), 1695 (amide C=O), 1665 (ketone C=O) cm^{-1}. Anal. ($C_{15}H_{11}Cl_3N_2O_2$) C, H, N.

The hydrochloride salt **10a** was prepared by the addition of an excess of 6% methanolic HCl to a MeOH solution of the free base and precipitated by the addition of Et_2O. Recrystallization from a mixture of MeOH and Et_2O gave **10a** as fine colorless needles: mp 242–244 °C; NMR (Me_2SO-d_6) δ 3.33 (s, 4, NH_3^+, $0.5H_2O$), 4.03 (s, 2, CH_2), 7.28 (d, J = 2 Hz, 1, aromatic H), 7.63 (s, 3, aromatic H), 7.83 (dd, J = 2 and 9 Hz, 1, aromatic H), 8.47 (br s, 1, NH), 8.50 (d, J = 9 Hz), 1, aromatic H). Anal. ($C_{15}H_{12}Cl_4N_2O_2{\cdot}0.5H_2O$) C, H, N.

2-Bromo-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-methylacetamide (9b). A mixture of **4b** (4.4 g, 14 mmol) and bromoacetyl bromide (4.0 g, 20 mmol) in benzene (100 mL) was refluxed for 60 min. The mixture was cooled and washed with saturated aqueous $NaHCO_3$ and water. The benzene solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a white solid. Trituration with ether gave 5.5 g (mp 161–163 °C, 91.5%) of **9b** as a white solid. Recrystallization from a mixture of $CHCl_3$ and hexane gave **9b** as colorless needles: mp 162–163 °C; IR ($CHCl_3$) 1675 (C=O) and 1680 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.16 (s, 3, CH_3), 3.38 (d, 1) and 3.80 (d, 1) (AB system, J = 12 Hz, CH_2), 7.3–7.7 (m, 6, aromatic H); mass spectrum, *m/e* 443 (M^+). Anal. ($C_{16}H_{11}BrCl_3NO_2$) C, H, N.

2-Azido-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-methylacetamide (12b). A mixture of **9b** (4.5 g, 10.3 mmol) and sodium azide (4.5 g, 82 mmol) in DMF (100 mL) was stirred at room temperature for 4 h. The mixture was diluted with water (1000 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a brown solid. Recrystallization from a mixture of $CHCl_3$ and hexane gave 4.0 g (91%) of **12b** as colorless needles: mp 137–138 °C; IR ($CHCl_3$) 2100 (N_3), 1680 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.23 (s, 3, CH_3), 3.64 (m, 2, CH_2), 7.2–7.8 (m, 6, aromatic H); mass spectrum, *m/e* 396 (M^+). Anal. ($C_{16}H_{11}Cl_3N_4O_2$) C, H, N.

2-[[4-Chloro-2-(2,6-dichlorobenzoyl)phenyl]amino]-*N*-methylacetamide (11). A solution of **9b** (2.55 g, 5.7 mmol) in THF (25 mL) which was saturated with ammonia was stirred at room temperature for 4 h. The resulting precipitate was removed by filtration, and the THF was removed in vacuo to give 2.1 g (100%) of **11** as a yellow solid. Recrystallization from a mixture of CH_2Cl_2 and hexane gave **11** as yellow needles: mp 221–222 °C; IR 3435, 3330, (NH), 1674 (ketone C=O), 1640, (amide C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.33 (d, J = 5 Hz, 3, CH_3), 3.99 (d, J = 6 Hz, 2, CH_2), 6.4 (br s, 1, NH), 6.65 (d, J = 10 Hz, 1, aromatic H), 7.1–7.5 (m, 5, aromatic H), 9.12 (br s, 1, NH); mass spectrum, *m/e* 370 (M^+). Anal. ($C_{10}H_{13}Cl_3N_2O_2$) C, H, N.

2-Amido-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-methylacetamide Hydrochloride Hemihydrate (10b). A mixture of **12b** (4.0 g, 10 mmol), platinum oxide (0.1 g), and concentrated hydrochloric acid (5 mL, 60 mmol) in EtOH (300 mL) was hydrogenated at atmospheric pressure for 3 h. The platinum was removed by filtration, and the EtOH removed in vacuo to give a pale yellow solid. Recrystallization from a mixture of EtOH and Et_2O gave 3.9 g (94%) of **10b** as fine white needles: mp 168–175 °C; IR (KBr) 1675 (C=O) cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 3.23 (s, 3, CH_3), 3.18 (d, 1) and 3.60 (d, 1) (AB system, J = 16 Hz, CH_2), 7.6–8.1 (m, 6, aromatic H), and 8.6 (br s, 4, NH_3^+, $0.5H_2O$). Anal. ($C_{16}H_{14}Cl_4N_2O_2{\cdot}0.5H_2O$) C, H, N.

2-Bromo-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-(phenylmethyl)acetamide (9c). A solution of **4c** (4.5 g, 11.5 mmol) and bromoacetyl bromide (3.0 mL, 34 mmol) in Et_2O (200 mL) was stirred at room temperature for 20 min. Pyridine (3.0 mL, 37 mmol) was added, and the resulting mixture was stirred for 2 h. The mixture was washed with water, saturated aqueous $NaHCO_3$, and water. The Et_2O solution was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to give 5.9 g (100%) of **9c** as colorless needles: mp 155–156 °C; IR ($CHCl_3$) 1685 (amide C=O), 1675 (ketone C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.55 (d, 1) and 3.76 (d, 1) (AB system, J = 11 Hz, CH_2Br), 3.95 (d, 1) and 5.71 (d, 1) (AB system, J = 14 Hz, $PhCH_2$), 6.8–7.6 (m, 11, aromatic H); mass spectrum, m/e 430 (M^+ – Br). Anal. ($C_{22}H_{15}BrCl_3NO_2$) C, H, N.

2-Azido-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-(phenylmethyl)acetamide (12c). A mixture of **9c** (5.2 g, 10 mmol) and sodium azide (6.0 g, 92 mmol) in Me_2SO (100 mL) was stirred at room temperature for 12 h. The mixture was diluted with water (500 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to dryness. The residue was triturated with a mixture of Et_2O and petroleum ether to give 4.5 g (95%) of **12c** as a tan solid. Recrystallization from a mixture of Et_2O and CH_2Cl_2 gave **12c** as colorless prisms: mp 169–170 °C; IR ($CHCl_3$) 2105 (N_3), 1683 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.44 (d, 1) and 3.72 (d, 1) (AB system, J = 16 Hz, CH_2N_3), 3.94 (d, 1) and 5.75 (d, 1) (AB system, J = 14 Hz, $PhCH_2$), 6.72 (d, J = 8 Hz, 1, aromatic H), 7.1–7.6 (m, 10, aromatic H); mass spectrum, m/e 444 (M^+ – N_2). Anal. ($C_{22}H_{15}Cl_3N_4O_2$) C, H, N.

2-Amino-*N*-[4-chloro-2-(2,6-dichlorobenzoyl)phenyl]-*N*-(phenylmethyl)acetamide Hydrochloride (10c). A mixture of **12c** (2.0 g, 4.2 mmol), platinum oxide (100 mg), 6% methanolic hydrogen chloride (5 mL), THF (30 mL) and ethanol (100 mL) was hydrogenated at room temperature and atmospheric pressure for 4 h. The platinum was removed by filtration, and the solvents were removed in vacuo to dryness. Trituration of the residue with Et_2O gave 1.9 g (93%) of a colorless solid. Recrystallization from a mixture of Et_2O and 2-propanol gave **10c** as fine colorless needles: mp 236–237 °C; IR (KBr) 2930, 2880 (NH_3^+), 1680 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.11 (d, 1) and 3.59 (d, 1) (AB system, J = 16 Hz, CH_2C=O), 4.08 (d, 1) and 5.16 (d, 1) (AB system, J = 15 Hz, $PhCH_2$), 7.2–7.9 (m, 11, aromatic H), 8.56 (br s, 3, NH_3^+). Anal. ($C_{22}H_{18}Cl_4N_2O_2$) C, H. N.

7-Chloro-5-(2,6-dichlorophenyl)-1-(phenylmethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (13c). A solution of **10c** (from 1.6 g, 3.3 mmol of the HCl salt) and pivalic acid (3.0 g, 33 mmol) in toluene (500 mL) was refluxed for 12 h. The solution was cooled, washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to dryness. The residue was triturated with Et_2O to give 1.1 g (78%) of **13c** as a colorless solid. Recrystallization from a mixture of CH_2Cl_2 and Et_2O gave **13c** as colorless needles: mp 206–207 °C; IR ($CHCl_3$) 1683 (C=O) and 1628 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 4.06 (br s, 1, C_3 H), 4.95 (br s, 2, C_3 H, PhCH), 5.27 (br s, 1, PhCH), 7.09 (d, J = 2 Hz, 1, aromatic H), 7.1–7.4 (m, 10, aromatic H); mass spectrum, m/e 428 (M^+). Anal. ($C_{22}H_{15}Cl_3N_2O$) C, H, N.

spectrum, m/e 428 (M^+). Anal. ($C_{22}H_{15}Cl_3N_2O$) C, H, N.

7-Chloro-5-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (13a). A mixture of **13c** (1.5 g, 3.5 mmol), water (0.5 mL), and sulfuric acid (15 mL) was heated to 100 °C for 1 h. The mixture was cooled, poured over ice, basified with concentrated aqueous NH_4OH solution, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 1.0 g of a light-yellow solid. Purification by column chromatography (SiO_2, 20 g; 9:1, CH_2Cl_2/Et_2O) gave 0.6 g (51%) of **13a** as a colorless solid. Recrystallization from a mixture of Et_2O and CH_2Cl_2 gave **13a** as colorless prisms: mp 231–233 °C; IR (KBr) 3210, 3110 (NH), 1683 (C=O), 1626 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 4.47 (s, 2, CH_2), 7.1–7.6 (m, 6, aromatic H), 9.98 (s, 1, NH); mass spectrum, m/e 338 (M^+). Anal. ($C_{15}H_9Cl_3N_2O$) C, H, N.

[[[5-Chloro-2-(methylamino)phenyl](2,6-dichlorophenyl)methylene]amino]acetic Acid (14). A solution of **13b**[6] (2.0 g, 5.6 mmol), 3 N aqueous NaOH solution (100 mL), and methanol (75 mL) was refluxed for 4 h. The mixture was cooled, acidified to pH 6 with 3 N aqueous hydrochloric acid, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 2.1 g (100%) of **14** as an amorphous yellow solid: mp 165–166 °C dec; IR ($CHCl_3$) 3200 (OH, NH), 1760 and 1725 (C=O) cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 2.98 (s, 3, CH_3), 3.94 (s, 2, CH_2), 6.6–6.8 (m, 2, aromatic H), 7.1–7.5 (m, 4, aromatic H), 10.12 (br s, 2, NH, OH); mass spectrum, m/e 370 (M^+). Anal. ($C_{16}H_{13}N_2O_2$) C, H, N.

7-Chloro-5-(2,6-dichlorophenyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (13b). A solution of **14** (1.0 g, 2.7 mmol) in 3 N aqueous hydrochloric acid (100 mL) was refluxed for 1 h. The solution was cooled, neutralized with Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 0.9 g (95%) of **13b** as a white solid. Recrystallization from a mixture of Et_2O and petroleum ether gave **13b** as fine colorless plates, mp 160–161 °C, identical in every respect with authentic sample.[6]

2-Amino-*N*-(2-benzoyl-4-chlorophenyl)-*N*-methylacetamide Hydrochloride (15). A mixture of 2-azido-4′-chloro-2-benzyl-*N*-methylacetanilide[9] (4 g, 12 mmol), prehydrogenated platinum oxide (0.3 g), and concentrated hydrochloric acid (10 mL) in ethanol (200 mL) was hydrogenated at room temperature and atmospheric pressure for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to dryness. The residue was crystallized from a mixture of 2-propanol and ether to give 1.7 g (mp 159–161 °C dec, 41%) of the salt as a hygroscopic solid: IR (KBr) 2930 (NH_3^+), 1694 (amide C=O) 1674 (ketone C=O) cm^{-1}. Anal. ($C_{16}H_{15}ClN_2O_2$·HCl) C, H, N.

Acknowledgment. The authors thank Dr. H. Möhler, F. Hoffmann-La Roche and Co., Basle, Switzerland, for the [^{3}H]diazepam binding assay data, Dr. W. Dairman and Mrs. B. Kappell, Department of Toxicology for the antimetrazole data, and the staff of the Physical Chemistry Department of Hoffmann-La Roche, Inc., for spectral and microanalytical data.