concentration of 0.2 nM using 10 μM (+)-butaclamol to determine nonspecific binding. IC_{50} values were determined by linear regression analysis with three to five concentrations of each compound assayed in triplicate. Results are expressed as the mean IC_{50} for three to five separate observations.

Contralateral Turning in 6-Hydroxydopamine-Lesioned Rats. In the anesthetized female Sprague–Dawley rat, weighing 140–170 g, 6-hydroxydopamine (8 μg/4 μL of 0.9% saline) was infused into the substantia nigra over a 4-min period with a Sage syringe pump. The 30-gauge injection needle was stereotaxically positioned rostral to the right substantia nigra with coordinates derived from König and Klippel.[16] One and two weeks after surgery, each rat was given apomorphine (1 mg/kg ip), and it was observed for contralateral turning, a sign of CNS dopamine receptor activation. Each rat that did turn was added to a colony that was used not more than once a week. With a random and blind design, three to eight doses of each compound were given ip to six rats housed three per cage. The presence or absence of contraversive turning was ascertained at 0.5 h after dosing. ED_{50} values and the 95% confidence limits were determined using log probit analysis.[17]

Acknowledgment. The authors are indebted to Mr. J. P. Moreau for chemical analysis, Dr. D. W. Cochran and Ms. J. S. Murphy for spectral data, and Ms. T. H. Brunner for manuscript preparation.

Registry No. (±)-1, 84057-01-2; (±)-**2**, 84056-98-4; (±)-**3**, 77291-60-2; (±)-4, 77306-59-3; (±)-**5**, 77291-61-3; (±)-**6a**, 77306-60-6; (±)-**6b**, 77291-64-6; (−)-**6b**, 81244-91-9; (+)-**6b** di-*p*-toluoyl-*l*-tartaric acid salt, 84064-66-4; (−)-**6b** di-*p*-toluoyl-*d*-tartaric acid salt, 84057-00-1; (±)-**6c**, 77291-65-7; (±)-**6d**, 77291-66-8; (±)-**6e**, 84056-99-5; (±)-**9**, 81274-84-2; chloroacetyl chloride, 79-04-9; dopamine, 51-61-6; $CH_3CH{=}CH_2Br$, 106-95-6; CH_3CHO, 75-07-0; CH_3CH_2CHO, 123-38-6; $CH_3(CH_2)_2CHO$, 123-72-8; $CH_3(CH_2)_3CHO$, 110-62-3.

Supplementary Material Available: Tables I, II, and III containing fractional unit cell coordinates, bond lengths, and bond angles and a figure showing the crystallographic numbering system for (−)-**6b** and di-*p*-toluoyl-*d*-tartaric acid (5 pages). Ordering information is given on any current masthead page.

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2-Benzazepines. 4.[1,2] [1,2,3]Triazolo[4,5-*d*][2]benzazepines and Dibenzo[*c*,*f*][1,2,3]triazolo[3,4-*a*]azepines: Synthesis and Evaluation as Central Nervous System Agents

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The facile synthesis of [1,2,3]triazolo[4,5-*d*][2]benzazepines and dibenzo[*c*,*f*][1,2,3]triazolo[3,4-*a*]azepines by the addition of sodium azide to acetylenic benzophenones is described. Examination of the pharmacological data indicates that selected triazolobenzazepines are as potent as diazepam in the anti-pentylenetetrazole test and are weaker in the inclined screen and rotarod tests, suggesting that these compounds have antianxiety properties similar to diazepam with fewer deficits in motor coordination. In addition, a possible diazepam antagonist was found in the triazolobenzazepine series. The dibenzotriazoloazepines were found to be inactive in four standard CNS screening procedures.

The 1,4-benzodiazepine ring system has been extensively explored in CNS drug research, especially in the search for new antianxiety agents.[3] The 2-benzazepine ring system, a carbon isostere of a 1,4-benzodiazepine, has received much less attention in this area[4] but has been investigated for other therapeutic uses.[5] As part of our continuing program to develop novel heterocyclic systems of therapeutic benefit in the CNS area, we have investigated the synthesis and the biological activity of 4,5-heteroring-fused 2-benzazepines. In this report we describe the facile synthesis and some of the pharmacological activities of triazolobenzazepines and the related dibenzotriazoloazepines.

Chemistry. The readily available acetylenic benzophenones **1**, whose preparation has been previously described,[6] provided a convenient starting point for the synthesis of these ring systems, as shown in Scheme I. Treatment of **1a–e** with sodium azide in warm dimethyl sulfoxide containing acetic acid resulted in the formation of the triazoles **2a–e**.[7] Removal of the phthaloyl group from **2a–e** with 40% aqueous methylamine in ethanol generated the opened derivatives **3a–e**, which spontaneously ring closed to the desired triazolobenzazepines **4a–e**,[7] respectively.

When the benzophenone was substituted in the ortho position with a halogen atom, the sodium azide addition to the acetylene required the use of at least 1 equiv of acetic acid or a similar proton source. In the absence of acetic acid the initially formed triazole anion displaced the

(1) Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.

(2) For previous paper, see Gilman, N. W. *Synth. Commun.* **1982**, *12*, 373.

(3) (a) Sternbach, L. H. "The Benzodiazepines"; Garattini, S.; Mussini, E.; Randall, L. O. Eds.; Raven Press: New York, 1973, pp 1–26. (b) Gschwend, H. W. "Anxiolytics"; Fielding, S.; Lal, H., Eds.; Futura: Mt. Kisco, NY., 1979; pp 1–40.

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(5) (a) Wittekind, R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8* 495. (b) Loer, B. U.S. Patent 3686165, 1972. (c) Shtacher, G.; Erez, M.; Cohen, S. *J. Med. Chem.* **1973**, *16*, 516. (d) Sawa, Y.; Kato, T.; Masuda, T.; Hori, M.; Fujimura, H. *Chem. Pharm. Bull.* **1975**, *23*, 1927.

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(7) The position of the triazolo hydrogen was arbitrarily assigned to the 2-position For the conversion of **2b** into **5**, the anion must be on the 3-position of the triazole ring.

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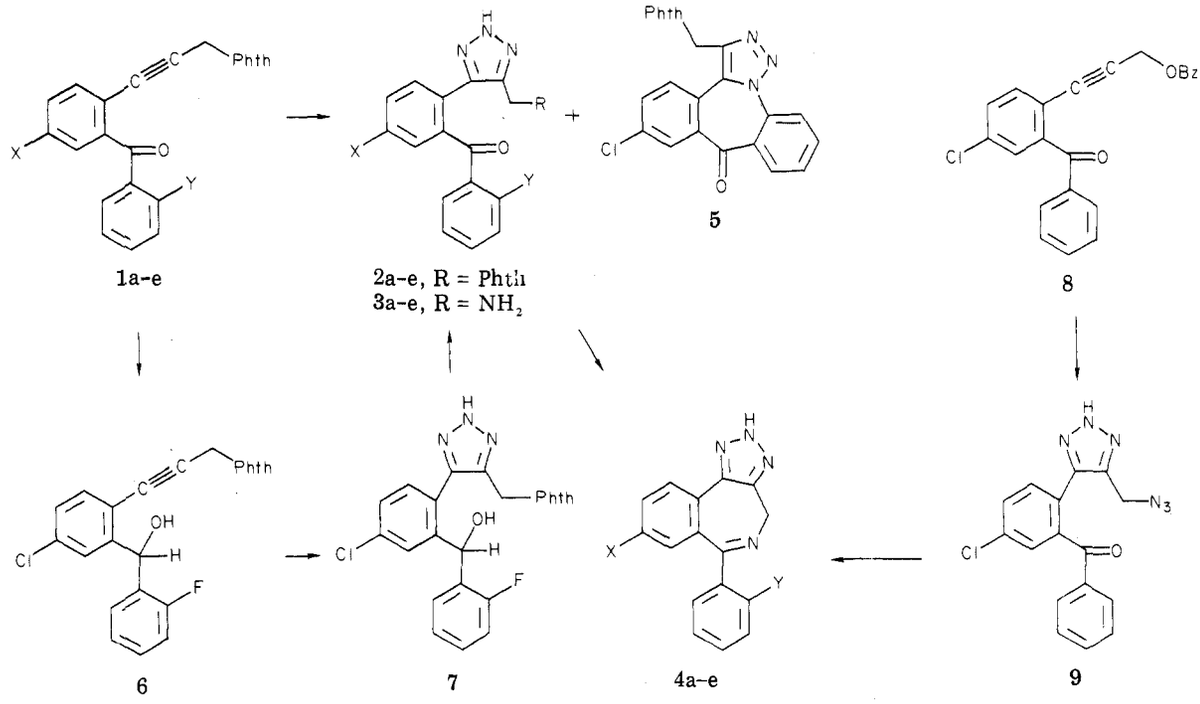
Scheme I[a]



[a] a: X = Cl; Y = H. b: X = Cl; Y = F. c: X = Y = Cl. d: X = H; Y = Cl. e: X = Y = H.

ortho halogen[8] and resulted in the formation of the triazolodibenzazepine **5**. The use of acetic acid allowed protonation of the initially formed anion, and the resulting triazole, a weaker nucleophile, was less likely to displace the halogen. This method worked well where the ortho substituent was chlorine (e.g., **2c** and **2d**). The displacement of fluorine in **2b** could not be satisfactorily suppressed with acetic acid; thus, it was necessary to deactivate the carbon atom bearing fluorine by reduction of the carbonyl group to give the benzhydrol **6**. Reaction of **6** with sodium azide and acetic acid in dimethyl sulfoxide gave the triazole **7**. Oxidation of **7** with Jones reagent[9] gave **2b**.

An alternate procedure for the synthesis of **4a** utilized the reaction of sodium azide with the benzoate **8**. By this method, not only was the triazole ring formed but also azide ion displaced the benzoate group in **8**, resulting in the triazolo azide **9**. Hydrogenation of **9** with Raney nickel as catalyst gave the amino compound **3a**, which cyclized in situ to the triazolobenzazepine **4a**.

The displacement of fluoride ion and the formation of the triazolodibenzazepines also occurred in this sequence of reactions and was not affected by the use of acetic acid. In addition, the complete conversion of benzoate into azide in the formation of the triazolodibenzazepine was not attained. Since the conversion of **1** into the desired triazolobenzazepine or triazolodibenzazepine was straightforward, this method was not pursued further.

In the absence of a proton source, the reaction of **1b** with sodium azide provided a facile synthetic entry into the dibenzotriazoloazepine ring system. Structurally this ring system resembles the tricyclic antidepressants and/or neuroleptics in which there is a 6-7-6 tricyclic ring system with a basic side chain attached to the seven-membered ring.[10] In order to evaluate these novel tetracyclic derivatives as potential CNS agents, we synthesized a limited number of analogues (Scheme II) in which the 1-position of the triazole ring was substituted with a basic side chain.

Reaction of sodium azide with **1b** in dimethyl sulfoxide at 100 °C gave excellent yields of the triazolodibenzazepine **5**. Removal of the phthaloyl group from **5** with 40% aqueous methylamine in ethanol yielded the amino compound **10**. Methylation of **10** by the Eschweiler–Clark[11] procedure gave the corresponding dimethylamino derivative **11**.

Addition of sodium azide to the acetylenic benzophenones **12** and **13** in dimethyl sulfoxide at 100 °C gave, after treatment of the reaction mixture with aqueous hydrochloric acid, the corresponding alcohols **14** and **15**. Oxidation of **14** with Jones reagent[9] led to the carboxylic acid **16**. Treatment of **16** with phosphorous pentachloride, followed by *N*-methylpiperazine, gave the amide **17**. Reduction of **17** with lithium aluminum hydride gave **18**, whereas reduction of **17** with sodium borohydride gave **19**.

Treatment of the alcohol **15** with methanesulfonyl chloride in the presence of triethylamine gave the mesylate **20**, which was subsequently treated with methylamine to yield **21**. Methylation of **21** by the Eschweiler–Clark procedure[11] gave the dimethylamino derivative **22**. Reduction of the ketones in **21** and **22** with sodium borohydride gave the corresponding alcohols **23** and **24**.

Results and Discussion

The triazolobenzazepines **4a–e** were evaluated for their antianxiety properties by the anti-pentylenetetrazole test.[12] Compounds active in the anti-pentylenetetrazole test

(8) For an example of fluoride displacement, see Walser, A.; Flynn, T.; Fryer, R. I. *J. Heterocycl. Chem.* **1975**, *12*, 737.
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Table I. Triazolobenzophenones[a]

no.	X	Y	reaction time, h	reaction temp, °C	mp, °C	yield, %	formula	anal.
2a	Cl	H	90	72	135-137	57	$C_{24}H_{15}ClN_4O_3$	C, H, N
2b	Cl	F	48	50	147-148[b]	26	$C_{24}H_{14}ClFN_4O_3 \cdot 0.65CH_2Cl_2$	C, H, N
2c	Cl	Cl	48	50	186-187	63	$C_{24}H_{14}Cl_2N_4O_3$	C, H, N
2d	H	Cl	24	90	105-106[b]	47	$C_{24}H_{15}ClN_4O_3 \cdot 0.9CH_2Cl_2$	C, H, N
2e	H	H	60	90	204-205	66	$C_{24}H_{16}N_4O_3$	C, H, N

[a] Compounds were prepared by the procedure for synthesis of 2c described under Experimental Section. [b] Compound foams at the melting point.

Table II. Triazolobenzazepines[a]

no.	X	Y	mp, °C	yield, %	formula	anal.
4a	Cl	H	199-200	60	$C_{16}H_{11}ClN_4$	C, H, N
4b	Cl	F	192-193	88	$C_{16}H_{10}ClFN_4$	C, H, N
4c	Cl	Cl	176-177	76	$C_{16}H_{10}Cl_2N_4$	C, H, N
4d	H	Cl	191-193	60	$C_{16}H_{11}ClN_4$	C, H, N
4e	H	H	205-207	91	$C_{16}H_{12}N_4$	C, H, N

[a] Compounds were prepared by the procedure for the synthesis of 4c described under Experimental Section.

(**4a–e**) were further tested in the rotarod[13] and inclined screen[14] procedures. In addition, the compounds were tested in vitro in the [^{3}H]diazepam binding assay as described by Mohler.[15] Table III lists the results of these tests, the toxicity data for **4a–e**, and the corresponding data for diazepam.

The triazolobenzazepines follow the well-established structure–activity relationships of the benzodiazepines in the anti-pentylenetetrazole test. Substitution of a halogen atom at the ortho position of the 6-phenyl substituent increased the activity (compounds **4b,c**) whereas removal of the halogen substituent from the 8-position (compounds **4d,e**) greatly diminished the activity.

The discovery of the benzodiazepine receptor sites[15] and the development of the [^{3}H]diazepam binding assay have greatly facilitated the search for new anxiolytic agents. Since this discovery, the description of antagonists and partial agonists of the receptor sites has been reported.[16]

The assay procedure in its most simple form, however, does not distinguish between agonists and antagonists,[17] since the assay only quantitates a compound's ability to displace radiolabeled diazepam from the receptor sites and, presumably, its ability to bind to the same receptor sites. The agonist or antagonist profile of a compound that has been found active in the [^{3}H]diazepam binding assay can, however, be roughly determined by comparison of these results with data obtained from an in vivo screening procedure. For preliminary work we have used the anti-pentylenetetrazole test as our in vivo screening procedure.[12] The triazolobenzazepines **4a–c** are potent in the [^{3}H]diazepam binding assay, which parallels their activity in the anti-pentylenetetrazole test. Compound **4d**, which lacks a chlorine in the 8-position, however, was unexpectedly potent in the [^{3}H]diazepam binding assay, yet inactive in the anti-pentylenetetrazole test. These results suggest that **4d** will have antagonist-type properties and **4a–c** will have diazepam agonist like activity.

The dibenzotriazoloazepines, on the other hand, were found to be inactive in a number of CNS screens, including [^{3}H]diazepam binding (IC_{50} > 1000 nM), anti-pentylenetetrazole (ED_{50} > 60 mg/kg), rotarod (ED_{50} > 100 mg/kg), and tetrabenezine ptosis (ED_{50} > 100 mg/kg, po).[18]

In summary, the triazolobenzazepines represent a novel series of compounds that resemble diazepam in their activity in the anti-pentylenetetrazole test and are weaker than diazepam in the rotarod and inclined screen procedures. The possible antagonist properties of compound **4d** have been noted, and a more detailed description of **4d** and other antagonist-like 2-benzazepines will be the subject of forthcoming reports.

The dibenzotriazoloazepines despite their tricyclic structure were found to be inactive in a series of standard CNS screening procedures.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were determined on a Beckmann IR-9 or a Perkin-Elmer 621 grating spectrometer; mass spectra were determined on a CEC-21-100 instrument, and NMR spectra were recorded on either a Varian A-60 or HA-100 spectrometer, with tetramethylsilane as a standard. Merck silica gel 60, 70–230 mesh, was used for all column chromatography separations. Anhydrous sodium sulfate was used for drying of organic solutions.

4-[4-Chloro-2-(2-chlorobenzoyl)phenyl]-5-(*N*-phthalimidomethyl)-2*H*-1,2,3-triazole (2c). A mixture of 6.8 g (15.6 mmol) of **1c**,[6] 5.0 g (85 mmol) of sodium azide, 1.0 mL (17 mmol) of acetic acid, and 75 mL of Me_2SO was heated to 50 °C for 48 h. The mixture was cooled, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried, and concentrated in vacuo to give 6.5 g of a yellow foam. Purification by column chromatography (eluent CH_2Cl_2 to 5% ether in CH_2Cl_2 gradient) gave 4.7 g (63%) of **2c** as colorless prisms: mp 186–187 °C; IR (KBr) 3300 (N-H), 1773 and 1710 (C=O) and 1660 (C=O) cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6) δ 4.82 (s, 2, CH_2), 7.1–7.9 (m, 11, arom H), 14.00 (br s, 1, N-H); mass spectrum, *m/e* 476 (M^+). Anal. ($C_{24}H_{14}Cl_2N_4O_3$) C, H, N.

8-Chloro-6-(2-chlorophenyl)-2*H*,4*H*-[1,2,3]triazolo[4,5-*d*][2]benzazepine (4c). A mixture of 4.7 g (10 mmol) of **2c** and 10 mL of 40% aqueous methylamine in 50 mL of ethanol was stirred at room temperature for 12 h. The mixture was concentrated in vacuo, and the residue was triturated with a 1:2 mixture of CH_2Cl_2 and ether. The filtrate was washed with water, dried, and concentrated in vacuo to give 2.0 g (60%) of **4c** after crystallization from ether. A sample was recrystallized from a mixture of ether and CH_2Cl_2 to give **4c** as colorless prisms: mp 176–177 °C; IR ($CHCl_3$) 3435 (N-H) and 1620 (C=N) cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6) δ 4.86 (s, 2, CH_2), 7.1–8.0 (m, 8, arom H and N-H); mass spectrum, *m/e* 328 (M^+). Anal. ($C_{16}H_{10}Cl_2N_4$) C, H, N.

The methanesulfonate salt of **4c** was prepared by the addition of equimolar amounts of **4c** and methanesulfonic acid to methanol,

(13) Dunham, N. W.; Miya, T. S. *J. Pharm. Sci.* **1957**, *46*, 208.
(14) Randall, L. O.; Schallek, W.; Heise, G. A.; Keith, E. F.; Bagdon, R. E. *J. Pharmacol. Exp. Ther.* **1960**, *129*, 163.
(15) (a) Mohler, H.; Okada, T. *Life Sci.* **1977**, *20*, 2101. (b) Squires, R. F.; Braestrup, C. *Science* **1977**, *198*, 849.
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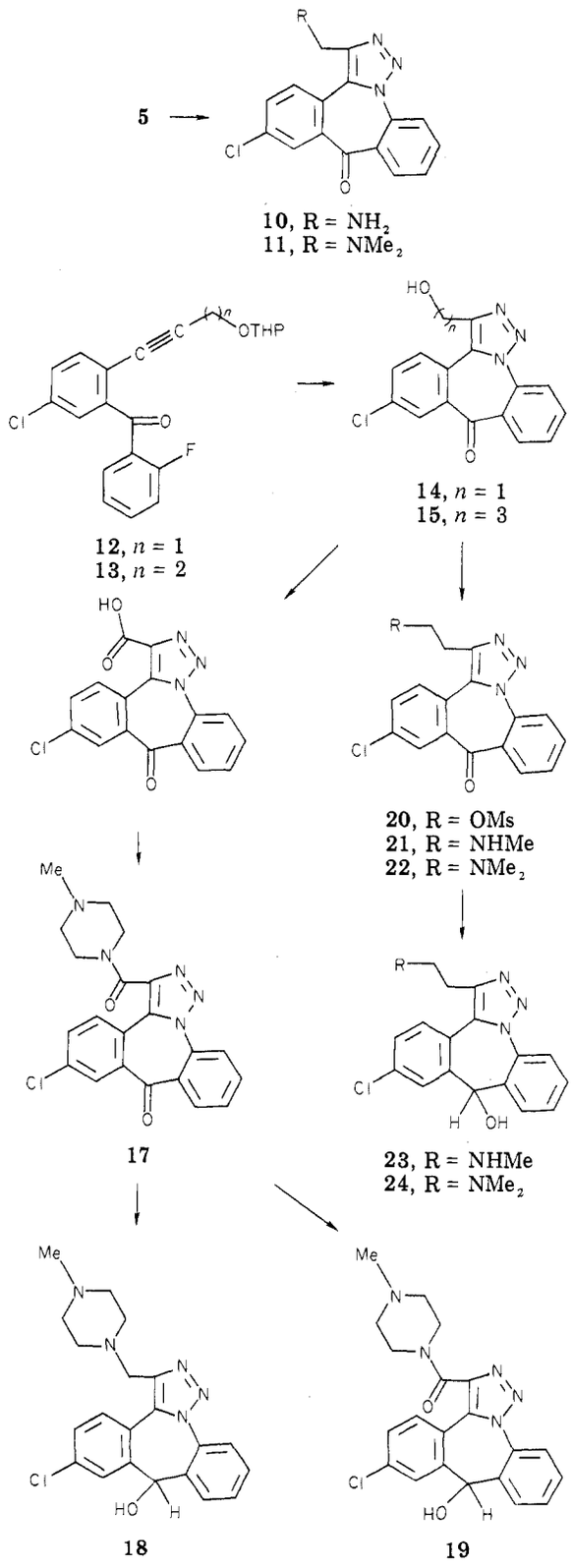
(17) For description of an in vitro assay to distinguish agonists from antagonists, see Mohler, H.; Richards, J. G. *Nature (London)* **1981**, *294*, 763.

(18) A number of the dibenzotriazoloazepines were active (IC_{50} = 11–660 μM) in an [^{3}H]imipramine binding assay. However, the interpretation of these findings is not clear.

Scheme II



and it was isolated by precipitation of the salt by the addition of ether. Recrystallization from a mixture of methanol and ether gave the methanesulfonate salt of **4c** as yellow prisms: mp 326–327 °C; IR (KBr) 2400–2850 (N-H), and 1642 (C=N) cm^{-1}; NMR (Me_2SO-d_6) δ 2.46 (s, 3, CH_3), 4.78 (s, 2, CH_2), 7.08 (d, J = 2 Hz, 1, arom H), 7.3–8.1 (m, 8, arom H and 2 N-H). Anal. ($C_{17}H_{14}Cl_2N_4O_3S$) C, H, N.

11-Chloro-1-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9(9*H*)-one (5). A mixture of 30 g (72 mmol) of **1b** and 12 g (184 mmol) of sodium azide in 500 mL of Me_2SO was heated to 80 °C for 6 h. The mixture was cooled and diluted with water, and the resulting precipitate was collected by filtration. The precipitate was washed with water and when air-dried to constant weight gave 27 g (81%, mp 247–252) of **5** as an off-white solid. Recrystallization of a small sample from $CHCl_3$ gave **5** as colorless crystals: mp 252–253 °C; IR ($CHCl_3$) 1773, 1720 (C=O) and 1673 (C=O) cm^{-1}; NMR (Me_2SO-d_6, TFA) δ 5.13 (s, 2, CH_2), 7.6–8.3 (m, 11, arom H); mass spectrum, m/e 440 (M^+). Anal. ($C_{24}H_{13}ClN_4O_3$) C, H, N.

4-[4-Chloro-2-[(2-fluorophenyl)hydroxymethyl]-phenyl]-5-(*N*-phthalimidomethyl)-2*H*-1,2,3-triazole (7). A mixture of 1.5 g (3.5 mmol) of **6**,[19] 1.0 g (30 mmol) of sodium azide, and 0.4 mL (6.6 mmol) of acetic acid in 30 mL of Me_2SO was heated in an oil bath to 90 °C for 4 days. The mixture was cooled and diluted with water, and the resulting precipitate was collected by filtration to give 1.3 g of **7** as a yellow solid. A sample of the yellow solid was recrystallized from ether to give **7** as off-white prisms: mp 160–162 °C; IR ($CHCl_3$) 3500 (OH), 3430 (NH), 1772, 1718 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.77 (s, 2, CH_2), 5.88 (s, 1, CHOH), 6.6–7.9 (m, 11, arom H), 13.30 (br s, 1, NH); mass spectrum, m/e 462 (M^+). Anal. ($C_{24}H_{16}ClFN_4O$) C, H, N.

4-[4-Chloro-2-(2-fluorobenzoyl)phenyl]-5-[*N*-phthalimidomethyl]-2*H*-1,2,3-triazole (2b). A solution of 2.66 M Jones reagent (**5** mL, 13.3 mmol) was added dropwise to a solution of 1.0 g (2.1 mmol) of **7** in 20 mL of acetone. The mixture was stirred at room temperature for 1 h, and the excess Jones reagent was discharged by the addition of 2-propanol. The acetone solution was decanted and concentrated at reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, and dried. Concentration of the CH_2Cl_2 solution in vacuo and trituration of the residue with ether gave 0.6 g (60%) of **2b** as pale yellow crystals. Recrystallization from a mixture of CH_2Cl_2 and ether gave **2b** as light-sensitive prisms: mp 147–148 °C (foams); IR ($CHCl_3$) 3240 (N-H), 1773, 1710 (imide C=O), and 1663 (ketone C=O) cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 4.86 (s, 2, CH_2), 5.23 (s, CH_2Cl_2), 6.8–7.8 (m, 12, arom H); mass spectrum, m/e 460 (M^+). Anal. ($C_{24}H_{14}ClFN_4O_3 \cdot 0.65CH_2Cl_2$) C, H, N.

3-(Benzoyloxy)-1-(2-benzoyl-4-chlorophenyl)propyne (8). A mixture of 10.1 g (36 mmol) of 3-(2-benzoyl-4-chlorophenyl)-1-hydroxy-2-propyne,[20] 13 g (57 mmol) of benzoic anhydride, 13 mL (160 mmol) of pyridine, and 50 mg of 4-(dimethylamino)pyridine in 250 mL of CH_2Cl_2 was stirred at room temperature for 24 h. The CH_2Cl_2 solution was washed with aqueous $CuSO_4$ and water, dried, and concentrated in vacuo to give 10 g of a brown oil. Trituration of the oil with a mixture of ether and petroleum ether gave 5.8 g (36%) of **8** as a colorless solid. A sample was recrystallized from ether to give **8** as colorless crystals: mp 66–67 °C; IR ($CHCl_3$) 1725 (C=O), 1668 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.82 (s, 2, CH_2), 7.3–8.1 (m, 13, arom H); mass spectrum, m/e 374 (M^+). Anal. ($C_{23}H_{15}ClO_4$) C, H, N.

4-(Azidomethyl)-5-(2-benzoyl-4-chlorophenyl)-2*H*-1,2,3-triazole (9). A mixture of 5.9 g (16 mmol) of **8**, 5.2 g (80 mmol) of sodium azide, and 210 mL of DMF was heated in an oil bath to 80–90 °C for 30 h. After cooling, the mixture was poured into 520 mL of ice–water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried, and concentrated in vacuo. The residual oil was crystallized from a mixture of CH_2Cl_2 and hexane to give 2.4 g (45%) of **9** as light tan crystals. Recrystallization from a mixture of CH_2Cl_2 and hexane gave **9** as off-white crystals: mp 128–131 °C; IR ($CHCl_3$) 3435 (N-H), 2105 (N_3), 1668 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.37 (s, 2, CH_2), 7.25 (m, 9, arom H and NH). Anal. ($C_{16}H_{11}ClN_6O$) C, H, N.

8-Chloro-6-phenyl-2*H*,4*H*-[1,2,3]triazolo[4,5-*d*][2]benzazepine (4a). A mixture of 3 g (8.9 mmol) of **9** and 3 teaspoonfuls of Raney nickel in 150 mL of ethanol was hydrogenated in a Parr apparatus at 5 psi for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give 2 g of a gummy solid. Purification of the residue by column chromatography (eluent, 1:1 CH_2Cl_2–ethyl acetate) gave as the major component 0.7 g of **4a** as colorless crystals. Recrystallization from a mixture of ethyl acetate and petroleum ether gave **4a** as colorless prisms:

(19) Prepared from the corresponding iodobenzhydrol by an adaptation of the preparation of **1b**,[6] mp 158–160 °C.

(20) Prepared from the corresponding iodobenzophenone by an adaptation of the preparation of **1a**,[6] mp 79–80 °C.

Table III. Pharmacological Activity of Triazolobenzazepines

compd	IC_{50}, nM: [^{3}H]diazepam binding[a] (rat)	ED_{50}, mg/kg, po: antipentylenetetrazole[b,c] (mice)	rotarod[c,d] (mice)	inclined screen[c,e] (mice)	LD_{50}, mg/kg, po (mice)
4a	11	4.2	26	>400	>1000
4b	0.76	2.1	48	302	>1000
4c	0.76	2.6	57	>400	>1000
4d	5.2	>100			900
4e	420	>100			775
diazepam	5.4	1.4	2.6	25	710

[a] The conditions of Mohler and Okada[15a] were used for this assay procedure. [b] The test was carried out on 50–54 day old CF-1 male mice by a modification of the method of Everett and Richards.[12b] The ED_{50} is 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. [c] Results are reported as 95% fiducial limits. [d] The conditions of Randall were used in this procedure.[13] [e] The conditions of Dunham were used in this procedure.

mp 203–208 °C; IR ($CHCl_3$) 3200 (NH), 1612 (C=N) cm^{-1}; NMR (Me_2SO-d_6, $CHCl_3$) δ 3.1 (s, 1, NH), 4.83 (s, 2, C_4 H), 7.2–8.1 (m, 8, arom H); mass spectrum, *m/e* 294 (M^+). Anal. ($C_{16}H_{11}ClN_4$) C, H, N.

1-(Aminomethyl)-11-chlorodibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9(9*H*)-one Hydrochloride (10). A mixture of 27 g (61 mmol) of **5** and 50 mL of 40% aqueous methylamine in 500 mL of ethanol was stirred for 12 h. The solvent was removed in vacuo and the residue was dissolved in a mixture of ether and CH_2Cl_2. The organic solution was washed with water, dried, and concentrated in vacuo to a yellow glass. The glass was dissolved in an excess of 6% methanolic HCl, and the resulting salt was precipitated by the addition of ether to give 21 g (98%) of **10** as a light yellow solid. Recrystallization from a mixture of methanol and ether gave **10** as colorless needles: mp 265–268 °C; IR (KBr) 3050–2640 (NH_3^+) and 1665 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 4.35 (s, 2, CH_2), 7.5–8.2 (m, 7, arom H), 8.94 (br s, 3, NH_3^+). Anal. ($C_{16}H_{12}Cl_2N_4O$) C, H, N.

11-Chloro-1-[(dimethylamino)methyl]dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9(9*H*)-one (11). A mixture of 13.9 g (45 mmol) of **10** (from 15.5 g of the HCl salt), 100 mL of 40% aqueous formaldehyde, and 100 mL of formic acid was refluxed for 12 h. The volatiles were removed at reduced pressure, and the residue was basified with NH_4OH. The resulting precipitate was collected by filtration, washed with water, and air-dried to constant weight to give 13.0 g (86%) of pale yellow crystals. Recrystallization from a mixture of CH_2Cl_2 and petroleum ether gave **11** as pale yellow prisms: mp 176–178 °C; IR ($CHCl_3$) 1670 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.4 (s, 6, CH_3), 3.55 (s, 2, CH_2), 7.5–8.0 (m, 5, arom H), 8.24 (dd, *J* = 2 and 8 Hz, 1, arom H), 8.56 (d, *J* = 9 Hz, 1, arom H); mass spectrum, *m/e* 338 (M^+). Anal. ($C_{18}H_{15}ClN_4C$) C, H, N.

[5-Chloro-2-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyl]phenyl](2-fluorophenyl)methanone (12). Dihydropyran (8.4 mL, 100 mmol) was added dropwise to a solution of 18 g (66 mmol) of [5-chloro-2-(3-hydroxy-1-propynyl)-phenyl](2-fluorophenyl)methanone[21] and 0.5 g of *p*-toluenesulfonic acid in 125 mL of CH_2Cl_2, which was cooled to 0 °C. After stirring for 30 min, the solution was poured into a stirred solution of $NaHCO_3$. The CH_2Cl_2 solution was washed with water, dried, and concentrated in vacuo to dryness. The residue was purifed by plug filtration (CH_2Cl_2, eluent) to give 16 g of **12** as a red oil, which was used without purification in the next step: IR ($CHCl_3$) 1665 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.4–1.9 (m, 6, CH_2), 3.4–4.0 (m, 2, CH_2), 4.16 (s, 2, CH_2), 4.50 (br s, 1, CH), 7.4–8.0 (m, 8, arom H); mass spectrum, *m/e* 354 (M^+).

[5-Chloro-2-[4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butynyl]phenyl](2-fluorophenyl)methanone (13). Compound **13** was prepared from [5-chloro-2-(4-hydroxy-1-butynyl)phenyl](2-fluorophenyl)methanone[22] by the procedure described for compound **12** to give light yellow prisms, mp 61–63 °C: IR ($CHCl_3$) 2235 (C≡C), 1667 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.55 (m, 6, 3 CH_2), 2.34 (t, *J* = 7 Hz, 2, CH_2), 3.1–3.9 (m, 4, CH_2OTHP, CH_2O), 4.51 (s, 1, CHO_2), 7.0–7.8 (m, 7, arom H); mass spectrum, *m/e* 386 (M^+). Anal. ($C_{22}H_{20}ClFO$) C, H, N.

11-Chloro-1-(hydroxymethyl)-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[3,4-*a*]azepin-9-one (14). A mixture of 41 g (0.11 mol) of **13** and 22 g (0.34 mol) of sodium azide in 880 mL of Me_2SO was heated on a steam bath for 24 h. The solution was cooled, poured over ice, and filtered to give a gummy tan solid. The solid was dissolved in 440 mL of methanol and treated with 200 mL of 6 N aqueous HCl. Stirring at room temperature was continued for 30 min, followed by filtration of the resulting precipitate. The solid was washed successively with water, methanol, and ether to give, after air-drying, 16.2 g (48%) of **14** as an off-white solid. A sample was recrystallized from a mixture of ethanol and CH_2Cl_2 to give **14** as off-white crystals: mp 226–227 °C; IR (KBr) 3240 (OH) and 1665 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 4.69 (d, *J* = 2 Hz, 2, CH_2), 5.71 (t, *J* = 2 Hz, 1, OH), 7.7–8.3 (m, 7, arom H). Anal. ($C_{16}H_{10}ClN_3O_2$) C, H, N.

11-Chloro-1-(2-hydroxyethyl)-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-one (15). Compound **15** was prepared in the same manner as **14** from **13** to give off-white crystals: mp 201–203 °C; IR (KBr) 3535 (OH), 1670 (C=O) cm^{-1}, NMR (Me_2SO-d_6) δ 3.03 (t, *J* = 4 Hz, 2, CH_2), 3.87 (q, *J* = 4 Hz, 2, CH_2O), 4.79 (t, *J* = 4 Hz, 1, OH), 7.6–8.2 (m, 7, arom H). Anal. ($C_{17}H_{12}ClN_3O_2$) C, H, N.

11-Chloro-9-oxo-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepine-1-carboxylic Acid (16). A solution of 2.7 M Jones reagent[9] (45 mL, 120 mmol) was added dropwise to a solution of 9.0 g (27 mmol) of **14** in 1350 mL of acetone over 10 min. Stirring was continued at room temperature for 1 h, followed by the addition of 2-propanol until the orange color of the excess Jones reagent was discharged. The acetone solution was decanted and poured over ice. The resulting precipitate was collected by filtration, washed with water, and dried to constant weight to give 6.4 g (73%) of **16** as an off-white solid. A sample was recrystallized from a mixture of CH_2Cl_2 and methanol to give **16** as off-white needles: mp 285–287 °C; IR (KBr) 2750–2565 (OH), 1687 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 7.6–8.3 (m, 7, arom H); mass spectrum, *m/e* 325 (M^+). Anal. ($C_{16}H_8ClN_3O_3$) C, H, N.

11-Chloro-1-[(4-methyl-1-piperazinyl)carbonyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-one (17). A stirred suspension of 6.0 g (18 mmol) of **16** and 6.0 g (29 mmol) of PCl_5 in 450 mL of CH_2Cl_2 was refluxed for 1 h. The solution was cooled in an ice bath, and a solution of 12 g (120 mmol) of *N*-methylpiperazine in 300 mL of CH_2Cl_2 was added dropwise. The mixture was stirred at 0 °C for 1 h, washed with water, dried, and concentrated in vacuo to dryness. The residue was triturated with ether to give 7.2 g (98%) of **17** as an off-white solid. A sample was recrystallized from a mixture of ethanol and CH_2Cl_2 to give **17** as off-white needles: mp 228–230 °C; IR (KBr) 1672 (C=O), 1640 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 2.03 (br s, 2, CH_2), 2.13 (s, 3, CH_3), 2.36 (br s, 2, CH_2), 3.31 (br s, 2, CH_2), 3.67 (br s, 2, CH_2), 7.6–8.3 (m, 7, arom H). Anal. ($C_{21}H_{18}ClN_5O_2$) C, H, N.

11-Chloro-1-[(4-methyl-1-piperazinyl)methyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-ol (18). A stirred suspension of 2.0 g (52 mmol) of $LiAlH_4$ and 3.2 g (8 mmol) of **17** in 160 mL of dry THF was refluxed for 2.5 h. The mixture was cooled, and 7 mL of water and 3.5 mL of 1 N aqueous NaOH

(21) Prepared from the corresponding iodobenzophenone by an adaptation of the preparation of **1a**:[6] oil.

(22) Prepared from the corresponding iodobenzophenone by an adaptation of the preparation of **1a**,[6] mp 76–77 °C.

solution were added successively dropwise. The resulting precipitate was removed by filtration, and the filtrate was concentrated in vacuo. Trituration of the residue with warm ether gave 2 g (63%) of **18** as an off-white solid. A sample was recrystallized from a mixture of ethanol and CH_2Cl_2 to give **18** as colorless prisms: mp 233–236 °C; IR (KBr) 3085 cm^{-1}; NMR (Me_2SO-d_6) δ 2.14 (s, 3, CH_3), 2.2–2.6 (m, 8, 4 CH_2), 3.61 (s, 0.2) and 3.64 (s, 0.8) (CH_2 conformers), 5.4 (d, J = 4 Hz, 0.8) and 5.7 (d, J = 3 Hz, 0.2) (C_9 H conformers), 5.8 (d, J = 3 Hz, 0.2) and 6.71 (d, J = 4 Hz, 0.8) (OH), 7.3–8.2 (m, 7, arom H). Anal. ($C_{21}H_{22}ClN_5O$) C, H, N.

11-Chloro-1-[(4-methyl-1-piperazinyl)carbonyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-ol (19). Sodium borohydride (0.3 g, 9 mmol) was added portionwise over 3 min to a suspension of 2.4 g (6 mmol) of **17** in a 1:1 mixture of THF and methanol. Stirring at room temperature was continued for 1 h. The solution was diluted with CH_2Cl_2, washed with water, dried, and concentrated in vacuo to give 1.7 g (69%) and **19** as off-white crystals. Recrystallization from a mixture of ethanol and CH_2Cl_2 gave **19** as off-white plates: mp 234–236 °C; IR (KBr) 3370 (OH), 1650 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 2.09 (s, 1) and 2.15 (s, 2) (conformers CH_3), 2.1–2.5 (m, 4, 2 CH_2), 3.1–3.8 (m, 4, 2 CH_2), 5.57 (d, J = 4 Hz, 0.67) and 5.85 (br s, 0.33) (C_9 H conformers), 5.89 (br s, 0.33) and 6.77 (d, J = 4 Hz, 0.67) (OH conformers), 7.4–8.0 (m, 7, arom H). Anal. ($C_{21}H_{10}ClN_5O_2$) C, H, N.

11-Chloro-1-[2-[(methylsulfonyl)oxy]ethyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-one (20). Methanesulfonyl chloride (2.3 mL, 30 mmol) was added dropwise to a mixture of 9.0 g (28 mmol) of **15**, 8 mL of triethylamine, and 200 mL of CH_2Cl_2 at 0 °C. The resulting solution was stirred at 0 °C for 15 min and washed with cold water, 1 N HCl solution, and aqueous $NaHCO_3$. The CH_2Cl_2 solution was dried and concentrated in vacuo to yield 10.1 g (91%) of **20** as a yellow solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave **20** as off-white prisms: mp 193–194 °C; IR ($CHCl_3$) 1675 (C=O), 1363, 1177 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 3.15 (s, 3, CH_3), 3.38 (t, J = 6 Hz, 2, CH_2), 4.65 (t, J = 6 Hz, 2, CH_2), 7.7–8.0 (m, 6, arom H), 8.20 (d, J = 7 Hz, 1, arom H); mass spectrum, m/e 403 (M^+). Anal. ($C_{18}H_{14}ClN_3O_4S$) C, H, N.

11-Chloro-1-[2-(methylamino)ethyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-one Hydrochloride (21). A solution of 8.4 g (21 mmol) of **20** and an excess of anhydrous methylamine in 400 mL of DMF was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic solution was dried and concentrated in vacuo to dryness. The resulting yellow oil was dissolved in a mixture of CH_2Cl_2 and ether, treated with an excess of 1.4 M methanolic HCl solution, and concentrated in vacuo to yield 6.5 g (83%) of **21** as a yellow solid. Recrystallization from methanol gave **21** as off-white needles: mp 285–286 °C; IR (KBr) 3420 (OH), 2750, 2680 (NH_2^+), 1688 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 2.58 (s, 3, CH_3), 3.36 (s, 4, 2 CH_2), 7.6–8.1 (m, 6, arom H), 8.16 (d, J = 8 Hz, 1, arom H), 9.34 (m, 2, NH_2^+); mass spectrum, m/e 295 ($M^+ - CH_2NCH_3$·HCl). Anal. ($C_{18}H_{16}Cl_2N_4O$) C, H, N.

11-Chloro-1-[2-(dimethylamino)ethyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-one (22). A mixture of 2.7 g of **21** (from 3.0 g, 7.9 mmol, of its HCl salt), 25 mL of 37% formaldehyde solution, and 25 mL of 95% formic acid was heated on the steam bath for 90 min. The reaction mixture was concentrated in vacuo to a small volume, diluted with CH_2Cl_2, and poured slowly into ice-cold aqueous $NaHCO_3$. The CH_2Cl_2 solution was washed with water, dried, and concentrated in vacuo. The residue crystallized from ether to yield 2.0 g (71%) of **22** as a pale yellow solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave **22** as off-white prisms: mp 91–93 °C; IR ($CHCl_3$), 1675 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 6, CH_3), 2.83 (m, 2, CH_2), 3.13 (m, 2, CH_2), 7.5–8.0 (m, 6, arom H), 8.24 (d, J = 7, 1, arom H); mass spectrum, m/e 352 (M^+). Anal. ($C_{19}H_{17}ClN_4O$) C, H, N.

11-Chloro-1-[2-(methylamino)ethyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-ol (23). Sodium borohydride (0.2 g, 5.2 mmol) was added to a solution of 0.9 g of **21** (from 1.0 g, 2.6 mmol, of its HCl salt) in 25 mL of methanol at 0 °C. The resulting mixture was stirred for 45 min and then concentrated in vacuo. The residue was triturated with water and collected by filtration to yield 0.8 g (89%) of **23** as a colorless solid. Recrystallization from ethyl acetate gave **23** as colorless prisms: mp 183–185 °C; IR (KBr) 3255 (NH), 2800–2680 (OH) cm^{-1}; NMR (Me_2SO-d_6) δ 2.29 (s, 3, CH_3), 2.96 (m, 4, 2 CH_2), 5.42 (s, 0.75) and 5.78 (s, 0.25) (C_9 H conformers), 6.72 (br s, 1, OH), 7.3–8.0 (m, 8, arom H, NH); mass spectrum, m/e 297 ($M^+ - CH_3N{=}CH_2$). Anal. ($C_{18}H_{17}ClN_4O$) C, H, N.

11-Chloro-1-[2-(dimethylamino)ethyl]-9*H*-dibenzo[*c*,*f*][1,2,3]triazolo[1,5-*a*]azepin-9-ol Hydrochloride (24). Sodium borohydride (0.3 g, 7.8 mmol) was added to a solution of 1.4 g (3.9 mmol) of **22** in 60 mL of methanol. The resulting solution was stirred at 0 °C for 45 min and concentrated in vacuo. The residue was dissolved in ether, decolorized with charcoal, and acidified with 2.6 mL of a 1.4 M methanol solution of HCl. The resulting precipitate was collected by filtration to give 0.9 g (60%) of **24** as a colorless solid. Recrystallization from a mixture of methanol and ether gave **24** as colorless prisms: mp 257–260 °C; IR (KBr) 3210 (OH), 2550, 2460 (NH^+) cm^{-1}; NMR (Me_2SO-d_6) δ 2.84 (s, 6, CH_3), 3.25–2.65 (m, 4, CH_2), 5.48 (d, J = 4 Hz, 1, axial CH), 5.82 (s, 1, equatorial CH), 6.89 (d, J = 5 Hz, 1, OH), 7.4–8.0 (m, 2 CH_2, 7, arom H); mass spectrum, m/e 354 (M^+ - HCl). Anal. ($C_{19}H_{20}Cl_2N_4O$) C, H, N.

Acknowledgment. We thank Dr. J. Blount and his staff in our Physical Chemistry Department, in particular Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, S. Traiman for IR spectra, and Dr. T. Williams for NMR spectra. We thank Drs. W. Dairman, W. D. Horst, and R. O. Brien and their staffs for determining and providing the pharmacological data and W. May for technical assistance.

Registry No. **1a**, 76049-52-0; **1b**, 76049-53-1; 1c, 76049-54-2; **1d**, 76049-55-3; 1e, 76049-56-4; **2a**, 83948-80-5; **2b**, 83948-81-6; **2c**, 83948-82-7; **2d**, 83948-83-8; **2e**, 83948-84-9; **4a**, 78131-52-9; **4b**, 78131-53-0; **4c**, 78131-55-2; **4c** methanesulfonate, 78131-56-3; **4d**, 78131-57-4; **4e**, 78131-59-6; **5**, 83948-85-0; **6**, 78131-62-1; **7**, 83948-86-1; **8**, 78131-65-4; **9**, 83948-87-2; **10**·HCl, 83948-88-3; 11, 83948-89-4; **12**, 83948-90-7; **13**, 83948-91-8; 14, 83948-92-9; **15**, 83948-93-0; **16**, 83948-94-1; **17**, 83948-95-2; **18**, 83966-26-1; **19**, 83948-96-3; **20**, 83948-97-4; **21**·HCl, 83948-98-5; **22**, 83948-99-6; **23**, 83949-00-2; **24**·HCl, 83949-01-3; 3-(2-benzoyl-4-chlorophenyl)-1-hydroxy-2-propyne, 76049-57-5; benzoic anhydride, 93-97-0; [5-chloro-2-(3-hydroxy-1-propynyl)phenyl](2-fluorobenzyl)methanone, 76049-58-6; [5-chloro-2-(3-hydroxy-2-butynyl)phenyl](2-fluorophenyl)methanone, 83949-02-4; *N*-methylpiperazine, 109-01-3; methylamine, 74-89-5.