nephrectomy and replacement of the drinking water with 1% w/v, NaCl solution for the first 5 weeks after nephrectomy. The rats were left at least 2 months after the operative procedure, by which time their body weights were between 300 and 450 g and their blood pressure had usually attained a stable level. A minimum value of systolic blood pressure of 160 mmHg (1 mmHg ≈ 133 Pa) was taken for selection of animals as hypertensive. Systolic blood pressure was recorded by the tail-cuff method using a W + W B.P. recorder, Model No. 8002. For all measurements of blood pressure, the rats were held in restraining cages in a heated environment (33.5 ± 0.5 °C), and each determination was the mean of at least six recordings.

All compounds were administered orally (by an oral dosing needle placed in the esophagus) as a solution or suspension in 1%, w/v, methylcellulose solution. Doses are expressed as free base.

**Rat Isolated Portal Vein.** Male Sprague-Dawley rats (250–350 g) were killed by cervical dislocation. Portal veins were set up under 1-g tension in a 10-mL organ bath containing Krebs-Henseleit solution of the following composition (mM): NaCl, 118; $NaHCO_3$, 25; glucose, 5; $KH_2PO_4$, 1.18; KCl, 4.69; $MgSO_4$, 0.59; $CaCl_2 \cdot H_2O$, 1.87. The tissue was aerated with a 95% oxygen and 5% carbon dioxide mixture. Isometric tension was recorded with a Devices strain gauge and recorder. Each preparation was allowed 1 h to equilibrate before the addition of drug. The percentage inhibition (mean ± SEM; six tissues for each drug) of the amplitude of the spontaneous contractions in each tissue was determined after 15-min contact time with the drug.

**Registry No.** **1**, 58740-91-3; **1**·HCl, 58740-62-8; **2**, 86823-96-3; **2**·HCl, 86823-97-4; **3**, 86823-98-5; **3**·HCl, 58740-63-9; **4**, 86823-99-6; **4**·HCl, 58740-64-0; **5**, 86824-00-2; **5**·HCl, 58740-65-1; **6**, 86824-01-3; **6**·$MeSO_3H$, 86834-45-9; **7**, 86824-02-4; **7**·$MeSO_3H$, 86824-03-5; **8**, 86824-04-6; **8**·HCl, 58740-67-3; **9**, 86824-05-7; **9**·HCl, 58740-66-2; **10**, 86824-06-8; **10**·HCl, 86824-07-9; **11**, 66343-26-8; **11**·HCl, 66343-25-7; **12**, 86824-08-0; **12**·2HCl, 86824-09-1; **13**, 86824-10-4; **13**·$MeSO_3H$, 86824-11-5; **14**, 64169-71-7; **14**·$MeSO_3H$, 86824-12-6; **15**, 86824-13-7; **15**·HCl, 58740-73-1; **16**, 86824-14-8; **16**·HCl, 58740-74-2; **17**, 86824-15-9; **17**·$MeSO_3H$, 86824-16-0; **18**, 86824-17-1; **18**·HCl, 58740-76-4; **19**, 86824-18-2; **19**·HCl, 58740-72-0; **20**, 86824-19-3; **20**·HCl, 58740-70-8; **21**, 86824-20-6; **21**·HCl, 86824-21-7; **22**, 86824-22-8; **22**·HCl, 86824-23-9; **23**, 86824-24-0; **23**·HCl, 86824-25-1; **24**, 72592-00-8; **24**·HCl, 86824-26-2; **25**, 86824-27-3; **25**·$MeSO_3H$, 86824-28-4; **26**, 86824-29-5; **26**·HCl, 86824-30-8; **27**, 86824-31-9; **27**·HCl, 65018-83-9; **28**, 86824-32-0; **28**·HCl, 86824-33-1; **29**, 86824-34-2; **29**·HCl, 86824-35-3; **30**, 86824-36-4; **30**·HCl, 86824-37-5; **31**, 86824-38-6; **31**·HCl, 86824-39-7; **32**, 86824-40-0; **32**·HCl, 86824-41-1; **33**, 86824-42-2; **33**·HCl, 86824-43-3; **34**, 86824-44-4; **34**·HCl, 86824-45-5; **35**, 86824-46-6; **35**·HCl, 86824-47-7; **36**, 65018-79-3; **36**·$MeSO_3H$, 65018-80-6; **37**, 86824-48-8; **37**·HCl, 65018-71-5; **38**, 86824-49-9; **38**·HCl, 86824-50-2; **39**, 86824-51-3; **39**·HCl, 65018-77-1; **40**, 65018-73-7; **40**·$MeSO_3H$, 65018-74-8; **41**, 65018-84-0; **41**·$MeSO_3H$, 65018-85-1; **42**, 86824-52-4; **42**·$MeSO_3H$, 86824-53-5; **43**, 86824-54-6; **43**·$MeSO_3H$, 86824-55-7; **44**, 86824-56-8; **44**·$MeSO_3H$, 86824-57-9; **45**, 86824-58-0; **45**·HCl, 86824-59-1; **46**, 58747-00-5; **46**·$C_4H_6O_6$, 58747-01-6; **47**, 86824-60-4; **48**, 86824-61-5; **48**·2HCl, 86824-62-6; **49**, 86824-63-7; **50**, 86824-64-8; **51**, 86824-65-9; **52**, 86824-66-0; **53**, 86824-67-1; **54**, 82305-06-4; **55**, 64169-76-2; **56**, 86824-68-2; **57**, 86824-69-3; **58**, 80055-54-5; **59**, 34818-57-0; **60**, 64169-74-0; **61**, 64169-75-1; **62**, 86824-70-6; **63**, 86824-71-7; **64**, 58740-89-9; **65**, 64169-77-3; **66**, 86824-72-8; **67**, 65018-89-5; **68**, 86824-73-9; **69**, 86824-74-0; **70**, 86824-75-1; **71**, 86824-76-2; **72**, 86824-77-3; **73**, 65018-81-7; **74**, 65018-69-1; **75**, 58740-92-4; **76**, 86824-78-4; **77**, 58740-90-2; **78**, 64169-78-4; **79**, 86824-79-5; **80**, 65018-90-8; **81**, 86824-80-8; **82**, 13229-61-3; **83**, 65018-82-8; **84**, 65018-70-4; **85**, 58740-93-5; **86**, 58740-86-6; *m*-nitrophenol, 554-84-7; *o*-cyanophenol, 611-20-1; *m*-cyanophenol, 873-62-1; *o*-methoxyphenol, 90-05-1; *p*-chlorophenol, 106-48-9; 3-chloro-3-methylbutyne, 1111-97-3; 7-cyano-2,2-dimethyl-2*H*-1-benzopyran, 86824-81-9; 6-(acetylamino)-2,2-dimethyl-2*H*-1-benzopyran, 19849-34-4.

# 2-Benzazepines. 5.[1,2] Synthesis of Pyrimido[5,4-*d*][2]benzazepines and Their Evaluation as Anxiolytic Agents

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A series of 5*H*-pyrimido[5,4-*d*][2]benzazepines has been synthesized, starting from the corresponding 2-benzazepin-5-ones, and evaluated as potential anxiolytic agents. Selected compounds from this series show a pharmacological profile of action different than that of diazepam. They are more potent than diazepam in the anti-pentylenetetrazole test and in the [$^3$H]diazepam binding assay, yet show less activity in the inclined screen test. A pharmacological data profile is given for 9-chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (**7c**). The structure–activity relationships of these potential anxiolytic agents are discussed.

Since the discovery of chlordiazepoxide and diazepam,[3] the 1,4-benzodiazepines have been a fruitful source of research activity for both the medicinal chemist and the pharmacologist.[4] In the search for new anxiolytic agents, the 1,4-benzodiazepine structure has been modified in a variety of ways.[5] As part of a program directed toward the discovery of novel anxiolytic agents, the synthesis and pharmacological evaluation of 2-benzazepine derivatives were a logical extension of the work in the 1,4-benzodiazepine area. The preparation and pharmacological profile of thiazolo-[6] and triazolo-2-benzazepine[2] derivatives, in which the heteroaromatic ring was annulated to the corresponding 4,5-positions of the 2-benzazepine ring system, have recently been reported. This report describes the synthesis of pyrimido[5,4-*d*][2]benzazepines and the pharmacological evaluation of these compounds as anxiolytic agents.

**Chemistry.** The preparation of the pyrimido[5,4-*d*]-[2]benzazepine ring system I was readily accomplished

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(1) Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.
(2) For the previous paper in the series, see Trybulski, E. J.; Benjamin, L.; Vitone, S.; Walser, A.; Fryer, R. I. *J. Med. Chem.* **1983**, *26*, 367.
(3) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
(4) Garattini, S.; Mussini, E.; Randall, L. O. "The Benzodiazepines"; Gerattini, S.; Mussini, E.; Randall, L. O., Eds.; Raven Press: New York, 1973.
(5) For reviews, see (a) Sternbach, L. H. In ref 4, pp 1–25. (b) Gschwend, H. "Industrial Pharmacology"; Fielding, S.; Lal, H., Eds.; Futura: Mount Kisco, NY, 1979; Chapter 1.
(6) Benjamin, L.; Fryer, R. I.; Gilman, N. W.; Trybulski, E. J. *J. Med. Chem.* **1983**, *26*, 100.

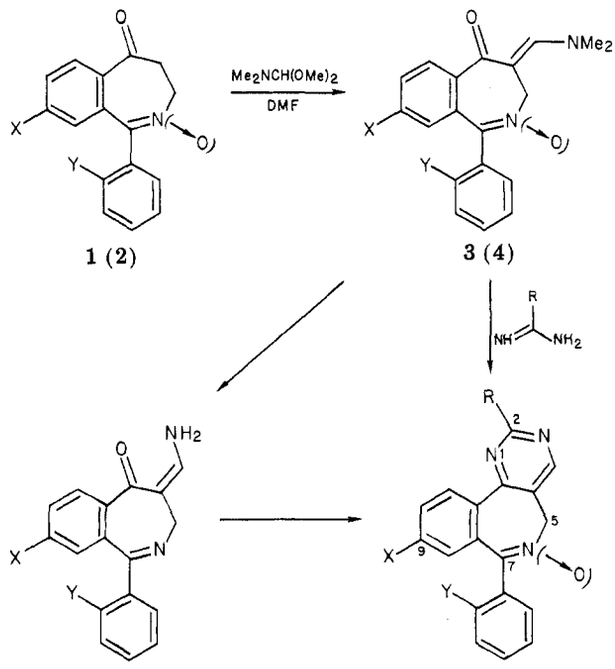
0022-2623/83/1826-1589$01.50/0 

Table I. (Dimethylamino)methylene Ketones

| no. | X | Y | *N*-oxide | time, h | temp, °C | yield, % | mp, °C | solvent | formula | anal. |
|---|---|---|---|---|---|---|---|---|---|---|
| 3a | Cl | H | | 2 | 80–85 | 82 | 179–180 | $Et_2O$ | $C_{19}H_{17}ClN_2O$ | C, H, N |
| 3b | Cl | F | | 2 | 80–85 | 85 | 228–232 | $Et_2O$ | $C_{19}H_{16}ClFN_2O$ | C, H, N |
| 3c | Cl | Cl | | 2 | 80–85 | 71 | 170–171 | $Et_2O$ | $C_{19}H_{16}Cl_2N_2O$ | C, H, N |
| 3d | H | H | | 2 | 80–85 | 74 | 131–132 | $Et_2O$ | $C_{19}H_{18}N_2O$ | C, H, N |
| 4b | Cl | F | 2-oxide | 12 | 25 | 96 | 193–194 | EtOAc/$Et_2O$ | $C_{19}H_{16}ClFN_2O_2$ | C, H, N |
| 4c | Cl | Cl | 2-oxide | 12 | 25 | 75 | 196–198 | EtOAc/$Et_2O$ | $C_{19}H_{16}Cl_2N_2O_2$ | C, H, N |

[a] Literature[7] mp 179–189 °C. [b] Literature[7] mp 224 °C. [c] Literature[7] mp 207 °C. [d] Literature[7] mp 134–136 °C.

Scheme I[a]




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

starting from the previously described 2-benzazepine-5-ones **1** and their corresponding *N*-oxides **2**[7,8] (Scheme I). Treatment of either **1** or **2** with dimethylformamide dimethyl acetal in DMF between room temperature and 80 °C gave in high yield the (dimethylamino)methylene ketones **3**[7] or **4**, respectively (Table I). The addition of acetamidine, isobutyramidine, thiourea, and guanidine to **3** or **4** in the presence of sodium methoxide led to the corresponding 2-substituted pyrimidobenzazepines I (compounds **9–12**, **14**, and **15**), which are listed in Table II. When compound **3c** was reacted with formamidine in the presence of sodium methoxide, a mixture of the desired pyrimidine **7c** and the amino compound **5c** resulted. Under these basic reaction conditions, **5c**, a possible precursor of **7c**, was not converted into **7c** and was not easily separated from the product mixture. The conversion of **3c** into **7c** was best achieved with slightly acidic, rather than basic, conditions. When compound **3c** was added to a formamide solution of formamidine acetate, preheated to 100 °C, compound **7c** was exclusively produced after 6 h. A small amount of **5c** was formed during the reaction and was slowly converted into **7c**. The same reaction parameters were observed in the conversion of **5b** and **4b,c** into the corresponding pyrimidobenzazepines **7b** and **8b,c**.

The formation of **5c** resulted from the addition of ammonia, a product of formamidine decomposition, to **3c**, followed by the elimination of dimethylamine, which is a better leaving group than ammonia. Once formed, **5c** was unreactive under basic conditions not only because of the decreased leaving ability of the amino group but also due to the stabilization of **5c** by hydrogen bonding of the amino group to the ketone oxygen. The reactivity of **5c** was improved by conducting the reaction in acidic media, so that the amino group was protonated and, therefore, became a better leaving group.

The 2-amino derivative **15b** (Scheme II) proved to be a useful compound for preparing pyrimidobenzazepines having substituents in the 2-position that were not readily accessible via **3** and the appropriately substituted guanidine or amidine. Hydrolysis of **15b** with aqueous sulfuric acid gave the pyrimidone **17**, which when treated with phosphorous oxychloride led to the chloro derivative **18**. Displacement of the chloride in **18** with sodium methoxide or an amine gave the corresponding methoxy or amino derivatives **19–23** (Table II). In addition, reaction of **18** with sodium diethyl malonate gave upon workup the ethyl ester **24**. Hydrolysis of **24** with aqueous sodium hydroxide led to the acid **25**; treatment of **24** with methylamine yielded **26**.

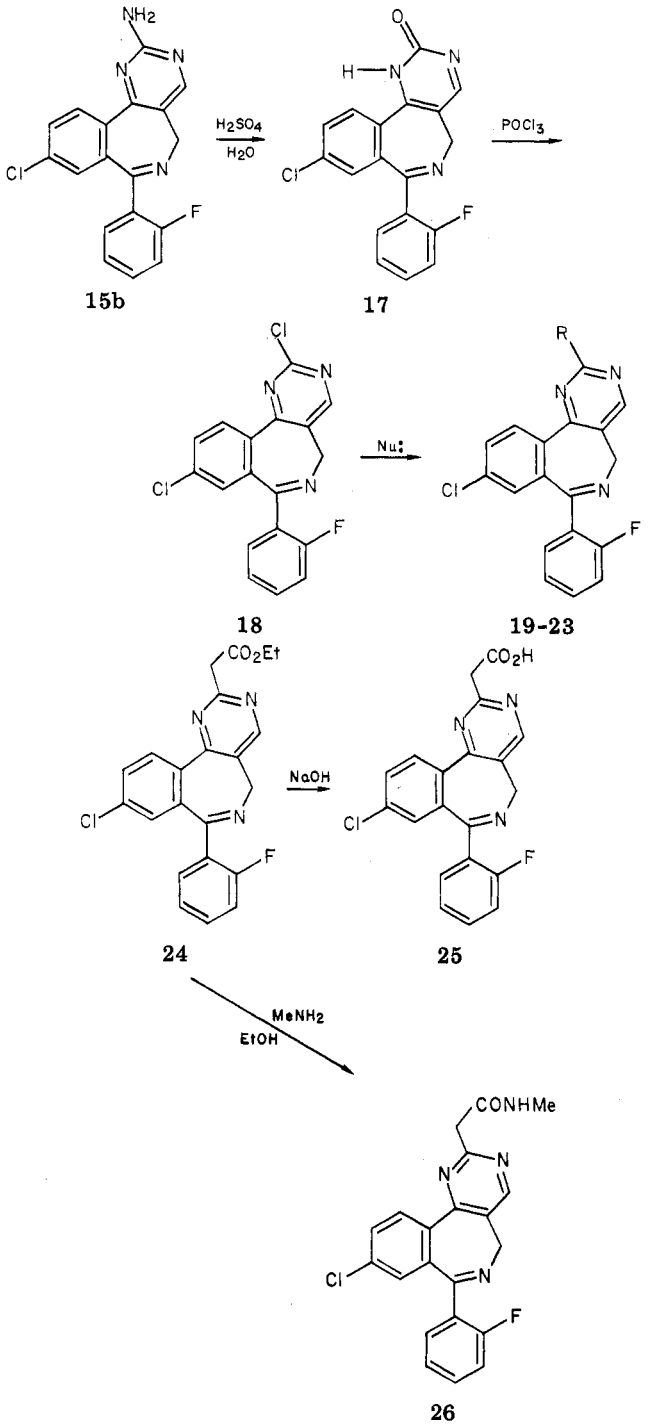
The direct oxidation of the imine nitrogen atom in the pyrimidobenzazepines to give the corresponding 6-*N*-oxide was also successful in those derivatives where the 2-substituent was not concomitantly oxidized. Oxidation of **7b,c** and **9c** with 1 equiv of *m*-chloroperbenzoic acid gave **8b,c** and **10**, respectively. If an excess of peracid was used, however, as in the oxidation of **9c**, the di-*N*-oxide **27** was isolated (Scheme III).

Reduction of the imine bond in **7c** and **9c** was achieved with either zinc and acetic acid at −20 °C or with sodium cyanoborohydride in methanol to give **28** and **29**, respectively. Hydrogenation of **9c** using platinum oxide as catalyst gave the tetrahydro derivative **31**. Methylation of **29** using the Eschweiler–Clark procedure yielded compound **30** (Scheme III, Table III).

**Pharmacology.** The pyrimidobenzazepines were tested in the following pharmacological screens: [$^3$H]diazepam binding assay,[9] anti-pentylenetetrazole test,[10] inclined screen test,[11] and rotarod test.[12] More than one-half of the pyrimidobenzazepines evaluated in the [$^3$H]diazepam binding assay had $IC_{50}$ values (2.3–15 nM) comparable to that of diazepam (5 nM). In the anti-pentylenetetrazole

(7) Gschwend, H. W. U.S. Patent 3 947 585, March 30, 1976.
(8) Trybulski, E. J.; Reeder, E.; Blount, J. F.; Walser, A.; Fryer, R. I. *J. Org. Chem.* **1982**, *47*, 2441.
(9) (a) Squires, R. F.; Braestrup, C. *Nature (London)* **1977**, *266*, 732. (b) Mohler, H.; Okada, T. *Life Sci.* **1977**, *20*, 2101.
(10) Everett, G. M.; Richards, R. K. *J. Pharmacol. Exp. Ther.* **1944**, *81*, 402.
(11) Randall, L. O.; Schallek, W.; Heise, G. A.; Keith, E. F.; Bagdon, R. E. *J. Pharmacol. Exp. Ther.* **1960**, *129*, 163–171.
(12) Dunham, N. W.; Miya, T. S. *J. Pharm. Sci.* **1957**, *46*, 208.

Scheme II

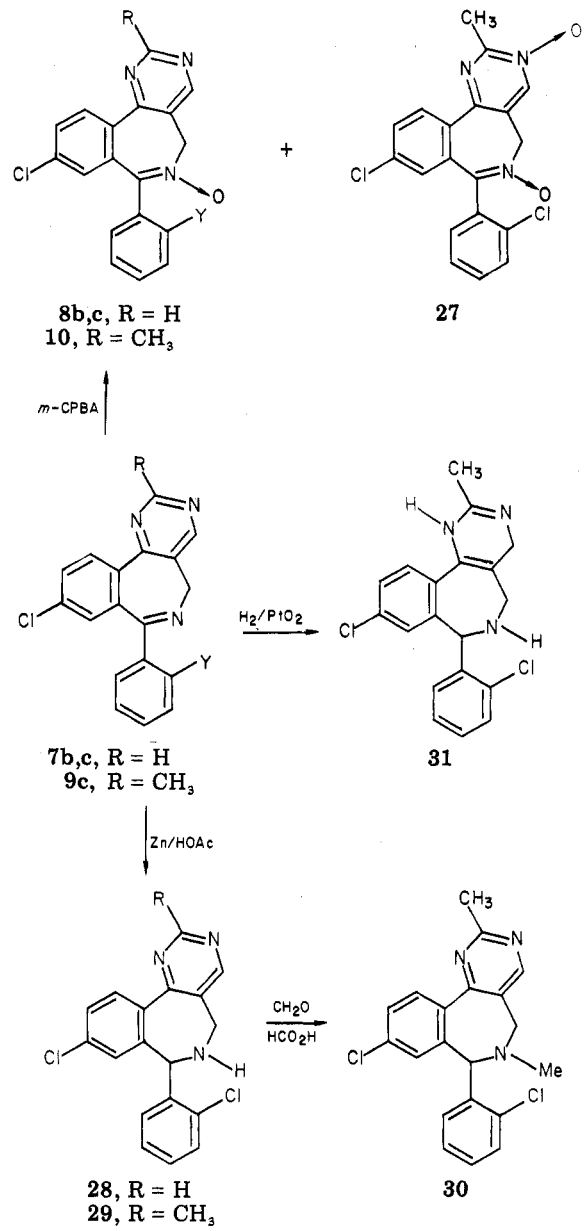



test, more than one-half of the pyrimidobenzazepines were found to have activities ($ED_{50}$ = 0.07–6.6 mg/kg po) in the range of diazepam ($ED_{50}$ = 1.4 mg/kg po). Taken together, these data were used as a first approximation for predicting the anxiolytic activity of the pyrimidobenzazepines.

The rotarod and inclined screen tests were used to estimate potential adverse effects on neuromotor coordination and the muscle-relaxant properties of the compound. On a qualtative basis, the pyrimidobenzazepines were similar to diazepam in the rotarod test but substantially less active than diazepam in the inclined screen test. This suggests that the pyrimidobenzazepines may have weaker muscle-relaxant properties when compared to diazepam.

A structure–activity relationship within the pyrimidobenzazepine series was determined by using the results of the anti-pentylenetetrazole test. Substitution of a halogen

Scheme III[a]



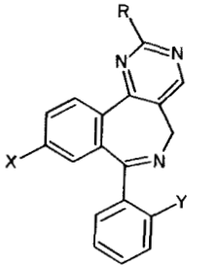

[a] b: Y = F. c: Y = Cl.

atom (most notably chlorine) at the ortho position of the 7-phenyl group increased the activity of the compound (relative potency **9c** > **9b** > **9a** and **15c** > **15b** > **15a**). Removal of the 9-chloro substituent diminished the activity (relative potency **9a** > **9d**). Substitution of a bulky group at the 2-position decreased the activity (relative potency **7c** > **9c** > **11**). Reduction of the pyrimidobenzazepine, first to the 6,7-dihydro derivative **28** and then to the 1,4,6,7-tetrahydro derivative **31**, successively weakened the activity (relative potency **9c** > **28** > **31**). Oxidation of the imine nitrogen atom of the pyrimidobenzazepine had either no effect or weakened the activity relative to the parent compound. These relationships parallel those established for the benzodiazepines, such as diazepam.[5a]

The 2-unsubstituted derivative **7c** was selected as a possible candidate for further testing, based upon its potency in the [$^3$H]diazepam binding assay and in the anti-pentylenetetrazole test. Derivative **7c** was negative in the Ames test,[13] an in vitro test for potential mutagenic

(13) Ames, B.; McCann, J.; Yamasaki, E. *Mutat. Res.* **1975**, *31*, 347.

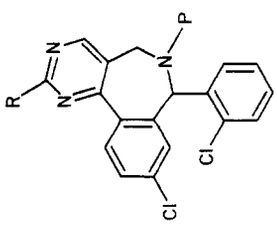
Table II. Pyrimido[5,4-*d*][2]benzazepines: Chemical and Pharmacological Data




| compd | R | X | Y | *N*-oxide | mp, °C | method[a] | yield, % | formula | anal. | [$^3$H]diazepam: $IC_{50}$,[b] nM (rat) | $ED_{50}$, mg/kg, po (mice)[f,g] anti-pentylenetetrazole[c] | inclined screen[d] | rotarod[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **7b** | H | Cl | F | | 123–125 | B | 50 | $C_{18}H_{11}ClFN_3$ | C, H, N | 3.4 | 0.37 | >400 | 0.8 |
| **7c** | H | Cl | Cl | | 122–124 | A (B) | 90 (69) | $C_{18}H_{11}Cl_2N_3$ | C, H, N | 2.8 | 0.59 | 215 | 3.6 |
| **8b** | H | Cl | F | 6-oxide | 185–186 | A (C) | 77 (77) | $C_{18}H_{11}ClFN_3O$ | C, H, N | 41 | 3.9 | 277 | 3.95 |
| **8c** | H | Cl | Cl | 6-oxide | 216–217 | A (C) | 77 (75) | $C_{18}H_{11}Cl_2N_3O$ | C, H, N | 39 | 0.87 | 141 | 4.9 |
| **9a** | $CH_3$ | Cl | H | | 120–122 | B | 74 | $C_{19}H_{14}ClN_3$ | C, H, N | 17 | 9.3 | | |
| **9b** | $CH_3$ | Cl | F | | 104–107 | B | 70 | $C_{19}H_{13}ClFN_3$ | C, H, N | 3.1 | 6.6 | >400 | 7.8 |
| **9c** | $CH_3$ | Cl | Cl | | 193–197 | B | 73 | $C_{19}H_{13}Cl_2N_3 \cdot CH_4SO_3$ | C, H, N | 9.2 | 0.74 | >400 | 7.2 |
| **9d** | $CH_3$ | H | H | | 211–221 | B | 80 | $C_{19}H_{15}N_3 \cdot 2HCl$ | C, H, N | 54 | 84 | | 200 |
| **10** | $CH_3$ | Cl | Cl | 6-oxide | 215–216 | C | 75 | $C_{19}H_{13}Cl_2N_3O$ | C, H, N | 15 | 0.72 | >400 | 6.3 |
| **11** | $CH(CH_3)_2$ | Cl | Cl | | 127–129 | B | 78 | $C_{21}H_{17}Cl_2N_3$ | C, H, N | 25 | 3.8 | >400 | 21 |
| **12** | SH | Cl | Cl | | 238–239 | B | 75 | $C_{18}H_{11}Cl_2N_3S$ | C, H, N | 270 | 18 | >400 | 214 |
| **13** | $SCH_3$ | Cl | Cl | | 165–166 | D | 100 | $C_{19}H_{13}Cl_2N_3S \cdot CH_4SO_3$ | C, H, N | 18.5 | 13 | >400 | 33 |
| **14** | SH | Cl | F | 6-oxide | 323–325 | B | 54 | $C_{18}H_{11}ClFN_3OS$ | C, H, N | 490 | >100 | >400 | >200 |
| **15a** | $NH_2$ | Cl | H | | 210–211 | B | 92 | $C_{18}H_{13}ClN_4$ | C, H, N | 17 | 4.9 | >400 | 19 |
| **15b** | $NH_2$ | Cl | F | | 245–248 | B | 76 | $C_{18}H_{12}ClFN_4$ | C, H, N | 2.8 | 1.1 | >400 | 5.1 |
| **15c** | $NH_2$ | Cl | Cl | | 240–241 | B | 67 | $C_{18}H_{12}Cl_2N_4$ | C, H, N | 2.6 | 0.07 | >400 | 1.4 |
| **15d** | $NH_2$ | H | H | | 201–205 | B | 20 | $C_{18}H_{14}N_4$ | C, H, N | 60 | 17 | | |
| **16** | $NH_2$ | Cl | F | 6-oxide | 320–323 | B | 31 | $C_{18}H_{12}ClFN_4O$ | C, H, N | 38 | | | |
| **17** | OH | Cl | F | | 297–299 | | 83 | $C_{18}H_{11}ClFN_3$ | C, H, N | 9.6 | 6.3 | >400 | 29 |
| **18** | Cl | Cl | F | | 157–160 | | 73 | $C_{18}H_{10}Cl_2FN_3$ | C, H, N | 5.3 | 4.7 | >400 | 24 |
| **19** | OMe | Cl | F | | 137–141 | | 60 | $C_{19}H_{13}ClFN_3O$ | C, H, N | 3.5 | 2.6 | >400 | 9 |
| **20** | NHMe | Cl | F | | 172–179 | E | 60 | $C_{19}H_{14}ClFN_4$ | C, H, N | 2.8 | 0.58 | >400 | 4 |
| **21** | $NMe_2$ | Cl | F | | 175–179 | E | 88 | $C_{20}H_{16}ClFN_4$ | C, H, N | 8.2 | 1.1 | >400 | 2.2 |
| **22** | $NH(CH_2)_3NMe_2$ | Cl | F | | 90–101 | E | 48 | $C_{23}H_{23}ClFN_5$ | C, H, N | 2.3 | 1.6 | 187 | 16 |
| **23** | $N(C_2H_4)_2NMe$ | Cl | F | | 187–194 | E | 95 | $C_{23}H_{21}ClFN_5 \cdot HCl$ | C, H, N | 7.1 | 1.2 | >400 | 16 |
| **24** | $CH_2CO_2Et$ | Cl | F | | 98–103 | | 74 | $C_{22}H_{17}ClFN_3O_2$ | C, H, N | 20 | 13 | | >200 |
| **25** | $CH_2CO_2H$ | Cl | F | | 138–140 | | 35 | $C_{20}H_{13}ClFN_3O_2$ | C, H, N | 9.6 | 12 | >400 | 30 |
| **26** | $CH_2CONHMe$ | Cl | F | | 175–177 | | 92 | $C_{21}H_{16}ClFN_4O$ | C, H, N | 7.6 | 2.3 | >400 | 4 |
| **27** | $CH_3$ | Cl | Cl | 3,6-dioxide | 241–243 | C | 26 | $C_{19}H_{13}Cl_2N_3O_2$ | C, H, N | 31 | 2.7 | 240 | 5.6 |
| diazepam | | | | | | | | | | 5.4 | 1.4 | 25 | 3.2 |

[a] Method A: compound **3** or **4**, formamidine acetate in formamide at 100 °C, exemplified by **7c**. Method B: compound **3** or **4**, an amidine, guanidine, or thiourea and sodium methoxide in a mixture of MeOH and $CH_2Cl_2$ at room temperature, exemplified by **9c**. Method C: *m*-CPBA in $CH_2Cl_2$, exemplified by **8c**. Method D: NaOH and $Me_2SO_4$ in $H_2O$, exemplified by **13**. Method E: compound **18** and nucleophile, exemplified by **21**. [b] The method of Mohler and Okada[9] was used for this assay. [c] A modification of the Everett and Richards[10] method was used for this assay. Results are reported as 95% fiducial limits. [d] The method of Randall et al.[11] was used in this procedure. [e] The method of Dunham and Miya[12] was used in this procedure. [f] Results are reported as 95% fiducial limits. [g] Three mice per dose were used.

Table III. Reduced Pyrimido[5,4-*d*][2]benzazepines



| compd | R | P | mp, °C | formula | anal. | $ED_{50}$, mg/kg, po (mice)[a] [$^3$H]diazepam binding: $IC_{50}$[a] nM | anti-pentylene-tetrazole[b] | inclined screen[c] | rotarod[d] |
|---|---|---|---|---|---|---|---|---|---|
| **7c** | H | | | | | 2.8 | 0.59 | 215 | 3.6 |
| **28** | H | H | 169–170 | $C_{18}H_{13}Cl_2N_3$ | C, H, N | 54 | 6.9 | >400 | 22 |
| **9c** | $CH_3$ | | | | | 9.2 | 0.74 | >400 | 7.2 |
| **29** | $CH_3$ | H | 171–174 | $C_{19}H_{15}Cl_2N_3 \cdot 2HCl$ | C, H, N | 30 | 2.3 | >400 | 18 |
| **30** | $CH_3$ | $CH_3$ | 238–239 | $C_{20}H_{17}Cl_2N_3 \cdot 2CH_4SO_3$ | C, H, N | 25 | 7.7 | >400 | 74 |
| **31** | $CH_3$ | H | 275–276 | $C_{19}H_{17}Cl_2N_3 \cdot 2HCl$ | C, H, N | 140 | 34 | 200 | 109 |
| | | 1,4,5,6-tetrahydro | | | | | | | |

[a] The methods are identical with those described in Table II.

Table IV. Secondary Pharmacological Tests of 7c and Diazepam

| test | species | parameter | 7c, mg/kg, po | diazepam, mg/kg, po |
|---|---|---|---|---|
| conflict behavior | | | | |
| anticonflict effect | rat | MED[a] | 0.31 | 1.25 |
| depressant effect | rat | DUR[b] | 2.5 | 20 |
| anticonflict effect | monkey | MED | 0.04 | 0.31 |
| depressant effect | monkey | HED[c] | 5 | 20 |
| ethanol interaction | mouse | $ED_{50}$[d] | 2.2 | 0.97 |
| observable symptomatology | cat | MED[e] | 0.5 | 0.2 |

[a] MED = minimum effective dose. [b] DUR = lowest dose at which a significant decrease in unpunished responding is observed. [c] HED = highest effective dose with no significant decrease in unpunished responding. [d] $ED_{50}$ = drug dose that produces a loss of righting reflex in 50% of animals pretreated with an $ED_5$ dose of ethanol. [e] Minimum effective dose that produces drug-induced ataxia. [f] Results are reported as 95% fiducial limits.

liability, and additional pharmacological test results are listed in Table IV.

In both the rate multiple VI FR conflict test[14] and the squirrel monkey concurrent VI–VI conflict test,[15] **7c** was found to be between four and eight times more potent than diazepam (Table IV). In addition, when compared to diazepam, **7c** was two and a half times less potent in its interaction with ethanol in the loss of righting reflex.[16]

In summary, the pyrimido[5,4-*d*][2]benzazepines demonstrate that the nitrogen atom in the 1-position of the 1,4-benzodiazepine ring system is not a requirement for anxiolytic-like activity. In addition, the preclinical testing data suggest that members of this novel series of compounds should produce potent anxiolytic activity with fewer deficits in motor coordination and less ethanol interaction than diazepam. Based upon those testing results and its novel structure, **7c** was selected for clinical trial as an anxiolytic agent. The therapeutic profile of this class of compounds will be more accurately determined by the results of the clinical studies of **7c**.

## Experimental Section

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal $Me_4Si$. Infrared and mass spectra (MS) were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Merck silica gel 60, mesh 70–230, was used for all column chromatography separations. Anhydrous sodium sulfate was used for drying of organic solutions.

**General Procedure for the Preparation of (Dimethylamino)methylene Ketones 3 and 4.** A mixture of 1 part of the ketone[8] and 2 parts of a 4:1, v/v, mixture of dimethylformamide dimethyl acetal and DMF was stirred under the specified conditions of time and temperature. The resulting precipitate was collected by filtration and washed with a cold 9:1, v/v, mixture of ether and 2-propanol. The resulting yellow precipitate was recrystallized from the appropriate solvent (see Table I).

**Method A. 9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (7c).** A mixture of 90.5 g (0.25 mol) of **3c**, 100 g (0.96 mol) of formamidine acetate, and 1.0 L of formamide was heated on a steam bath for 16 h. The mixture was cooled to 0 °C, and the resulting precipitate was collected by

(14) Davidson, A. B.; Cook, L. *Psychopharmacologia (Berlin)* **1969**, *15*, 159.
(15) (a) Sepinwall, J.; Grodsky, F. S.; Cook, L. *J. Pharmacol. Exp. Ther.* **1978**, *88*, 204. (b) Sepinwall, J.; Grodsky, F. S.; Sullivan, J. W.; Cook, L. *Psychopharmacologia* **1973**, *31*, 375.
(16) See Experimental Section for details.

filtration. The precipitate was washed with water and dried to constant weight to give 77 g of **7c** as off-white crystals. Recrystallization from ether gave colorless prisms: IR ($CHCl_3$) 1647, 1620 (C=N) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.0–5.0 (vbr s, 2, $C_5$ H), 7.2–7.7 (m, 6, arom H), 8.28 (d, $J$ = 10 Hz, 1, arom H), 8.81 (s, 1, $C_4$ H), 9.38 (s, 1, $C_2$ H); MS, $m/e$ 339 ($M^+$). Anal. ($C_{18}H_{11}Cl_2N_2$) C, H, N.

**Method B. 9-Chloro-7-(2-chlorophenyl)-2-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepine Methanesulfonate (9c).** Acetamidine hydrochloride (1.1 g, 10 mmol) and a 4.1 M methanol solution of sodium methoxide (3.0 mL, 12.3 mmol) was added in five equal portions over 3 h to a solution of 3.5 g (10 mmol) of **3c** in a mixture of 140 mL of methanol and 140 mL of $CH_2Cl_2$. The $CH_2Cl_2$ solution was washed with water, dried, and concentrated at reduced pressure to give 3.15 g of an amber oil. The oil was dissolved in 10 mL (10 mmol) of a 1 M methanol solution of methanesulfonic acid, and the resulting salt was precipitated by the addition of ether to give 3.3 g of **9c**. Recrystallization from methanol/ether gave **9c** as yellow prisms: IR (KBr) 2560, 1980 ($C{=}NH^+$), 1653 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 2.51 (s, 3, $CH_3$), 2.76 (s, 3, $CH_3$), 4.0–5.0 (vbr s, 2, $C_5$ H), 6.86 (s, 1, NH), 7.15 (d, $J$ = 2 Hz, 1 arom H), 7.4–7.9 (m, 4, arom H), 8.29 (d, $J$ = 8 Hz, 1 arom H), 8.94 (s, 1, $C_4$ H). Anal. ($C_{19}H_{13}Cl_2N_3{\cdot}CH_4SO_3$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (7b):** IR ($CHCl_3$) 1615 (C=N) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.1 (br s, 1) and 4.9 (br s, 1) (AB system, $C_5$ H), 6.8–7.7 (m, 6, arom H), 8.25 (d, $J$ = 9 Hz, 1, $C_{11}$ H), 8.78 (s, 1, $C_4$ H), 9.24 (s, 1, $C_2$ H); MS, $m/e$ 323 ($M^+$). Anal. ($C_{18}H_{11}ClFN_3$) C, H, N.

**9-Chloro-2-methyl-7-phenyl-5*H*-pyrimido[5,4-*d*][2]benzazepine (9a):** NMR ($CDCl_3$) $\delta$ 2.90 (s, 3, $CH_3$), 2.94 (br d, $J$ = 12 Hz, 1) and 5.00 (br d, $J$ = 12 Hz, 1) (AB system, $C_5$ H), 7.3–8.0 (m, 4, arom H), 8.33 (d, $J$ = 8 Hz, 1, arom H), 8.71 (s, 1, $C_4$ H). Anal. ($C_{19}H_{14}ClN_3$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-2-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepine (9b):** NMR ($CDCl_3$) $\delta$ 2.93 (s, 3, $CH_3$), 4.1 (br s, 1) and 5.0 (br s, 1) (AB system, $C_5$ H), 7.1–7.8 (m, 6, arom H), 8.41 (s, 1, $C_4$ H). Anal. ($C_{19}H_{13}ClFN_3$) C, H, N.

**2-Methyl-7-phenyl-5*H*-pyrimido[5,4-*d*][2]benzazepine dihydrochloride (9d):** NMR ($Me_2SO$-$d_6$) $\delta$ 2.76 (s, 3, $CH_3$), 4.36 (br s, 1) and 5.16 (br s, 1) (AB system, $C_5$ H), 7.5–8.2 (m, 8, arom H), 8.46 (br d, $J$ = 8 Hz, 1, arom H), 8.98 (s, 1, $C_4$ H), 11.3 (vbr s, 2, NH). Anal. ($C_{19}H_{15}N_3{\cdot}2HCl$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-2-isopropyl-5*H*-pyrimido[5,4-*d*][2]benzazepine (11):** IR ($CHCl_3$) 1620 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.39 (d, $J$ = 7 Hz, 6, $CH_3$), 3.31 (septet, $J$ = 7 Hz, CH), 4.0–4.8 (br s, 2, $C_5$ H), 7.1–7.6 (m, 6, arom H), 8.24 (d, $J$ = 8 Hz, 1, arom H), 8.67 (s, 1, $C_4$ H); MS, $m/e$ 381 ($M^+$). Anal. ($C_{21}H_{17}Cl_2N_3$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine-2-thiol (12):** NMR ($Me_2SO$-$d_6$) $\delta$ 3.9 (vbr s, 1) and 4.7 (vbr s, 1) (AB system, $C_5$ H), 7.08 (d, $J$ = 2 Hz, 1, arom H), 7.3–7.7 (m, 4, arom H), 7.79 (dd, $J$ = 2 and 8 Hz, 1, arom H), 8.13 (d, $J$ = 8 Hz, 1, arom H), 8.30 (s, 1, $C_4$ H), and 13.98 (br s, 1, SH); MS, $m/e$ 371 ($M^+$). Anal. ($C_{18}H_{11}Cl_2N_3S$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine-2-thiol 6-oxide (14):** IR (KBr) 3200 (SH), 1630 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 5.02 (m, 2, $C_5$ H), 5.15 (br s, 1, SH), 6.93 (d, $J$ = 2 Hz, 1, arom H), 7.0–7.7 (m, 5, arom H), 8.13 (s, $J$ = 8 Hz, 1, $C_{11}$ H), 8.39 (s, 1, $C_4$ H); MS, $m/e$ 371 ($M^+$). Anal. ($C_{18}H_{11}ClFN_3SO$) C, H, N.

**2-Amino-9-chloro-7-phenyl-5*H*-pyrimido[5,4-*d*][2]benzazepine (15a):** NMR ($Me_2SO$-$d_6$) $\delta$ 3.61 (d, $J$ = 12 Hz, 1) and 4.68 (d, $J$ = 12 Hz, 1) (AB system, $C_5$ H), 6.59 (s, 2, $NH_2$), 7.2–8.1 (m, 6, arom H), 8.31 (s, 1, $C_4$ H). Anal. ($C_{18}H_{13}ClN_4$) C, H, N.

**2-Amino-9-chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (15b):** IR (KBr) 3325, 3180 ($NH_2$), 1650 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 3.72 (br s, 1) and 4.70 (br s, 1) (AB system, $C_5$ H), 6.62 (s, 2, $NH_2$), 7.05–7.55 (m, 6, arom H), 8.15 (d, $J$ = 10 Hz, 1, arom H), 8.33 (s, 1, $C_4$ H). Anal. ($C_{18}H_{12}ClFN_4$) C, H, N.

**2-Amino-9-chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (15c):** IR ($CHCl_3$) 3535, 3425 ($NH_2$), 1608 (C=N) $cm^{-1}$; NMR ($CDCl_3$–$Me_2SO$-$d_6$) $\delta$ 4.0 (br s, 1) and 4.7 (br s, 1) (AB system, $C_5$ H), 5.43 (br s, 2, $NH_2$), 7.12 (d, $J$ = 12 Hz, 1, arom H), 7.2–7.6 (m, 5, arom H), 8.15 (d, $J$ = 8 Hz, 1, arom H), 8.33 (d, $J$ = 8 Hz, 1, $C_4$ H); MS, $m/e$ 354 ($M^+$). Anal. ($C_{18}H_{12}Cl_2N_4$) C, H, N.

**2-Amino-7-phenyl-5*H*-pyrimido[5,4-*d*][2]benzazepine (15d):** IR (KBr) 3320, 3190 ($NH_2$) $cm^{-1}$; MS, $m/e$ 286 ($M^+$). Anal. ($C_{18}H_{14}N_4$) C, H, N.

**2-Amino-9-chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine 7-oxide (16):** IR (KBr) 3500 ($NH_2$), 1620 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 4.94 (s, 2, $C_5$ H), 6.8–7.6 (m, 8, arom H, $NH_2$), 8.14 (d, $J$ = 8 Hz, 1, arom H), 8.42 (s, 1, $C_4$ H); MS, $m/e$ 354 ($M^+$). Anal. ($C_{18}H_{12}ClFN_4O$) C, H, N.

**Method C. 9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine 6-Oxide (8c).** A solution of 6.8 g (20 mmol) of **7c** and 6 g (30 mmol) of 85% *m*-chloroperbenzoic acid in 200 mL of $CH_2Cl_2$ was stirred at room temperature for 4 h. The mixture was washed with an excess of ice-cold dilute NaOH, dried, and concentrated at reduced pressure to dryness. The residue was crystallized from $CH_2Cl_2$/ether to give 5.4 g of **8c** as off-white crystals: NMR ($CDCl_3$) $\delta$ 5.08 (s, 2, $C_5$ H), 7.0–7.7 (m, 6, arom H), 8.25 (d, $J$ = 8 Hz, 1, $C_{11}$ H), 8.90 (s, 1, $C_4$ H), 9.36 (s, 1, $C_2$ H); MS, $m/e$ 355 ($M^+$). Anal. ($C_{18}H_{11}Cl_2N_3O$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine 6-oxide (8b):** IR ($CHCl_3$) 1615 (C=N) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.11 (br s, 2, $C_5$ H), 8.94 (s, 1, $C_4$ H), 9.42 (s, 1, $C_2$ H); MS, $m/e$ 339 ($M^+$). Anal. ($C_{18}H_{11}ClFN_3O$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-2-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepine 6-oxide (10):** NMR ($CDCl_3$) $\delta$ 2.87 (s, 3, $CH_3$), 5.07 (s, 2, $C_5$ H), 7.05 (d, $J$ = 2 Hz, 1, arom H), 7.2–7.6 (m, 5, arom H), 8.25 (d, $J$ = 8 Hz, 1, arom H), 8.79 (s, 1, $C_4$ H); MS, $m/e$ 369 ($M^+$). Anal. ($C_{19}H_{13}Cl_2N_3O$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-2-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepine 3,6-dioxide (27):** NMR ($CDCl_3$) $\delta$ 2.83 (s, 3, $CH_3$), 5.03 (s, 2, $CH_2$), 7.04 (d, $J$ = 2 Hz, 1, arom H), 7.1–7.6 (m, 5, arom H), 8.17 (d, $J$ = 8 Hz, 1, arom H), 8.59 (s, 1, $C_4$ H); MS, $m/e$ 385 ($M^+$). Anal. ($C_{19}H_{13}Cl_2N_3O_3$) C, H, N.

**Method D. 9-Chloro-7-(2-chlorophenyl)-2-(methylthio)-5*H*-pyrimido[5,4-*d*][2]benzazepine Methanesulfonate (13).** A mixture of 1.1 g (3.0 mmol) of **12**, 1.0 mL (10 mmol) of dimethyl sulfate, 20 mL of 1 N aqueous NaOH, and 10 mL of ethanol was stirred at room temperature for 15 min. The mixture was diluted with water and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure to give 1.3 g of **13** as colorless prisms, mp 187–188 °C.

The methanesulfonate salt of **13** was prepared by the addition of equimolar amounts of **13** and methanesulfonic acid to methanol and by precipitating the resulting salt by the addition of ether. Recrystallization from ethanol gave the salt of **13** as cream-colored needles: IR (KBr) 3400, 2600, 1975 ($NH^+$), 1648 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 2.63 (s, 3, $CH_3$), 2.67 (s, 3, $CH_3$), 4.2–5.4 (vbr s, 2, $C_5$ H), 7.2–8.0 (m, 6, arom H), 8.43 (d, $J$ = 8 Hz, 1, arom H), 8.84 (s, 1, $C_4$ H), 9.43 (s, 1, OH). Anal. ($C_{19}H_{13}Cl_2N_3S$) C, H, N.

**Method E. 9-Chloro-*N*,*N*-dimethyl-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-amine (21).** A solution of 4.0 g (11 mmol) of **18** in 15 mL of DMF was cooled in an ice bath and saturated with dimethylamine. After 18 h at room temperature, 80 mL of ice–water was added, and the precipitate was collected by filtration. Recrystallization of the resulting solid from methanol gave **21** as colorless rods: NMR ($Me_2SO$-$d_6$) $\delta$ 3.23 (s, 6, $CH_3$), 3.8 (vbr s, 1) and 4.7 (vbr s, 1) (AB system, $C_5$ H), 6.9–7.7 (m, 6, arom H), 8.17 (d, $J$ = 8 Hz, 1, arom H), 8.36 (s, 1, $C_4$ H). Anal. ($C_{20}H_{16}ClFN_4$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-*N*-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-amine (20):** IR ($CHCl_3$) 3455 (NH), 1600 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 2.88 (d, $J$ = 4 Hz, 3, $CH_3$), 3.75 (br s, 1) and 4.69 (br s, 1) (AB system, $C_5$ H), 7.0–7.9 (m, 7, arom H, NH), 8.21 (d, $J$ = 8 Hz, 1, arom H), 8.41 (s, 1, $C_4$ H). Anal. ($C_{19}H_{14}ClFN_4$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-*N*-[3-(dimethylamino)propyl]-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-amine (22):** IR ($CHCl_3$) 3450 (NH) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 1.77 (quintet, $J$ = 7 Hz, 1, $CH_2$), 2.27 (s, 6, $CH_3$), 2.50 (m, 2, $CH_2$), 3.38 (q, $J$ = 7 Hz, 2, $CH_2$), 3.8 (vbr s, 1) and 4.75 (vbr s, 1) (AB system, $C_5$ H), 7.0–7.8 (m, 7, arom H), 8.18 (d, $J$ = 8 Hz, 1, arom H), 8.41 (s, 1, $C_4$ H). Anal. ($C_{23}H_{23}ClFN_5$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-2-(4-methyl-1-piperazinyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine hydrochloride (23):** IR (KBr) 3440 ($NH^+$) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 2.79 (s, 3, $CH_3$), 3.26

(br s, 9, $CH_2$, $NH^+$), 3.80 (br s, 1), and 4.85 (br s, 1) (AB system, $C_5$ H), 6.9–7.8 (m, 6, arom H), 8.19 (d, $J$ = 8 Hz, 1, arom H), 8.52 (s, 1, $C_4$ H). Anal. ($C_{23}H_{21}ClFN_5$·HCl) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-ol (17).** A solution of 1.2 g (3.5 mmol) of **15b** in 20 mL of concentrated $H_2SO_4$ and 20 mL of water was refluxed for 12 h and then cooled. After the addition of ice, the reaction mixture was made basic with ammonium hydroxide and extracted with $CH_2Cl_2$. The remaining precipitate was collected by filtration and recrystallized from $CH_2Cl_2$/EtOH to give **17** as white prisms. The $CH_2Cl_2$ extract was dried, concentrated at reduced pressure, and crystallized from a mixture of $CH_2Cl_2$ and MeOH to give a total yield of 1.0 g of **17**: NMR ($Me_2SO$-$d_6$) $\delta$ 3.8 (br s, 1) and 4.72 (br s, 1) (AB system, $C_5$ H), 7.1–7.9 (m, 6, arom H), 8.10 (d, $J$ = 8 Hz, 1, arom H), 8.24 (s, 1, $C_4$ H); MS, $m/e$ 339 ($M^+$). Anal. ($C_{18}H_{11}ClFN_3$) C, H, N.

**2,9-Dichloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (18).** A solution of 1.0 g (2.9 mmol) of **17** in 5 mL of phosphorous oxychloride was heated on a steam bath for 4 h, followed by concentration at reduced pressure to dryness. The resulting solid was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The $CH_2Cl_2$ solution was dried, concentrated at reduced pressure, and crystallized from ether. Recrystallization from $CH_2Cl_2$/ether gave 0.8 g of **18** as off-white prisms: NMR ($Me_2SO$-$d_6$) $\delta$ 4.3 (vbr s, 1) and 5.8 (vbr s, 1) (AB system, $C_5$ H), 7.0–8.0 (m, 6, arom H), 8.22 (d, $J$ = 8 Hz, 1, arom H), 9.01 (s, 1, $C_4$ H). Anal. ($C_{18}H_{10}Cl_2FN_3$) C, H, N.

**9-Chloro-2-methoxy-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (19).** Sodium methoxide (0.18 g, 3.3 mmol) was added to a solution of **18** in 25 mL of methanol. The mixture was stirred for 18 h, followed by concentration at reduced pressure to dryness. The residue was dissolved in $CH_2Cl_2$ and washed with water. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure. The residue was crystallized from ether/petroleum ether to give 0.6 g of **19** as colorless prisms: IR ($CHCl_3$) 1615 (C=N) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 3.99 (s, 1, $CH_3$), 4.0 (br s, 1) and 4.8 (br s, 1) (AB system, $C_5$ H), 7.0–7.7 (m, 5, arom H), 7.80 (dd, $J$ = 2 and 8 Hz, 1, arom H), 8.24 (d, $J$ = 8 Hz, 1, arom H), 8.76 (s, 1, $C_4$ H). Anal. ($C_{19}H_{13}ClFN_3O$) C, H, N.

**Ethyl 9-Chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine-2-acetate (24).** Potassium *tert*-butoxide (1.9 g, 16.8 mmol) was added to 20 mL of diethyl malonate, followed 15 min later by the addition of 2.0 g (5.6 mmol) of **18**. The mixture was heated to 110 °C for 2 h and then to 140 °C for 4 h. The mixture was cooled with the addition of ice, acidified with concentrated HCl, and extracted with ether. The ether solution was extracted with 3 N aqueous HCl. The combined acid extracts were made basic with $NH_4OH$ and extracted with ether. The ether solution was dried and filtered over charcoal, and the filtrate was concentrated at reduced pressure. Crystallization from ether/petroleum ether gave 1.7 g of **24** as colorless rods: IR ($CHCl_3$) 1737 (C=O) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.27 (t, $J$ = 7 Hz, 3, $CH_3$), 4.08 (s, 2, $CH_2$), 4.21 (q, $J$ = 7 Hz, 2, $CH_2$), 4.2 (br s, 1) and 4.8 (br s, 1) (AB system, $C_5$ H), 6.8–7.7 (m, 6, arom H), 8.23 (d, $J$ = 8 Hz, 1, arom H), 8.73 (s, 1, $C_4$ H). Anal. ($C_{22}H_{17}ClFN_3O_2$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine-2-acetic Acid (25).** A solution of 4.0 g (9.8 mmol) of **24** in 30 mL of EtOH and 25 mL of 1 N aqueous NaOH was heated on the steam bath for 3 h. The mixture was partitioned between 75 mL of water and 75 mL of ether. The basic layer was acidified with acetic acid and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure, and the resulting oil was crystallized from MeOH. Recrystallization from $CH_2Cl_2$/ether/petroleum ether gave 1.3 g of **25** as off-white prisms: IR (KBr) 1718 (C=O) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.3 (br s, 2, $CH_2$), 4.3 (br s, 1), and 4.9 (br s, 1) (AB system, $C_5$ H), 6.8–7.8 (m, 6, arom H), 8.25 (d, $J$ = 8 Hz, 1, arom H), 8.74 (s, 1, $C_4$ H), 8.8 (br s, 1, $CO_2H$). Anal. ($C_{20}H_{13}ClFN_3O_2$) C, H, N.

**9-Chloro-7-(2-fluorophenyl)-*N*-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepine-2-acetamide (26).** Methylamine was bubbled into a solution of 2.6 g (6.3 mmol) of **24** in 60 mL of EtOH for 10 min. After standing for 18 h, the reaction was concentrated at reduced pressure, and the residue was partitioned between $CH_2Cl_2$ and water. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure to dryness. The residue was crystallized twice from $CH_2Cl_2$/ether to give 2.3 g of **26** as colorless rods: IR ($CHCl_3$) 3460 (NH), 1670 (C=O) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.86 (d, $J$ = 4 Hz, 3, $CH_3$), 4.05 (s, 2, $CH_2$), 4.2–5.2 (vbr s, 2, $C_5$ H), 6.8–7.7 (m, 7, arom H, NH), 8.21 (d, $J$ = 8 Hz, 1, arom H), 8.72 (s, 1, $C_4$ H). Anal. ($C_{21}H_{16}ClFN_4O$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-5*H*-pyrimido[5,4-*d*][2]benzazepine (28).** A mixture of 68 g (0.2 mol) of **7c**, 27 g of zinc dust, and 250 mL of acetic acid in 600 mL of $CH_2Cl_2$ was stirred at −30 °C for 2 h. The mixture was filtered over Hy-flo into a stirred mixture of 600 mL of concentrated $NH_4OH$ and 500 mL of ice. The $CH_2Cl_2$ solution was separated, dried, and concentrated at reduced pressure. The residue was crystallized twice from $CH_2Cl_2$/ether to give 5 g of **28** as colorless needles: IR ($CHCl_3$) 3330 (NH) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.36 (br s, 1, NH), 3.58 (d, $J$ = 14 Hz, 1) and 4.02 (d, $J$ = 14 Hz, 1) (AB system, $C_5$ H), 5.13 (s, 1, $C_6$ H), 6.67 (d, $J$ = 2 Hz, 1, arom H), 7.2–7.5 (m, 4, arom H), 7.8–8.0 (m, 2, arom H), 8.67 (s, 1, $C_4$ H), 9.33 (s, 1, $C_2$ H); MS, $m/e$ 341 ($M^+$). Anal. ($C_{18}H_{13}Cl_2N_3$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-2-methyl-5*H*-pyrimido[5,4-*d*][2]benzazepine Dihydrochloride (29).** A mixture 3.7 g (10.5 mmol) of **9c**, 1.3 g of zinc dust, and 40 mL of acetic acid in 90 mL of $CH_2Cl_2$ was stirred at −15 to −20 °C for 30 min. The mixture was filtered over Hy-flo, and the filtrate was basified with cold dilute aqueous NaOH and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure to give a yellow oil. The yellow oil was crystallized from an excess of 6% methanolic HCl to give 3.6 g (80%) of **29** as a colorless solid. Recrystallization from MeOH gave **29** as colorless rods: NMR ($D_2O$–DCl) $\delta$ 3.67 (s, 3, $CH_3$) 4.73 (d, $J$ = 14 Hz, 1) (AB system, $C_5$ H), 6.24 (s, 1, $C_7$ H), 7.63 (d, $J$ = 2 Hz, 1, arom H), 8.1–8.5 (m, 5, arom H), 8.68 (d, $J$ = 8 Hz, 1, arom H), 9.88 (s, 1, $C_4$ H). Anal. ($C_{19}H_{15}Cl_2N_3$·2HCl) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-6,7-dihydro-2,6-dimethyl-5*H*-pyrimido[5,4-*d*][2]benzazepine (30).** A mixture of 4 g (11 mmol) of **29**, 2 mL of formic acid, and 2 mL of 37.5% aqueous formaldehyde was heated on a steam bath for 3 h. The mixture was poured into an excess of dilute ice-cold NaOH and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure to dryness. The residue was crystallized twice from ether to give **30** as colorless prisms: NMR ($CDCl_3$) $\delta$ 2.27 (s, 3, $CH_3$), 2.88 (s, 3, $CH_3$), 3.57 (d, $J$ = 14 Hz, 1) and 3.84 (d, $J$ = 14 Hz, 1) (AB system, $C_5$ H), 4.49 (s, 1, $C_7$ H), 6.54 (d, $J$ = 2 Hz, 1, arom H), 7.2–7.5 (m, 4, arom H), 7.76 (d, $J$ = 8 Hz, 1, arom H), 7.97 (d, $J$ = 7 Hz, 1, arom H), 8.51 (s, 1, $C_4$ H); MS, $m/e$ 369 ($M^+$). Anal. ($C_{20}H_{17}Cl_2N_3$·$2CH_4SO_3$) C, H, N.

**9-Chloro-7-(2-chlorophenyl)-4,5,6,7-tetrahydro-2-methyl-1*H*-pyrimido[5,4-*d*][2]benzazepine Dihydrochloride (31).** A solution of 3.8 g (10.7 mmol) of **9c** in 50 mL of acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 0.5 g of prehydrogenated $PtO_2$. After 3 h, about 500 mL of hydrogen was absorbed, and the catalyst was separated by filtration. The filtrate was dissolved in $CH_2Cl_2$, washed with an excess of dilute ice-cold NaOH, and dried. The $CH_2Cl_2$ solution was diluted with isopropyl alcohol and an excess of methanolic HCl. Concentration of the mixture gave 3.1 g (66%) of **31** as a colorless solid. Recrystallization from MeOH gave colorless prisms: IR (KBr) 2920, 2780, 2470 ($NH^+$), 1687, 1663 (C=N) $cm^{-1}$.

The free base of **31** was prepared by partitioning **31** between aqueous NaOH and $CH_2Cl_2$. The $CH_2Cl_2$ solution was dried and concentrated at reduced pressure to dryness. Crystallization from $CH_2Cl_2$/ether gave the free base of **31** as colorless prisms: mp 197–199 °C dec; IR ($CHCl_3$) 3450 (NH), 1688 $cm^{-1}$; NMR ($CDCl_3$–$Me_2SO$-$d_6$) $\delta$ 1.96 (d, $J$ = 1 Hz, 3, $CH_3$), 3.17 (q, $J$ = 1 Hz, 2, $C_4$ H), 4.00 (d, $J$ = 15 Hz, 1) and 4.28 (d, $J$ = 15 Hz, 1) (AB system, $C_5$ H), 5.26 (s, 1, $C_7$ H), 6.34 (d, $J$ = 2 Hz, 1, arom H), 7.1–7.8 (m, 6, arom H); MS, $m/e$ 357 ($M^+$). Anal. ($C_{19}H_{17}Cl_2N_3$·2HCl) C, H, N.

**Ethanol Interaction with Compound 7c in Righting Reflex.** The subjects were CF-1 male mice, 34–64 days old (18–34 g). Ten mice per group were housed in plastic cages and had food and water available until the time of the experiment.

All the test substances were suspended in aqueous 5% acacia solution. Ethanol solutions were prepared by aqueous dilution of 95% grain alcohol. All compounds were administered orally by intubation at a volume of 0.01 mL/gram of body weight. In an initial experiment, a dose–response curve was obtained for

ethanol alone, using 20–40 mice at each dose level. In the interaction experiments, 7c or diazepam was administered at several dose levels 30 min before administration of a threshold dose of ethanol ($ED_5$ = 5.6 g/kg; based on dose–response experiment). Immediately after ethanol administration, each mouse was placed in an individual cage on a rack, without food or water, and periodically evaluated for loss of righting reflex by attempting to place them on their backs. Mice that remained on their backs for 10 min or more were counted as positive for loss of righting reflex. A computer program was used to calculate effective dose (ED) levels with 95% confidence limits. In the interaction experiments, the $ED_{50}$ represents the dose of test compound calculated to produce loss of righting reflex in half the mice when treated with an $ED_5$ dose of ethanol.

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**Registry No.** 1a, 58582-22-2; 1b, 58583-07-6; 1c, 76049-20-2; 1d, 76049-73-5; 2b, 76049-76-8; 2c, 76049-78-0; 3a, 58582-16-4; 3b, 58582-30-2; 3c, 58582-31-3; 3d, 58582-72-2; 4b, 76049-79-1; 4c, 76049-80-4; 7b, 76988-59-5; 7c, 76988-39-1; 8b, 76988-60-8; 8c, 76988-65-3; 9a, 76988-24-4; 9b, 76988-25-5; 9c, 86712-00-7; 9d, 76988-45-9; 10, 76988-46-0; 11, 76988-40-4; 12, 76988-52-8; 13, 76988-50-6; 13 methanesulfonate, 86712-01-8; 14, 76988-72-2; 15a, 86712-02-9; 15b, 76988-22-2; 15c, 76988-41-5; 15d, 76988-37-9; 16, 76988-62-0; 17, 76988-53-9; 18, 76988-54-0; 19, 76988-58-4; 20, 76988-55-1; 21, 76988-56-2; 22, 76988-57-3; 23, 86712-03-0; 24, 86712-04-1; 25, 86712-05-2; 26, 86712-06-3; 27, 76988-47-1; 28, 76988-73-3; 29, 77000-35-2; 30, 77000-37-4; 31, 77000-36-3; $Me_2NCH(OMe)_2$, 4637-24-5; formamidine acetate, 64392-62-7; acetamidine hydrochloride, 124-42-5; isobutyramidine, 57536-10-4; thiourea, 62-56-6; guanidine, 113-00-8.

# 2-Benzazepines. 6.[1,2] Synthesis and Pharmacological Properties of the Metabolites of 9-Chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine

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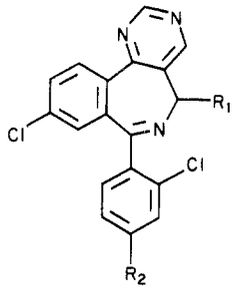
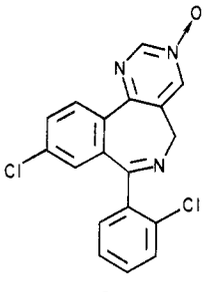
The 2-benzazepine 9-chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (1) has been selected for development as an anxiolytic agent. In support of this program, we have confirmed by chemical synthesis the structures of three in vitro (rat liver homogenate) metabolites of 1 and confirmed the structure of the major in vivo (dog and man) metabolite of 1, compound 2. Two of the metabolites, arising from hydroxylation of the pyrimidobenzazepine ring at the 5-position (2) and *N*-oxide formation at the 3-position of the pyrimidobenzazepine ring (3), were found to be as active as 1 in a series of pharmacological tests. The third metabolite, formed by hydroxylation of the 7-phenyl group in the 4-position (4), was found to be inactive in the same pharmacological screens.

The synthesis and biological activity of a series of pyrimido[5,4-*d*][2]benzazepine analogues was described in the preceding paper.[2] From this series of compounds, the dichloro derivative 1 was selected for further evaluation



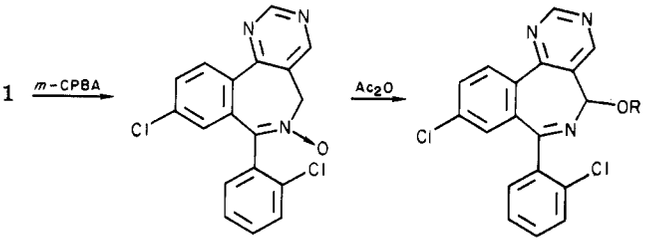
1, $R_1 = R_2 = H$
2, $R_1$ = OH; $R_2 = H$
4, $R_1 = H$; $R_2$ = OH



3

as an anxiolytic agent. The metabolism of 1 was studied[3] in vitro by using rat liver homogenate and resulted in the isolation of three metabolites. The structures of the metabolites were tentatively assigned formulas 2–4 on the basis of spectral data. The major in vivo metabolite of 1 in dogs and man was found to be compound 2, and the quantitative plasma levels of 1 and 2 in dogs (20-mg/kg dose) and man (5-mg/kg dose) have been described.[4] This report describes the syntheses of these compounds, confirming the assigned structures. The pharmacology of compounds 1–4 is also discussed.

Scheme I



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6, R = Ac
2, R = H

**Chemistry.** The initial structure assignments of the metabolites 2–4 were based on NMR and mass spectral data. The mass spectrum of metabolite A (compound 2) showed a molecular ion [*m/e* 355 ($M^+$)] that is 16 mass units greater than the molecular ion of compound 1 [*m/e* 339 ($M^+$)], indicating that an oxygen atom had been introduced in the metabolism of 1. The NMR spectrum of metabolite A showed the absence of the C-5 methylene protons ($\delta$ 4.51) of 1 and the appearance of a methine proton ($\delta$ 5.48). The mass spectrum of metabolite B (compound 3) showed a weak molecular ion [*m/e* 355 ($M^+$)] and a fragmentation pattern similar to compound

(1) Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.
(2) For paper 5 of this series, see Trybulski, E. J.; Benjamin, L. E.; Earley, J.; Fryer, R. I.; Gilman, N.; Reeder, E.; Walser, A.; Davidson, A. B.; Horst, W. D.; Sepinwall, J.; O'Brien, R.; Dairman, W. *J. Med. Chem.*, preceeding paper in this issue.
(3) The in vitro metabolism studies were performed under the direction of Dr. M. Schwartz, and the dog in vivo metabolism studies were conducted by Dr. F. Leinweber, both from our Department of Biochemistry and Drug Metabolism.
(4) Puglisi, C. V.; Ferrara, F. J.; de Silva, J. A. F. *J. Chromatogr. Biomed. Appl.*, in press.

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