Quinazolines and 1,4-Benzodiazepines. XCVI [1]. Compounds Derived from Benzodiazepine-2-acetic Acid

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1,4-Benzodiazepine-2-acetic acid derivatives were prepared and converted to compounds with a heterocyclic ring fused to the *a*-face of the benzodiazepine system. Representatives of pyrido[1,2-*a*][1,4]benzodiazepines, pyrimido[1,6-*a*][1,4]benzodiazepines and [1,3]oxazino[3,4-*a*][1,4]benzodiazepines are described. Some of the compounds showed marked CNS-activity as measured by the antimetrazole test which is a well established primary screening method for assessment of benzodiazepine type activity.

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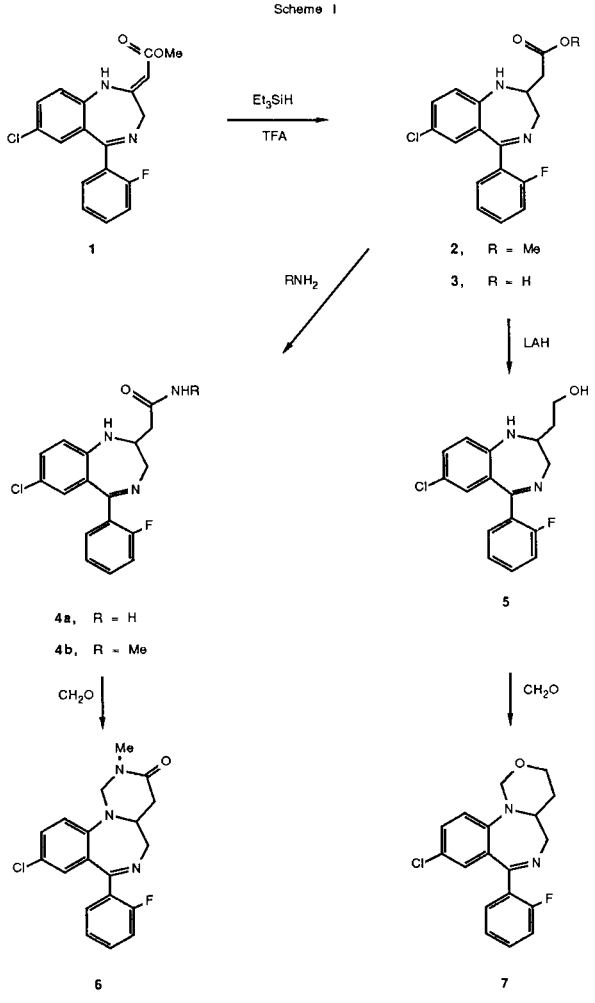
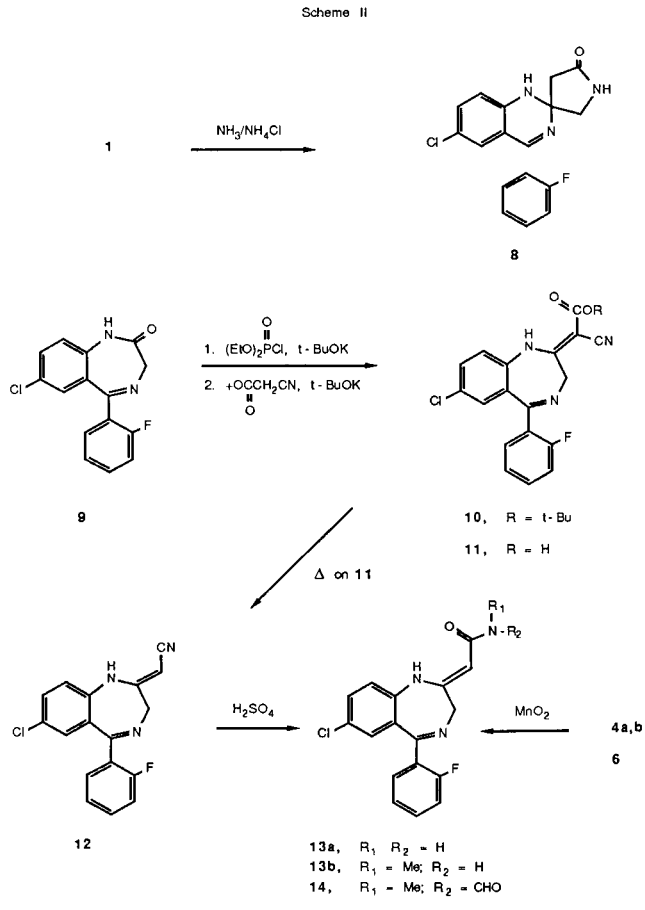
The fusion of heterocyclic rings to the *a*-face of the benzodiazepine system has led to clinically useful derivatives such as the triazolo[4,3-*a*][1,4]benzodiazepines [2] and imidazo[1,5-*a*][1,4]benzodiazepines [3]. The benzodiazepine-2-ylidene acetic acid ester **1** (Scheme I) has been an important intermediate in our synthesis of imidazo[1,5-*a*][1,4]-benzodiazepines. We now report the use of this compound for the preparation of new tricyclic benzodiazepines.

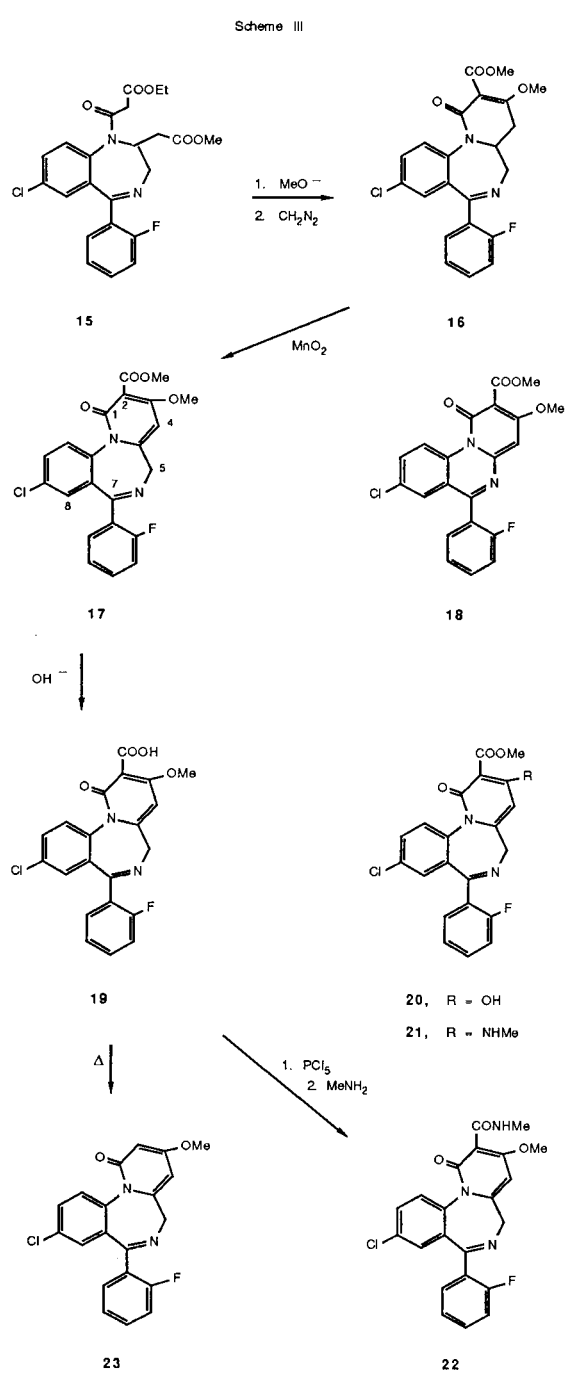
Scheme I



Reduction of **1** with triethylsilane in trifluoroacetic acid yielded the saturated ester **2**. Compound **2** was then hydrolysed to the acid **3**, converted to the amides **4** and reduced to the alcohol **5**. Reaction of the methylamide **4b** and the alcohol **5** with formaldehyde led to the pyrimido-[1,6-*a*][1,4]benzodiazepine **6** and the [1,3]oxazino[3,4-*a*]-[1,4]benzodiazepine **7**, respectively. We attempted to convert the methyl ester **1** to the corresponding primary amide **13a** (Scheme II) by direct amination with ammonia. Heating of **1** in methanolic ammonia in the presence of ammonium chloride at 100° in a steel bomb led instead to the spiroquinazoline **8**, the structure of which was derived from the spectroscopic and analytical data. Compounds **13** were obtained, however, by oxidation of the saturated amides **4** with activated manganese dioxide. Because of the interesting level of activity found with compound **13a**, a more practical synthesis of this amide was sought and found in the hydration of the nitrile **12**. This nitrile was obtained originally by ring expansion as previously described [1] but was prepared in better yield by decarboxylation of the acid **11**. This acid resulted from the cleavage of the corresponding *t*-butyl ester **10**, which was accessible from the lactam **9** by phosphorylation and reaction with the anion of 2-cyanoacetic acid *t*-butyl ester. Treatment of the tricyclic compound **6** with activated manganese dioxide led to the introduction of a double bond also, but ring cleavage could not be avoided, giving thus a mixture of **13b** and the formyl derivative **14**.

The elaboration of ester **2** to pyrido[1,2-*a*][1,4]benzodiazepines is shown in Scheme III. Acylation of **2** with malonic acid half ester chloride in boiling methylene chloride yielded compound **15**. Ring closure with sodium methoxide in methanol followed by re-esterification with diazomethane led to **16** which was oxidized with activated manganese dioxide in refluxing toluene. This oxidation gave **17** as the major and the pyrido[1,2-*a*]quinazoline **18** as the minor product. The latter was most likely formed by further oxidation of **17** at the 5-position to an intermediate 5-one, which could ring contract with loss of the carbonyl





Table

Compound	Toxicity in mice LD_{50} mg/kg p.o.	Antimetrazole activity in mice ED_{50} mg/kg p.o.	3*H*-Diazepam binding assay IC_{50} nm
2	>1000	58	
3	775	>100	
4a	>1000	0.6	
4b	900	14	
5	>1000	6.5	
6	>1000	40	
7	>1000	27.5	
8	>1000	>100	
13a	>1000	4.5	
13b	>1000	2.75	
16	>1000	>100	
17	650	>60	
18	>1000	>100	
20	NT [a]	NT	100
21	NT	NT	130
22	>1000	0.93	5.6
23	NT	NT	27.5
Diazepam	>1000	1.5	5

[a] Compounds were not tested.

function. The loss of the corresponding carbon in the 3-position of 1,4-benzodiazepin-2-ones during oxidation has been reported [4]. Alkaline hydrolysis of the ester **17** led to a mixture of the acid **19** and the hydroxypyridone **20** indicating that Michael addition/elimination occurs readily in this ring system. Accordingly, reaction of **17** with methylamine at room temperature afforded **21**. The analogous addition of methylamine was also observed during the conversion of the acid **19** to the methylamide **22** by reacting

19 with phosphorus pentachloride and subsequently with methylamine. Compound **23** was obtained by thermal decarboxylation of the acid **19**.

Most of the compounds were subjected to primary screening procedures established for benzodiazepines [5]. The results of the preliminary LD_{50} and the test for antagonism of metrazole induced convulsions are listed in the table below. The pyridobenzodiazepines **20-23** were tested *in vitro* as competitive inhibitors of 3*H*-diazepam in the benzodiazepine receptor binding assay [6]. Compound **22**, the most potent *in vitro* binder of the pyridobenzodiazepines was also tested in the antimetrazole procedure and was found to have activity in the range of diazepam. The carboxamides **4a** and **13a,b** were active at a similar level. Comparison of **4b** and **5** with the corresponding tricyclic derivatives **6** and **7** indicates, that fixation of the 2-position substituent in a ring diminished the activity.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus or a Reichert hot stage microscope. The uv spectra were measured in 2-propanol on a Carey Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with tetramethylsilane as internal standard. Ir spectra were determined on a Beckman IR-9 or a Perkin-Elmer 621 grating spectrometer. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying. The yields were generally not optimized.

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine-2-acetic Acid Methyl Ester (**2**).

A solution of 10.33 g (30 mmoles) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-ylidene acetic acid methyl ester (**1**) [7] in 50 ml of trifluoroacetic acid was stirred under an atmosphere of nitrogen and cooled on an ice bath. The solution was treated with 6.97 g (60 mmoles) of triethylsilane, added dropwise over a period of 5 minutes. This ice bath was removed and the stirring was continued for 30 minutes. The mixture was then poured into ice, made alkaline by addition of ammonia and extracted with dichloromethane. The extracts were combined, dried and evaporated. Crystallization of the residue from ether/petroleum ether yielded 9.0 g (86%) of product with mp 118-121°.

Anal. Calcd. for $C_{18}H_{16}ClFN_2O_2$: C, 62.34; H, 4.65; N, 8.08. Found: C, 62.39; H, 4.52; N, 8.18.

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine-2-acetic Acid (**3**).

A solution of 23.3 g (67 mmoles) of **2** and 4.5 g (80 mmoles) of potassium hydroxide in 500 ml of methanol was stirred and refluxed for 30 minutes and then evaporated. The residue was partitioned between ether and water. The organic phase was discarded and the aqueous layer was acidified with acetic acid. The precipitated product was filtered off, washed with water and sucked dry. After drying overnight in a vacuum oven 20.8 g (93%) of product with mp 122-125° was obtained. Recrystallization for analysis from methanol/water gave yellow crystals with mp 126-130°.

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_2$: C, 61.36; H, 4.24; N, 8.42. Found: C, 61.09; H, 4.15; N, 8.34.

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine-2-acetamide (**4a**).

A mixture of 8 g (23 mmoles) of **2** and 100 ml of methanol containing 25% (v/v) of ammonia was heated in a steel bomb at 100° for 17 hours. The solution was evaporated and the residue was crystallized from ether to yield 6.6 g (86%) of product with mp 223-226°. Recrystallization for analysis from tetrahydrofuran/ethyl acetate gave colorless crystals with mp 228-230°.

Anal.. Calcd. for $C_{17}H_{15}ClFN_3O$: C, 61.54; H, 4.56; N, 12.67. Found: C, 61.62; H, 4.65; N, 12.78.

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-*N*-methyl-1*H*-1,4-benzodiazepine-2-acetamide (**4b**).

A mixture of 3.46 g (10 mmoles) of **2** and 25 ml of methanol containing 20% (v/v) of methylamine was heated in a steel bomb at 100° for 3 hours. The solution was evaporated and the residue was crystallized from ether to give 2.7 g (78%) of product with mp 166-170°. Recrystallization for analysis from dichloromethane/hexane gave off white crystals with mp 167-170°.

Anal. Calcd. for $C_{18}H_{17}ClFN_3O$: C, 62.52; H, 4.96; N, 12.15. Found: C, 62.50; H, 5.05; N, 12.00.

7-Chloro-2,3-dihydro-4-(2-fluorophenyl)-2-(2-hydroxyethyl)-1*H*-1,4-benzodiazepine (**5**).

A solution of 1.04 g (3 mmoles) of **2** in 15 ml of tetrahydrofuran was added dropwise to a stirred suspension of 0.22 g (5.7 mmoles) of lithium aluminum hydride in 25 ml of ether. After having stirred under nitrogen for 15 minutes, the excess reagent was decomposed by the slow addition of 1 ml of water. The inorganic material was filtered off and washed with tetrahydrofuran. The filtrate was dried and evaporated. Crystallization from ether yielded 0.8 g (84%) of product with mp 139-141°. Recrystallization for analysis from ether/dichloromethane gave yellow crystals with the same mp.

Anal. Calcd. for $C_{17}H_{16}ClFN_2O$: C, 64.05; H, 5.06; N, 8.79. Found: C, 64.29; H, 5.22; N, 8.72.

9-Chloro-7-(2-fluorophenyl)-1,2,4,5-tetrahydro-2-methyl-3*H*-pyrimido-[1,6-*a*][1,4]benzodiazepin-3-one (**6**).

A mixture of 2 g (5.7 mmoles) of **4a**, 0.7 g (23 mmoles) of paraformaldehyde and 0.1 g of *para*-toluenesulfonic acid in 125 ml of ethanol was stirred and refluxed for 18 hours and then evaporated. The residue was partitioned between dichloromethane and aqueous sodium bicarbonate solution, dried and evaporated. Crystallization from ethyl acetate yielded 1.7 g (82%) of product with mp 251-254°. Recrystallization for analysis from dichloromethane/ethyl acetate gave colorless crystals with mp 256-258°; uv; λ max 235 nm (ε = 22750), infl 270 (6800), 332 (1820); ir (chloroform): 1650 cm^{-1} (CO), 1617 (CN).

Anal. Calcd. for $C_{19}H_{17}ClFN_3O$: C, 63.78; H, 4.79; N, 11.74. Found: C, 63.81; H, 4.62; N, 11.65.

9-Chloro-7-(2-fluorophenyl)-3,4,4a,5-tetrahydro-1*H*-[1,3]oxazino[3,4-*a*]-[1,4]benzodiazepine (**7**).

A solution of 1 g (3.1 mmoles) of **5**, 0.19 g (6.2 mmoles) of paraformaldehyde and 50 mg of *para*-toluenesulfonic acid in 40 ml of ethanol was stirred and refluxed for 6 hours and then evaporated. The residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was separated, dried and evaporated. Crystallization from ethyl acetate/ether yielded 0.55 g of product with mp 174-177°. Another 0.3 g of product was recovered from the filtrate for a total yield of 82%. Recrystallization for analysis from dichloromethane/-hexane gave colorless crystals with the same mp; nmr (deuteriochloroform): 1.0-2.2 (m, 2, C_4-H), 3.17 (t, 1, J = 11 Hz, C_5-H), 3.4-4.5 (m, 4, C_3-H, C_4a-H, C_5-H), 4.68 (d, 1), and 5.05 (d, 1), (AB-system, J = 12 Hz, C_1-H), 6.7-7.7 (m, 7, aromatic H).

Anal. Calcd. for $C_{18}H_{16}ClFN_2O$: C, 65.36; H, 4.88; N, 8.47. Found: C, 65.46; H, 5.06; N, 8.66.

6'-Chloro-4'-(2-fluorophenyl)spiro[pyrrolidine-3,2'(1'*H*)-quinazolin]-5-one (**8**).

A mixture of 1 g (2.9 mmoles) of **1** [7], 1 g of ammonium chloride and 20 ml of methanol containing 20% (v/v) of ammonia was heated in a steel

bomb at 100° for 18 hours. The product was precipitated by dilution with water and was filtered off. It was chromatographed over 30 g of silica gel using dichloromethane containing 5% (v/v) of ethanol. crystallization of the combined clean fractions from ethyl acetate/ether yielded 0.6 g (63%) of product which was recrystallized from the same solvents for analysis, mp 213-216°; uv: λ max 235 nm (ε = 32400), infl 269 (5000), max 395 (2400); ir (chloroform): 3320, 3260 cm^{-1} (NH) 1697 (CO); nmr (d-DMSO): 2.55 (s, 2, CH_2CO), 3.46 (s, 2, CH_2N), 6.4-7.8 (m, 9, aromatic H and 2 NH).

Anal. Calcd. for $C_{17}H_{13}ClFN_3O$: C, 61.92; H, 3.97; N, 12.74. Found: C, 61.87; H, 4.08; N, 12.68.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidenecyanoacetic Acid *t*-Butyl Ester (**10**).

A solution of 28.85 g (0.1 mole) of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, **9**, [8] in 500 ml of tetrahydrofuran was cooled on an ice bath and treated with 12.9 g (0.115 mole) of potassium *t*-butoxide with stirring under nitrogen. After 10 minutes, 25.9 g (0.15 mole) of diethyl chlorophosphate was added and stirring was continued for 10 minutes. A freshly prepared mixture of 28.2 g (0.2 mole) of *t*-butyl cyanoacetate, 22.4 g of potassium *t*-butoxide and 200 ml of dimethylformamide was then added. The ice bath was removed and the mixture was stirred for 1 hour. It was then acidified with acetic acid, diluted with water and extracted with toluene. The extracts were combined, dried and evaporated. Crystallization of the residue from ether yielded 11.4 g of product with mp 171-177°. An additional 4.5 g of product were obtained from the mother liquor for a total yield of 15.9 g (39%). Recrystallization for analysis from ether/hexane did not raise the mp; nmr (deuteriochloroform): 1.55 (s, 9, CMe_3), 4.67 (s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H), 11.65 (s, 1, NH).

Anal. Calcd. for $C_{22}H_{19}ClFN_3O_2$: C, 64.16; H, 4.65; N, 10.20. Found: C, 64.19; H, 4.47; N, 10.32.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidenecyanoacetic Acid (**11**).

A solution of 13 g (32 mmoles) of **10** in 100 ml of trifluoroacetic acid was allowed to sit at room temperature for 2 hours. The solvent was evaporated and the residue was crystallized from ether to yield 11 g (98%) of product with mp 182-185°. Recrystallization for analysis from tetrahydrofuran/hexane did not change the mp.

Anal. Calcd. for $C_{18}H_{11}ClFN_3O_2$: C, 60.77; H, 3.12; N, 11.81. Found: C, 60.97; H, 3.39; N, 11.59.

[7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene]acetonitrile (**12**).

A solution of 5 g of **11** in 300 ml of xylene was stirred and refluxed for 30 minutes and then evaporated. Crystallization of the residue from ether yielded 3.6 g (82%) of product which after recrystallization from ethanol had mp 189-191°. This compound was identical in every respect with that previously reported [1].

[7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene]-acetamide (**13a**).

A. A mixture of 1 g (3 mmoles) of **4a**, 5 g of activated manganese dioxide and 200 ml of 1,2-dichloroethane was stirred and refluxed for 5 hours. The manganese dioxide was filtered off, washed with dichloroethane and the filtrate was evaporated. Crystallization from ether yielded 0.42 g (42%) of product which was recrystallized for analysis from tetrahydrofuran/ethyl acetate to give yellowish crystals with mp 243-245°; uv: λ max 213 nm (ε = 27850) sh 271 (14500) 307 (31700) 362 (2900); ir (chloroform): 3535, 3420 cm^{-1} (NH, NH_2) 1650 (CO).

Anal. Calcd. for $C_{17}H_{13}ClFN_3O$: C, 61.92; H, 3.97; N, 12.74. Found: C, 61.89; H, 3.67; N, 12.79.

B. A solution of 0.2 g (0.67 mmoles) of **12** in 5 ml of concentrated sulfuric acid was allowed to sit at room temperature overnight. It was poured on ice and made alkaline by addition of ammonia. The precipitated product was filtered off, washed with water and sucked dry. Crystallization from dichloromethane/ethanol yielded 0.18 g (78%) of crystals with mp 239-242°.

[7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene]-*N*-methylacetamide (**13b**).

A mixture of 2 g (5.7 mmoles) of **4b**, 12 g of activated manganese dioxide and 300 ml of 1,2-dichloroethane was stirred and refluxed for 3 hours. The reagent was filtered off, washed with tetrahydrofuran and the filtrate was evaporated. Crystallization from ether yielded 0.5 g (25%) of product which was recrystallized for analysis from dichloromethane/hexane to leave pale yellow crystals with mp 203-205°; uv: λ infl 213 nm (ε = 33000), sh 275 (1500), max 308 (32500), 368 (3000); nmr (deuteriochloroform): 2.77 (d, 3, J = 5 Hz, NMe), 4.32 (s, 2, C_3-H), 4.74 (s, 1, -CH=), 6.03 (broad q, 1, J = 5 Hz, NHMe), 6.8-7.7 (m, 7, aromatic H), 11.4 (broad s, 1, NH).

Anal. Calcd. for $C_{18}H_{15}ClFN_3O$: C, 62.89; H, 4.40; N, 12.22. Found: C, 62.62; H, 4.47; N, 12.08.

[7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene]-*N*-formyl-*N*-methylacetamide (**14**).

A mixture of 0.5 g (1.4 mmoles) of **6**, 5 g of activated manganese dioxide and 100 ml of benzene was stirred and refluxed for 6 hours. The manganese dioxide was filtered off and washed with dichloromethane. The filtrate was evaporated and the residue was chromatographed over 5 g of silica gel using 20% (v/v) of ethyl acetate in dichloromethane for elution. Crystallization of the combined clean fractions from ether yielded 0.3 g (57%) of product with mp 180-183°; uv: λ max 219 nm (ε = 27750), infl 245 (17200), max 274 (7000), 328 (31500); ir (chloroform): 1702 cm^{-1} (CHO) 1633 (CO) 1610 (CN); nmr (deuteriochloroform): 3.14 (s, 3, NMe), 4.38 (s, 2, C_3-H), 5.23 (s, 1, -CH=), 6.8-7.8 (m, 7, aromatic H), 9.4 (s, 1, CHO), 11.65 (broad s, 1, NH).

Anal. Calcd. for $C_{19}H_{15}ClFN_3O_2$: C, 61.38; H, 4.07; N, 11.30. Found: C, 61.62; H, 4.40; N, 11.45.

7-Chloro-5-(2-fluorophenyl-2,3-dihydro-1-[(ethoxycarbonyl)acetyl]-1*H*-1,4-benzodiazepine-2-acetic Acid Methyl Ester (**15**).

A mixture of 46 g (0.132 mole) of **2**, 26 ml of (ethoxycarbonyl)acetyl chloride and 1300 ml of benzene was heated to reflux with stirring for 30 minutes. The cooled reaction mixture was washed with saturated sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from ether/hexane yielded 53.8 g (88%) of product. The analytical sample was recrystallized from the same solvents, mp 97-99°; nmr (deuteriochloroform): 1.22 (t, 3, J = 7 Hz, OEt), 2.6 (d, 2, J = 6.5 Hz, CH_2), 3.02 (dd, 1, J = 11 and 12 Hz, C_3-H), 3.13 (s, 2, CH_2), 3.68 (s, 3, OMe), 4.13 (q, 2, J = 7 Hz, OCH_2), 4.15 (dd, 1, J = 11 and 4 Hz, C_3-H), 5.53 (m, 1, C_2-H), 6.8-8.0 (m, 7, aromatic H).

Anal. Calcd. for $C_{23}H_{22}ClFN_2O_5$: C, 59.94; H, 4.81; N, 6.08. Found: C, 60.05; H, 4.98; N, 6.06.

9-Chloro-7-(2-fluorophenyl)-1,4,4a,5-tetrahydro-3-methoxy-1-oxopyrido[1,2-*a*][1,4]benzodiazepine-2-carboxylic Acid Methyl Ester (**16**).

Sodium, 25.5 g (1.1 moles) was dissolved in 3 l of methanol. After addition of 51.1 g (0.11 mole) of **15**, the mixture was stirred and refluxed under nitrogen for 5 minutes. The cooled reaction mixture was acidified with glacial acetic acid and evaporated to dryness. The residue was partitioned between 1 l of water and 1 l of dichloromethane containing 30 ml of ethanol and 25 ml of acetic acid. The organic layer was separated, dried and evaporated, at the end azeotropically with xylene to leave 47 g of oil. This material was dissolved in 500 ml of dichloromethane and the solution was treated with excess diazomethane in ether for 30 minutes. The excess diazomethane was destroyed by addition of acetic acid. The reaction mixture was washed with aqueous sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from ethyl acetate/ether gave 31.2 g (66%) of product. The analytical sample was recrystallized from ethyl acetate/hexane to leave colorless crystals with mp 225-227°; uv: λ max 222 nm (ε = 26500), sh 250 (20500), infl 276 (11000), infl 315 (1650); ir (chloroform): 1727 cm^{-1} (COOMe), 1652 (NCO); nmr (deuteriochloroform): 2.65 (dd, 1, J = 16 and 4 Hz, C_4-H), 3.20 (dd, 1, J = 16 Hz and 13 Hz, C_4-H), 3.53 (dd, 1, J = 12 and 4 Hz, C_5-H), 3.82 (s, 6, OMe), 4.01 (d, 1, J = 12 Hz, C_5-H), 4.50 (dd, 1, J = 13 and 4 Hz, C_{4a}-H),

7.03 (d, 1, J = 2.5 Hz, C_8-H), 7.05-7.6 (m, 5, aromatic H), 7.65 (d, 1, J = 8 Hz, C_{11}-H).

Anal. Calcd. for $C_{22}H_{18}ClFN_2O_4$: C, 61.62; H, 4.23; N, 6.53. Found: C, 61.72; H, 4.41; N, 6.35.

9-Chloro-7-(2-fluorophenyl)-1,5-dihydro-3-methoxy-1-oxopyrido[1,2-*a*][1,4]-benzodiazepine-2-carboxylic Acid Methyl Ester (**17**) and 8-Chloro-6-(2-fluorophenyl)-3-methoxy-1-oxo-1*H*-pyrido[1,2-*a*]quinazoline-2-carboxylic Acid Methyl Ester (**18**).

A mixture of 15.6 g (36 mmoles) of **16**, 1500 ml of toluene and 65 g of activated manganese dioxide was heated to reflux with stirring for 20 minutes. The manganese dioxide was separated by filtration over celite and washed well with dichloromethane. The filtrate was evaporated and the residue was chromatographed over 150 g of silica gel using 5% (v/v) of ethyl acetate in dichloromethane. The fractions containing the less polar by-product **18** were combined and evaporated and the residue was crystallized from dichloromethane/ether to yield 0.8 g (5.3%) of yellow crystals with mp 219-221°; uv: λ max 235 nm (ε = 43700), 239 (44100), infl 265 (13000), sh 305 (15300), 317 (18500), 422 (8180); ir (potassium bromide): 1732 cm^{-1} (COOMe), 1653 (CO); nmr (deuteriochloroform): 3.98 (s, 3, OMe), 4.02 (s, 3, OMe), 6.73 (s, 1, C_4-H), 7.0-8.0 (m, 6, aromatic H), 10.05 (d, 1, J = 9 Hz, C_{10}-H).

Anal. Calcd. for $C_{21}H_{14}ClFN_2O_4$: C, 61.09; H, 3.41; N, 6.78. Found: C, 61.27; H, 3.28; N, 6.90.

The more polar main product **17** was crystallized from benzene to yield 10 g (64%) of colorless crystals with mp 151-154°. Recrystallization for analysis from benzene/hexane did not raise the mp; nmr (deuteriochloroform): 3.88 (s, 3, OMe), 3.92 (s, 3, OMe), 4.08 (d, 1), and 4.98 (d, 1), (AB-system, J = 11 Hz, C_5-H), 6.17 (s, 1, C_4-H), 6.8-7.8 (m, 6, aromatic H), 7.8 (d, 1, J = 8 Hz, C_{11}-H).

Anal. Calcd. for $C_{22}H_{16}ClFN_2O_4$: C, 61.91; H, 3.78; N, 6.56. Found: C, 61.97; H, 3.59; N, 6.61.

9-Chloro-7-(2-fluorophenyl)-1,5-dihydro-3-methoxy-1-oxopyrido[1,2-*a*][1,4]-benzodiazepine-2-carboxylic Acid (**19**) and 9-Chloro-7-(2-fluorophenyl)-1,5-dihydro-3-hydroxy-1-oxopyrido[1,2-*a*][1,4]benzodiazepine-2-carboxylic Acid Methyl Ester (**20**).

A mixture of 4.26 g (10 mmoles) of **17**, 150 ml of methanol, 15 ml of water and 2.25 g (40 mmoles) of potassium hydroxide was heated to reflux for 4 hours under nitrogen. The bulk of the methanol was evaporated and the residue was partitioned between water and ether. The aqueous layer was acidified with acetic acid and extracted with dichloromethane. The extracts were dried and evaporated. Crystallization of the residue from ethyl acetate yielded 2 g (48%) of **19** which was recrystallized from methanol/ethyl acetate for analysis to give colorless crystals with mp 235-237° dec; uv: λ max 220 nm (ε = 50300), sh 255 (17200), sh 296 (7000), max 324 (9800), sh 337 (8000); ir (potassium bromide): 3440 cm^{-1} (OH) 1725 (COOH) 1633 (CO).

Anal. Calcd. for $C_{21}H_{14}ClFN_2O_4$: C, 61.10; H, 3.42; N, 6.79. Found: C, 61.07; H, 3.39; N, 6.56.

The evaporated mother liquor was chromatographed over 30 g of silica gel using dichloromethane/ethyl acetate 1:1 (v/v) for elution. The fractions containing the less polar product **20** were combined and evaporated. Crystallization from ethyl acetate/hexane gave yellowish crystals, 0.7 g (17%), with mp 228-230°; uv: λ max 220 nm (ε = 51600) sh 252 (17600) sh 302 (8600) max 326 (10600); ir (chloroform): 3090 cm^{-1} (OH), 1677 (COOMe), 1645 (CO); nmr (deuteriochloroform): 3.94 (s, 3, OMe), 4.03 (d, 1), and 4.83 (d, 1), (AB-system, J = 12 Hz, C_5-H), 6.1 (s, 1, C_4-H), 6.8-8.0 (m, 7, aromatic H), 13.45 (broad s, 1, OH).

Anal. Calcd. for $C_{21}H_{14}ClFN_2O_4$: C, 61.10; H, 3.42; N, 6.79. Found: C, 61.19; H, 3.45; N, 6.83.

9-Chloro-7-(2-fluorophenyl)-1,5-dihydro-3-methylamino-1-oxopyrido-[1,2-*a*][1,4]benzodiazepine-2-carboxylic Acid Methyl Ester (**21**).

A solution of 0.25 g (0.58 mmoles) of **17** in 5 ml of ethanol containing 20% (v/v) of methylamine was allowed to sit at room temperature for 3 hours. The solvent was evaporated and the residue was crystallized from methanol/ether to yield 0.2 g (80%) of product with mp 214-217°. The analytical sample was recrystallized from ethyl acetate/hexane to give colorless crystals with mp 216-218°; nmr (deuteriochloroform): 3.0 (d, 3, J = 5 Hz, NHMe), 3.86 (s, 3, OMe), 4.12 (d, 1) and 4.85 (d, 1) (AB-system, J = 11.5 Hz, C_5-H), 5.96 (s, 1, C_2-H), 6.8-8.1 (m, 7, aromatic H), 9.55 (broad q, 1, NH).

Anal. Calcd. for $C_{22}H_{17}ClFN_3O_3$: C, 62.05; H, 4.02; N, 9.87. Found: C, 62.21; H, 4.13; N, 9.63.

9-Chloro-7-(2-fluorophenyl)-1,5-dihydro-*N*-methyl-3-methylamino-1-oxopyrido[1,2-*a*][1,4]benzodiazepine-2-carboxamide (**22**).

A mixture of 0.42 g (1 mmoles) of **19**, 20 ml of dichloromethane and 0.3 g of phosphorus pentachloride was stirred at room temperature for 15 minutes. An excess of aqueous methylamine was added and the two phase system was stirred for 30 minutes. The organic layer was separated, dried and evaporated. The residue was chromatographed over 5 g of silica gel using ethyl acetate/dichloromethane 1:1 (v/v). The clean fractions were combined and evaporated and the residue was crystallized from ethyl acetate/hexane to yield 0.24 g (56%) of product with mp 257-258°; uv: λ max 249 nm (ε = 36300), 292 (19900), sh 310 (16000), sh 332 (5500); ir (chloroform): 3260 cm^{-1} (NH), 1663 (CO), 1617 (CN), 1550 (CON); nmr (deuteriochloroform): 2.85 (d, 3, J = 5 Hz, NHMe), 2.95 (d, 3, J = 5 Hz, NHMe), 4.08 (d, 1), and 4.82 (d, 1), (AB-system, J = 12 Hz, C_5-H), 6.0 (s, 1, C_4-H), 6.8-7.8 (m, 7, aromatic H), 10.0 (broad q, 1, NH), 10.9 (broad q, 1, NH).

Anal. Calcd. for $C_{22}H_{18}ClFN_4O_2$: C, 62.19; H, 4.27; N, 13.19. Found: C, 62.08; H, 4.26; N, 13.06.

9-Chloro-7-(2-fluorophenyl)-3-methoxypyrido[1,2-*a*][1,4]benzodiazepin-1(5*H*)-one (**23**).

A solution of 1 g (2.4 mmoles) of **19** in 25 ml of 1,2,4-trichlorobenzene was heated to reflux under nitrogen for 30 minutes. The reaction mixture was diluted with toluene and extracted 4 times with 2*N* hydrochloric acid. The extracts were washed with toluene and made alkaline with ammonia. The precipitated material was extraced with dichloromethane. The extracts were dried and evaporated and the residue was crystallized from ethyl acetate/ether to yield 0.6 g (67%) of product with mp 176-178°. The analytical sample was recrystallized from ether/hexane and had the same mp; uv: λ max 218 nm (ε = 55400), sh 245 (21400), max 288 (8200), sh 307 (7000); ir (chloroform): 1668 cm^{-1} (CO), 1614 (CN); nmr (deuteriochloroform): 3.73 (s, 3, OMe), 4.03 (d, 1), and 4.78 (d, 1), (AB-system, J = 11.5 Hz, C_5-H), 5.88 (d, 1), and 5.98 (d, 1), (AB-system, J = 2.5 Hz, C_2-H and C_4-H), 6.8-7.7 (m, 6, aromatic H), 7.75 (d, 1, J = 8.5 Hz, C_{11}-H).

Anal. Calcd. for $C_{20}H_{14}ClFN_2O_2$: C, 65.14; H, 3.83; N, 7.60. Found: C, 65.18; H, 3.95; N, 7.54.

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