2-Benzazepines. 10 [1]. New *d*-Fused 2-Benzazepines

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Pyrano[3,2-*d*][2]benzazepines were synthesized by reaction of the *beta*-dimethylamino unsaturated ketone **1** with malonic ester or the anion of *t*-butyl acetate. Conversion of the pyrano derivative to the pyrido[3,2-*d*]-[2]benzazepine was achieved in low yield. A pyrrolo[3,2-*d*][2]benzazepine was prepared *via* an oxazepino-[6,7-*d*][2]benzazepine which was obtained by reaction of **1** with the anion of ethyl isocyanoacetate.

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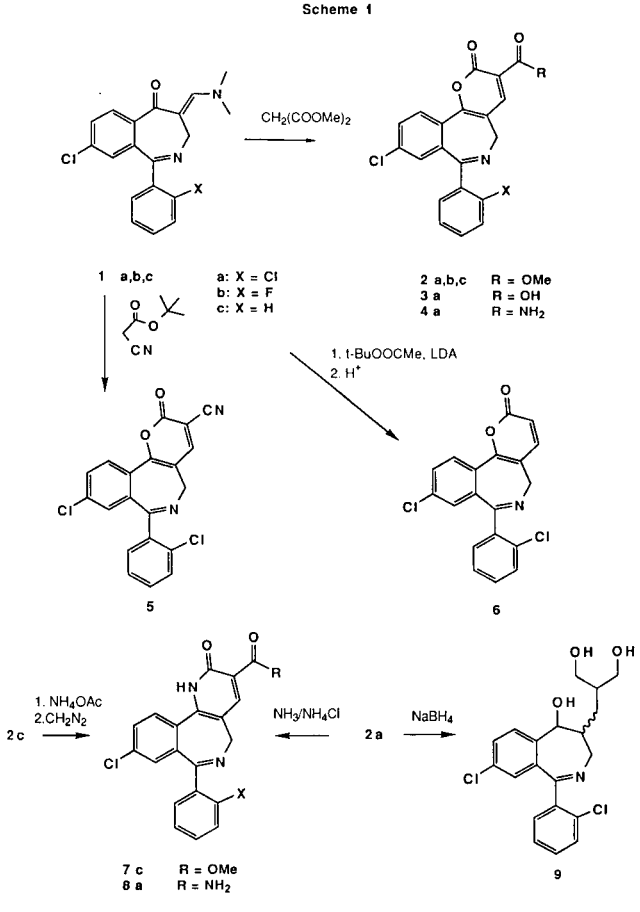
2-Benzazepines are carbon isosteres of the extensively investigated 1,4-benzodiazepines and have been studied by Gwchwend *et al.* [2] and in our laboratories by Trybulski *et al.* [3]. Several *d*-fused 2-benzazepines have shown activity on the central nervous system comparable to that of the well known *a*-fused 1,4-benzodiazepines, but none has yet advanced beyond the stage of clinical trials.

The *beta*-dimethylamino unsaturated ketone **1** has been a focal intermediate for the elaboration of pyrazolo[4,3-*d*]-[2]benzazepines [2a] and pyrimido[5,4-*d*][2]benzazepines [3a]. We have briefly explored the utility of compounds **1** for the synthesis of other *d*-fused [2]benzazepines which we anticipated to have similar effects on the central nervous system. The results of this limited study are reported here together with some biological data.

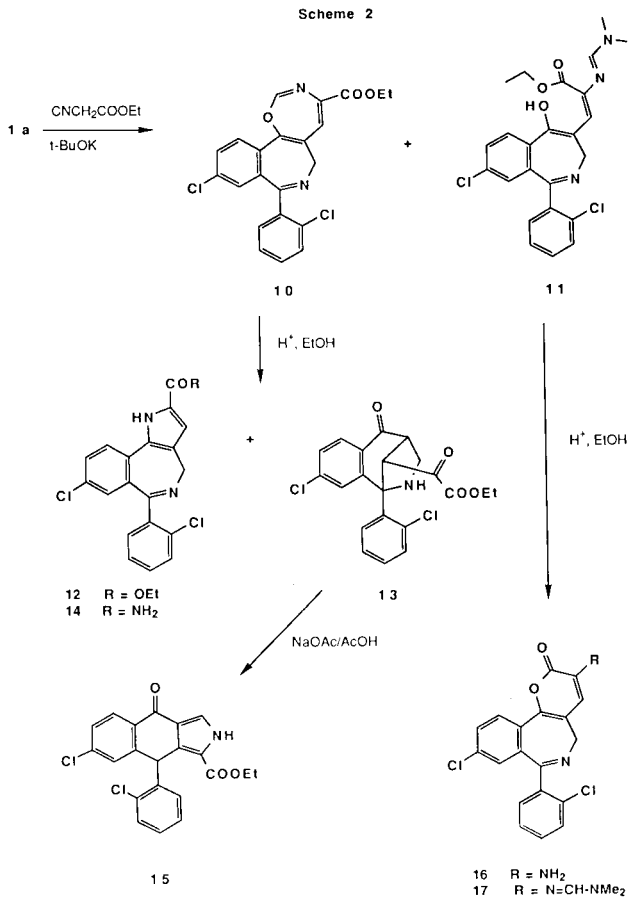
Reaction of the unsaturated ketones **1** (Scheme 1) with dimethyl malonate at reflux led to the highly fluorescent pyrano[3,2-*d*][2]benzazepines **2**. Hydrolysis of the methyl ester **2a** under acidic conditions gave the corresponding carboxylic acid **3a**. Since **3a** did not decarboxylate thermally to **6**, this compound was prepared by reacting the ketone **1a** with the anion of *t*-butyl acetate, generated with lithium diisopropylamide, and by treating the obtained intermediate ester with concentrated sulfuric acid. The amide **4a** resulted from the reaction of the methyl ester **3a** with methanolic ammonia at reflux. Condensation of **1a** with cyanoacetic acid *t*-butyl ester under reflux gave the nitrile **5** as the major product, isolated by chromatography from a rather complex mixture. Attempts to prepare the pyridone **8a** by reacting the ketone **1a** with malonodiamide in hot hexamethyl phosphoric triamide were unsuccessful and resulted in the formation of the *beta*-amino unsaturated ketone derived from **1a** by displacement of the dimethylamino moiety by ammonia. The conversion of the pyrone **2a** to the corresponding pyridone **8a** succeeded in poor yield by heating in methanolic ammonia at 100° in the presence of ammonium chloride. The pyridone ester **7c** was isolated, again in low yield, from the treatment of **2c** with ammonium acetate in boiling dimethylformamide followed by esterification of the recovered acid with diazomethane. While the pyrones are thus readily available from compounds **1**, they did not lend themselves for an efficient transformation to the pyridones, which we hoped to be pharmacologically more interesting.

Scheme 1



The high reactivity of the ester function in **2a**, evident from the easy conversion to the amide, prompted us to try its reduction to the corresponding alcohol. Reduction of this compound with sodium borohydride in ethanol/tetrahydrofuran at room temperature led to a mixture of two diastereomeric triols **9A** and **B** which were separated chromatographically and characterized spectroscopically. The

Scheme 2



pmr-spectra of these diastereomers allowed a tentative assignment of the stereochemistry. The more polar isomer **B** displays a proton at unusually high field (0.6 ppm). Shielding of this magnitude may be explained by positioning the hydroxypropyl chain over the aromatic ring. Such an arrangement is possible with the hydroxy group in 5-position and the chain in 4-position in *cis* configuration and the hydroxy group assuming an equatorial orientation, coplanar with the aromatic ring. Such coplanarity of the hydroxy group with the aromatic ring is supported by the deshielding effect on the C_6-proton observed in both isomers. This structure assignment was confirmed by single crystal X-ray analysis of the less polar diastereomer **9A**, which showed *trans* configuration of the hydroxy group at C_5 and the side chain at C_4. Since compounds **1** reacted with the carbanion of acetate, we envisaged to arrive at pyrrolo[3,2-*d*][2]benzazepines by condensing these compounds with the anion if isocyanoacetate.

As depicted in Scheme 2, the ketone **1a** reacted with the anion of ethyl isocyanoacetate to give a mixture of the oxazepino derivative **10** and the amidine **11**, which could be separated by fractional crystallization. The formation of **10** results from addition of the anion to the beta carbon with elimination of dimethylamine and intramolecular addition of the enol to the isonitrile. Addition of dimethylamine to the isocyano group would lead to compound **11**. Both these compounds were sensitive to acid. When the oxazepine **10**, the major product, was heated with ethanolic sulfuric acid two products were formed and separated by chromatography. The more polar compound was the expected pyrrolo[3,2-*d*][2]benzazepine **12**, while the interesting bridged bicyclic structure **13** was assigned to the less polar product. The structure of compound **13** could not be derived unequivocally from the spectroscopic data and was determined by X-ray analysis. The most characteristic features in the 200-MHz pmr spectrum of **13** are the inequivalence of the OCH_2-protons of the ester function, the deshielding of the 3-proton of the 2-chlorophenyl ring down to about 8.04 ppm and the NH signal at 2.04 ppm. The singlet at 5.09 ppm shows a very small coupling constant with the neighboring proton indicating a 90° dihedral angle. Its unusually downfield chemical shift has to be due to deshielding by both the ketoester carbonyl and by the 2-chlorophenyl group, an arrangement evident from the crystal structure (see Figure 1). The C_{10}-proton is shielded by the 2-chlorophenyl moiety and appears at 6.68 ppm well separated from the other aromatic hydrogens.

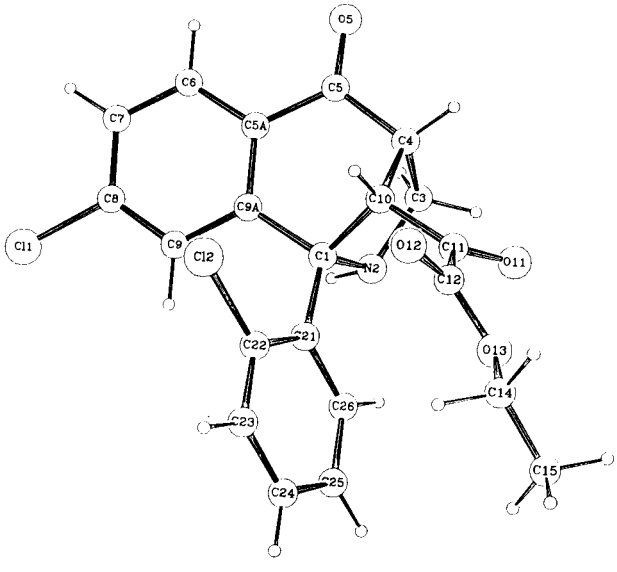
We hoped that **13** would undergo retroaldol cleavage to a benzazepine whose 1,4-dicarbonyl functionality could cyclize to a furo[3,2-*d*][2]benzazepine with loss of water. The reaction of **13** with sodium acetate in boiling acetic acid resulted in a clean rearrangement which yielded the pyrrolo derivative **15**, apparently by the preferred retro Michael reaction and subsequent cyclization of the amino group onto the ketone of the ketoester moiety. The structure of **15** was derived from the spectroscopic data. The 200-MHz pmr-spectrum was particularly informative. The methyl protons of the ethyl ester group are shielded by the *o*-chlorophenyl moiety and appear at 0.82 ppm as compared to 1.36 ppm for compounds **10** and **12**. Each aromatic proton could be detected and assigned. The doublet with fine-structure at the highest field was attributed to the 6-proton on the 2-chlorophenyl group and is apparently shielded by the pyrrole ring. The lowest field doublet at 7.94 ppm was assigned to the aromatic proton next to the carbonyl group (C_5-H). The aromatization of compound **15** to the phenol does not occur for steric reasons.

Reaction of the amidine **11** with ethanolic sulfuric acid afforded a mixture of the aminopyrone **16** and the corresponding dimethylformamidine **17**. The compounds were separated by chromatography. The propensity of compound **11** to form the pyrone rather than the pyrrole is remarkable and may be due to the disfavoured 5-endo-trigonal cyclization to the pyrrole. Another possible explanation would be the syn-orientation of the ester carbonyl with the enolized carbonyl group as depicted arbitrarily in compound **11**.

Most of the new *d*-fused 2-benzazepines described above were tested in vitro in the ^{3}H-Diazepam binding

assay [4]. Selected compounds were also tested *in vivo* for their ability to protect mice from pentylenetetrazole induced convulsions, a test that correlates well with the anticonvulsant and anxiolytic activity of 1,4-benzodiazepines [5]. The data are listed in the table below. All compounds showed good affinity for the benzodiazepine binding site with exception of the bridged bicyclic compound **13**. Although compounds **2a**, **6**, **8a**, **14** and **16** showed IC_{50} in the binding assay superior to diazepam, their *in vivo* activity did not reach that of diazepam (compound **8a** was not tested *in vivo*). Among the compound tested *in vivo*, the pyrone **17** was the most active. While the pyrrole ester **12** was inactive at 200 mg/kg orally, the corresponding amide **14** exhibited an ED_{50} of 16 mg/kg. The oxazepino derivative **10** was superior to the pyrone ester **2a** and the pyrrole ester **12**. We have not been able to determine, whether the compounds with high affinity *in vitro* and poor *in vivo* effect are partial agonists [6] or whether the lack of *in vivo* activity is due to poor bioavailability.

Figure 1



Biological Data

Compound	Diazepam binding assay IC_{50} (nM)	Antipentylenetetrazole ED_{50} mg/kg p.o.
2a	3.3	190
2b	NT	>100
3a	9.5	NT
4a	22	NT
5	12	NT
6	2.2	35
7c	37	NT
8a	2.0	NT
10	7.6	21
11	18	NT
12	12	>200
13	>1000	NT
14	2.3	16
16	3.2	2.8
17	5.6	1.2
Diazepam	5.0	

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. The ^1H nmr spectra were recorded on a Varian T-60 or a HA-100 instrument and are reported in ppm from TMS as internal standard. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Silica gel Merck (70-320 mesh) was used for column chromatography and anhydrous sodium sulfate for drying purposes.

9-Chloro-7-(2-chlorophenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-*d*][2]benzazepine-3-carboxylic Acid Methyl Ester (**2a**).

A mixture of 7.2 g (0.02 mole) of 8-chloro-1-(2-chlorophenyl)-4-dimethylaminomethylene-3,4-dihydro-2-benzazepin-5-one (**1a**) and 40 ml of dimethyl malonate was heated to reflux for 2 hours while 10 ml of the malonic ester was distilled off. The dimethyl malonate was evaporated under reduced pressure, at the end azeotropically with xylene. The residue was crystallized from ethyl acetate/ether to yield 5.3 g (64%) of yellow crystals which were recrystallized from ethyl acetate/hexane for analysis and had mp 189-191°; pmr (deuteriochloroform): 3.92 (s, 3, OMe), 4.23 (broad s, 2, CH_2), 7.1-7.8 (m, 6, aromatic H), 8.08 (d, 1, J = 8 Hz, C_{11}-H), 8.33 (s, 1, C_3-H).

Anal. Calcd. for $C_{21}H_{13}Cl_2NO_4$: C, 60.89; H, 3.16; N, 3.38. Found: C, 60.66; H, 3.17; N, 3.27.

9-Chloro-7-(2-fluorophenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-*d*][2]benzazepine-3-carboxylic Acid Methyl Ester (**2b**).

This compound was similarly obtained in 73% yield by reacting **1b** with dimethyl malonate. The product was crystallized from ether and the analytical sample was recrystallized from methylene chloride/ethyl acetate to give yellow crystals with mp 191-193°; pmr (deuteriochloroform): 3.9 ppm (s, 3, OMe), 4.18 (broad s, 2, CH_2), 6.8-7.8 (m, 6, aromatic H), 8.08 (d, 1, J = 8 Hz, C_{11}-H), 8.33 (s, 1, C_3-H).

Anal. Calcd. for $C_{21}H_{13}ClFNO_4$: C, 63.41; H, 3.29; N, 3.52. Found: C, 63.36; H, 3.26; N, 3.36.

9-Chloro-7-phenyl-2-oxo-2*H*,5*H*-pyrano[3,2-*d*][2]benzazepine-3-carboxylic Acid Methyl Ester (**2c**).

This compound was obtained analogously from **1c** and dimethyl malonate. Crystallized from ether it had mp 164-166°; uv: λ sh 224 nm (ε = 28700) max 255 (16700) 370 (17500); ir (chloroform): 1764 cm^{-1} (CO) 1740 and 1710 (COOMe); pmr (deuteriochloroform): 3.9 ppm (s, 3, OMe), *ca.* 4.17 (very broad s, 2 CH_2), 7.36 (s, 5, phenyl), 7.43 (d, 1, J = 2 Hz, C_8-H), 7.63 (dd, 1, J = 8 Hz and 2 Hz, C_{10}-H), 8.06 (d, 1, J = 8 Hz, C_{11}-H), 8.33 (s, 1, C_3-H)

Anal. Calcd. for $C_{21}H_{14}ClNO_4$: C, 66.41; H, 3.72; N, 3.69. Found: C, 66.34; H, 3.72; N, 3.63.

9-Chloro-7-(2-chlorophenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-*d*][2]benzazepine-3-carboxylic Acid (**3a**).

A mixture of 0.5 g of **2a**, 5 ml of concentrated sulfuric acid and 2 ml of water was heated on the steam bath for 15 minutes. After dilution with water, the precipitated product was filtered off, washed with water and dissolved in methylene chloride containing 10% (v/v) of ethanol. The solution was washed with water, dried and evaporated. Crystallization of the residue from methylene chloride/ethanol gave 0.38 g (79%), of yellow crystals which melted with decomposition at 255-260°; uv: λ sh 277 nm (ε = 26500), sh 253 (12200), max 368 (15500); ir (potassium bromide): 1765, 1652 cm^{-1} (CO), 1672 (COOH).

Anal. Calcd. for $C_{20}H_{11}Cl_2NO_4$: C, 60.02; H, 2.77; N, 3.50. Found: C, 60.09; H, 2.82; N, 3.58.

9-Chloro-7-(2-chlorophenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-*d*][2]benzazepine-3-carboxamide (**4a**).

A suspension of 0.5 g of **2a** in 40 ml of methanol containing 20% (v/v) of ammonia was heated to reflux for 30 minutes. After addition of another portion of 20 ml of methanolic ammonia, heating was continued for 15 minutes. The product crystallized partially during this process. The solvent was evaporated partially on the steam bath and the crystals were collected to yield 0.31 g (64%) of yellow product with mp >310°. The analytical sample was recrystallized from tetrahydrofuran/methanol; uv (ethanol containing 8% of methylene chloride): λ sh 228 (ε = 24800) sh 253 (13500), max 370 (18000); ir (potassium bromide): 3390 cm^{-1} (NH_2), 1711 (CO), 1670 ($CONH_2$).

Anal. Calcd. for $C_{20}H_{12}Cl_2N_2O_3$: C, 60.17; H, 3.03; N, 7.02. Found: C, 60.30; H, 3.04; N, 6.98.

Thin-layer chromatography indicated the presence of the bright blue fluorescent pyridone **8a** in the original mother liquor in addition to several other byproducts.

9-Chloro-7-(2-chlorophenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-*d*][2]benzazepine-3-carbonitrile (**5**).

A mixture of 1 g of **2a**, 10 ml of dimethylformamide and 5 ml of cyanoacetic acid *t*-butyl ester was heated to reflux for 1 hour. The dark brown solution was evaporated under reduced pressure azeotropically with xylene. The residue was chromatographed over 40 g of silica gel using 3% (v/v) of ethanol in methylene chloride for elution. The combined clean fractions containing the major component of the reaction mixture were evaporated and the residue was crystallized from ether/ethyl acetate/hexane and recrystallized from ethyl acetate/hexane to give 0.15 g (14%) of off-white crystals with mp 233-234°; uv: λ sh 228 nm (ε = 26100), sh 253 (12600), max 376 (18400), sh 399 (10800); ir (chloroform): 2235 cm^{-1} (CN), 1745 (CO); pmr (deuteriochloroform): 4.2 ppm (broad s, 2, CH_2), 7.1-7.9 (m, 6, aromatic H), 7.98 (s, 1, C_3-H), 8.05 (d, 1, J = 8 Hz, C_{11}-H).

Anal. Calcd. for $C_{20}H_{10}Cl_2N_2O_2$: C, 63.01; H, 2.64; N, 7.35. Found: C, 63.13; H, 2.54; N, 7.21.

9-Chloro-7-(2-chlorophenyl)-5*H*-pyrano[3,2-*d*][2]benzazepin-2-(2*H*)-one (**6**).

A solution of 1.75 ml of diisopropylamine in 30 ml of tetrahydrofuran was cooled to −50° with stirring under nitrogen. Butyllithium in hexane, 8 ml of 1.6 molar solution, and 2 ml of *t*-butyl acetate were added in sequence. After stirring at −50° to −40° for 5 minutes, a solution of 3.6 g (10 mmoles) of **1a** were added and the mixture was allowed to warm to room temperature. It was partitioned between saturated aqueous sodium bicarbonate and toluene. The organic layer was separated, dried and evaporated to leave an oily product which consisted according to nmr of a mixture of two geometrical isomers.

This mixture was dissolved in 10 ml of methylene chloride and treated with 25 ml of concentrated sulfuric acid. After heating on the steam bath for 5 minutes with evaporation of the methylene chloride, the reaction mixture was poured on ice, made alkaline with ammonia and extracted with methylene chloride/ether. The extracts were dried and evaporated and the residue was chromatographed over 120 g of silica gel using 10% (V/V) of ethyl acetate in methylene chloride for elution. Crystallization of the combined clean fractions from ethyl acetate/hexane yielded 1.2 g (34%) of yellow crystals with mp 184-186°; uv: λ max 224 nm (ε = 30500), sh 250 (14500), sh 295 (5200), sh 325 (9300), max 346 (11300), sh 374 (5100); ir (chloroform): 1720 cm^{-1} (CO); pmr (deuteriochloroform): 4.1 ppm (broad s, 2, CH_2), 6.31 (d, 1, J = 9 Hz, C_3-H), 7-7.8 (m, 7, aromatic H), 8.0 (d, 1, J = 8 Hz, C_{11}-H).

Anal. Calcd. for $C_{19}H_{11}Cl_2NO_2$: C, 64.07; H, 3.11; N, 3.93. Found: C, 63.84; H, 2.99; N, 4.00.

A more polar byproduct was eluated with methylene chloride/ethyl acetate 1:1. It was not obtained in a crystalline state and the spectral data indicated a dimer of unknown structure.

9-Chloro-1,2-dihydro-2-oxo-7-phenyl-5*H*-pyrido[3,2-*d*][2]benzazepine-3-carboxylic Acid Methyl Ester (**7c**).

A mixture of 1 g of **2c**, 1.5 g of ammonium acetate and 20 ml of dimethylformamide was heated to reflux for 1.5 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The aqueous layer was acidified with acetic acid and was extracted with methylene chloride. The extracts were dried and evaporated and the residue was crystallized from ethanol to give 0.3 g of crude acid. This material was dissolved in methylene chloride and treated with a solution of diazomethane in ether until the yellow color persisted. The excess diazomethane was destroyed by addition of acetic acid and the reaction mixture was evaporated and the residue was chromatographed over 7 g of silica gel using 20% methylene chloride in ethyl acetate for elution. The fractions containing the blue fluorescent (uv) product were combined and evaporated. Crystallization from ethyl acetate/hexane gave 90 mg of colorless crystals with mp 245-247°; uv: λ max 234 nm (ε = 28700), sh 255 (23000), sh 302 (5800), max 336 (11800), max 374 (5700); ir (potassium bromide): 3400-3140 cm^{-1} (NH or OH), 1738 (COOMe), 1693, 1683 (CO, H-bonded COOMe); pmr (deuteriochlorofrom): 3.81 ppm (d, 1) and 4.96 (d, 1) (AB-system, J = 12 Hz, CH_2), 3.93 (s, 3, OMe), 7.1-7.7 (m, 7, aromatic H), 8.16 (d, 1, J = 8 Hz, C_{11}-H), 8.2 (s, 1 C_4-H).

Anal. Calcd. for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.47; H, 4.03; N, 7.37.

9-Chloro-7-(2-chlorophenyl)-1,2-dihydro-2-oxo-5*H*-pyrido[3,2-*d*][2]-benzazepine-3-carboxamide (**8a**).

A mixture of 0.5 g of **2a**, 0.5 g of ammonium chloride and 15 ml of methanol containing 20% (v/v) of ammonia was heated in a steel autoclave for 18 hours at 100°. The methanolic ammonia was evaporated and the residue was partitioned between aqueous sodium bicarbonate solution and methylene chloride. The organic phase was dried and evaporated. The residue was a complex

mixture by tlc. Partial recrystallization from ethyl acetate yielded 90 mg of crystals which showed a blue fluorescence under uv-light. Chromatography of the mother liquor over 35 g of silica gel with 5% (v/v) of ethanol in methylene chloride afforded another 30 mg of the same material. It was recrystallized from ethanol/-ethyl acetate to give colorless crystals with mp >300°; uv: λ max 234 nm (ε = 27500) sh 257 (14800) sh 325 (4200) max 369 (13500); ir (potassium bromide): 3460, 3330 cm^{-1} (NH, OH) 1678 (CON); pmr (deuteriodimethyl sulfoxide): 3.58 ppm (broad d, 1) and 4.86 (broad d, 1) (AB-system, J = 12 Hz, CH_2), 7.1 (d, 1, J = 2 Hz, C_8-H), 7.2-7.85 (m, 6, aromatic H and NH), 7.98 (d, 1, J = 8 Hz, C_{11}-H), 8.51 (s, 1, C_4-H), 9.0 (broad s, 1, NH), 12.89 (broad s, 1, NH or OH).

Anal. Calcd. for $C_{20}H_{13}Cl_2N_3O_2$: C, 60.32; H, 3.29; N, 10.55. Found: C, 60.11; H, 3.34; N, 10.49.

8-Chloro-1-(2-chlorophenyl)-4,5-dihydro-4-[3-hydroxy-2-(hydroxymethyl)propyl]-5*H*-[2]benzazepin-5-ols **9A** and **9B**.

A mixture of 0.415 g (1 mmole) of **2a**, 5 ml of tetrahydrofuran, 5 ml of ethanol and 0.2 g of sodium borohydride was stirred at room temperature for 1.5 hours. It was partitioned between water and methylene chloride. The organic phase was dried and evaporated and the residue was chromatographed over 40 g of silica gel using 5% of ethanol in methylene chloride followed by 10% of ethanol in methylene chloride. The less polar component was crystallized from ethyl acetate/ether to give colorless crystals with mp 176-178°; uv: λ sh 211 nm (ε = 40950), max 247 (8950), 288 (1650); ir (chloroform): 3420, 3200 cm^{-1} (OH); pmr (deuteriochloroform + few drops of deuteriodimethyl sulfoxide): 1.5-2.6 (m, 4, CH_2, CH, CH), 3.08 (dd, 1, J = 5.5 and 10 Hz, C_3-H axial), 3.4-3.8 (m, 4, CH_2OH), 3.86 (d, 1, J = 10 Hz, C_3-H, equatorial), 4.06 (broad s, 2, OH), 4.5 (dd, 1, J = 5 and 8.5 Hz, C_5-H), 5.16 (d, 1, J = 5 Hz, OH), 6.78 (d, 1, J = 2 Hz, C_9-H), 7.2-7.6 (m, 5, aromatic H), 7.7 (d, 1, J = 8 Hz, C_6-H); ms: m/e 393 (M^+).

The more polar component was also crystallized from ethyl acetate/ether to give colorless crystals with mp 162-164°; uv: λ sh 212 nm (ε = 44050), max 246 (9400), 287 (1750); ir (chloroform): 3280 cm^{-1} (OH); pmr (deuteriochloroform + deuteriodimethyl sulfoxide): 0.6 ppm (m, 1, CH), 1.5-2.0 (m, 2, CH_2), 2.5 (dd, 1, J = 10 Hz and 11 Hz, C_3-H axial), 2.97 (m, 1, CH), 3.3-3.8 (m, 6, 2 CH_2, 2 OH), 3.98 (dd, 1, J = 10 Hz and 5.5 Hz, C_3-H equatorial), 4.7 (d, 1, J = 2.5 Hz, OH), 4.92 (dd, 1, J = 2.5 Hz and 6 Hz, C_5-H), 6.80 (d, 1, J = 2 Hz, C_9-H), 7.1-7.5 (m, 5, aromatic H), 7.66 (d, 1, J = 8 Hz, C_6-H); ms: m/e 393 (M^+).

10-Chloro-8-(2-chlorophenyl)-6*H*-1,3-oxazepino[6,7-*d*][2]benzazepine-4-carboxylic Acid Ethyl Ester (**10**) and 3- [8-Chloro-1-(2-chlorophenyl)-5-hydroxy-3*H*-[2]benzazepin-4-yl]-*alpha*[(dimethylamino)methylene]amino)-2-propenoic Acid Ethyl Ester (**11**).

A solution of 3.6 g (10 mmoles) of **1a** in 100 ml of dry tetrahydrofuran was cooled to 0°. Ethyl isocyanoacetate, 2.5 ml (22.8 mmoles), was added followed by 2.25 g (20 mmoles) of potassium *t*-butoxide. After stirring at 5-8° for 1 hour under an atmosphere of nitrogen, the mixture was partitioned between toluene and saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried and evaporated. Crystallization of the residue from ether yielded 2.5 g (58%) of **10** as yellow crystals which were recrystallized from ethyl acetate/hexane to have mp 171-173°; uv: λ max 228 nm (ε = 29700), infl 260 (10700), max 357 (12500); ir (chloroform); 1718 cm^{-1} (COOEt); pmr (deuteriochloroform): 1.36 (t, 3, J = 6.5 Hz, CH_3), 4.08 (broad s, 2, CH_2), 4.35 (q, 2, J = 6.5 Hz, OCH_2), 6.45 (s, 1, C_5-H), 7-7.8 (m, 7, C_2-H and aromatic H), 8.03 (d, 1, J = 8 Hz, C_{12}-H); ms: m/e 426 (M^+).

Anal. Calcd. for $C_{22}H_{16}Cl_2N_2O_3$: C, 61.84; H, 3.77; N, 6.56. Found: C, 62.05; H, 3.92; N, 6.49.

From the original mother liquor the second compound **11**, (1 g or 21%) was obtained, crystallizing from ether as orange crystals. They were recrystallized from ether for analysis and had mp 182-184°; uv: λ sh 228 nm (ε = 32700), sh 273 (11000), max 390 (14000); ir (chloroform): 1690 cm^{-1} (COOEt), 1635 (C=N); pmr (deuteriochloroform): 1.3 (t, 3, J = 7 Hz, CH_3), 3.1 (s, 6, NMe_2), 3.0-4.5 (very broad AB-system, 2, CH_2), 4.21 (q, 2, J = 7 Hz, OCH_2), 6.97 (s, 1, olefinic H), 7.04 (d, 1, J = 2 Hz, C_9-H), 7.2-7.5 (m, 6, aromatic H), 7.96 (d, 1, J = 8 Hz, C_6-H), 8.0 (s, 1, amidine H), 14.75 (broad s, 1, OH); ms: m/e 471 (M^+).

Anal. Calcd. for $C_{24}H_{23}Cl_2N_3O_3$: C, 61.02; H, 4.91; N, 8.90. Found: C, 61.07; H, 4.83; N, 8.91.

8-Chloro-6-(2-chlorophenyl)-1*H*,4*H*-pyrrolo[3.2-*d*][2]benzazepine-2-carboxylic Acid Ethyl Ester (**12**) and *rac*-8-Chloro-1-(2-chlorophenyl)-2,3,4,5-tetrahydro-α,5-dioxo-1,4-methano-1*H*-[2]benzazepine-10-acetic Acid Ethyl Ester (**13**).

A mixture of 0.43 g (1 mmole) of **10**, 10 ml of ethanol and 1 ml of concentrated sulfuric acid was heated to reflux for 5 minutes. The cooled yellow solution was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was separated, dried and evaporated. The residue was chromatographed over 15 g of silica gel using 5% (V/V) of ethyl acetate in methylene chloride for elution. The less polar product was crystallized from ether/hexane to yield 160 mg (38%) of **13** as colorless crystals with mp 126-127°; uv: λ max 214 nm (ε = 24200), 258 (14200), 306 (1950); ir (chloroform): 3350 cm^{-1} (NH), 1728 (COOEt), 1698 (CO); pmr (deuteriochloroform): 1.1 ppm (t, 3, J = 7 Hz, CH_3), 2.04 (broad s, 1, NH), 2.82 (d, 1, J = 11 Hz, CH_2-proton), 3.4-4.1 (m, 4, CH_2-proton, CH, OCH_2), 5.09 (s, 1, C_{10}-H), 6.68 (d, 1, J = 2 Hz, C_9-H), 7.2-7.5 (m, 4, aromatic H), 8.04 (d, 1, J = 8 Hz, C_6-H), *ca.* 8.05 (m, 1, aromatic H); ms: m/e 417 (M^+).

Anal. Calcd. for $C_{21}H_{17}Cl_2NO_4$: C, 60.31; H, 4.10; N, 3.35. Found: C, 60.32; H, 4.11; N, 3.34.

The more polar reaction product was crystallized from ether/-hexane to give 0.17 g (42%) of **12** as colorless crystals with mp 239-241°; uv: λ max 244 nm (ε = 20200), 317 (21700), 348 (6900); ir (chloroform): 3445, 3290 cm^{-1} (NH) 1688 (COOEt); pmr (deuteriochloroform): 1.36 ppm (t, 3, J = 6.5 Hz, CH_3), 4.36 (q, 2, J = 6.5 Hz, OCH_2), 4.45 (broad s, 2, CH_2), 6.96 (d, 1, J = 2 Hz, C_7-H), 7.1-7.7 (m, 6, aromatic H), 7.73 (d, 1, J = 8 Hz, C_{10}-H), 10.33 (broad s, 1, NH); ms: m/e 398 (M^+).

Anal. Calcd. for $C_{21}H_{16}Cl_2N_2O_2$: C, 63.17; H, 4.04; N, 7.02. Found: C, 63.13; H, 4.12; N, 7.12.

Compound **12** was also formed as the major product when compound **10** was treated with ethanolic hydrogen chloride at room temperature for 20 hours.

8-Chloro-6-(2-chlorophenyl)-1*H*,4*H*-pyrrolo[3,2-*d*][2]benzazepine-2-carboxamide (**14**).

a) A mixture of 0.2 g of **12**, 0.5 g of ammonium chloride and 10 ml of methanol containing 20% (v/v) of ammonia was heated in a steel autoclave for three days at 100°. The solvent was evaporated and the residue was partitioned between methylene chloride containing 10% of ethanol and saturated sodium bicarbonate solution. The organic layer was separated, dried and evapo-

rated and the residue was crystallized from ethanol/ethyl acetate to give 65 mg (35%) of off-white crystals which were recrystallized from tetrahydrofuran/ethanol for analysis, mp 295-297°; pmr (deuteriochloroform and deuteriodimethyl sulfoxide): 4.21 (s, 2, CH_2), *ca.* 6.4 (very broad s, 2, NH_2), 6.67 (d, 1, J = 2 Hz, C_7-H), 6.95 (d, 1, J = 2 Hz, C_3-H), 7.0-7.4 (m, 5, aromatic H), 7.63 (d, 1, J = 8 Hz, C_{10}-H), 11.13 (broad s, 1, NH).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O$: C, 61.64; H, 3.54; N, 11.35. Found: C, 61.34; H, 3.49; N, 11.18.

b) A mixture of 4 g (10 mmoles) of **12**, 150 ml of methanol, 15 ml of water and 2 g (50 mmoles) of sodium hydroxide was heated to reflux under nitrogen for 4.5 hours. The solution was acidified by addition of acetic acid, diluted with water and extracted with ethyl acetate. The extracts were dried and evaporated and the residue was crystallized from ethyl acetate/ether to yield 3.5 g of yellow acid with mp 200-210° dec. A portion of this acid, 1 g, was stirred in 100 ml of methylene chloride with 0.65 g of phosphorus pentachloride for 15 minutes with cooling in ice-water. Ammonia gas was introduced into the clear solution and stirring was continued for 15 minutes. The mixture was layered with ammonium hydroxide and the two-phase mixture was stirred for 1 hour at room temperature. The organic layer was diluted with ethyl acetate, separated, dried and evaporated. The residue was crystallized from ethyl acetate to give 0.75 g of the above amide which melted at 294-297° after recrystallization from tetrahydrofuran/-ethanol.

7-Chloro-9-(2-chlorophenyl)-2,9-dihydro-4-oxo-4*H*-benz[*f*]isoindole-1-carboxylic Acid Ethyl Ester (**15**).

A mixture of 0.1 g of **13**, 0.3 g of sodium acetate and 5 ml of acetic acid was heated to reflux under nitrogen for 15 minutes. It was then poured into 10% aqueous sodium carbonate solution and the precipitated product was extracted with a large volume of methylene chloride. The extracts were dried and evaporated and the residue was crystallized from ethanol/ether and recrystallized from ethyl acetate/hexane to give colorless crystals with mp 258-260°; uv: λ max 222 nm (ε = 29500), sh 243 (23400), max 265 (20000), sh 279 (14800), sh 310 (6300); ir (potassium bromide): 3240 cm^{-1} (NH), 1685 (COOEt), 1660 (CO); pmr (deuteriochloroform and 5 drops of deuteriosulfoxide): 0.82 ppm (t, 3, J = 6.5 Hz, CH_3), 3.94 (q, 2, J = 6.5 Hz, OCH_2), 6.0 (s, 1, C_9-H), 6.4 (d, with fine structure, 1, J = 8 Hz, *ortho*-phenyl-H), 6.7 (t with fine structure, 1, J = 8 Hz, C_5-H of phenyl), 6.81 (dt, 1, J = 8 Hz and 2 Hz, C_4-H of phenyl), 7.04 (dd, 1, J = 8 Hz and 2 Hz, C_5-H), 7.14 (d, with fine structure, 1, J = 8 Hz, C_3-H of phenyl), 7.36 (s, with fine structure, 1, C_3-H), 7.44 (d, 1, J = 2 Hz, C_8-H), 7.94 (d, 1, J = 8 Hz, C_5-H), 12.15 (broad s, 1, NH); ms: m/e 399 (M^+).

Anal. Calcd. for $C_{21}H_{15}Cl_2NO_3$: C, 63.02; H, 3.78; N, 3.50. Found: C, 62.87; H, 3.77; N, 3.55.

3-Amino-9-chloro-7-(2-chlorophenyl)-5*H*-pyrano[3,2-*d*][2]benzazepin-2(2*H*)-one (**16**) and 9-Chloro-7-(2-chlorophenyl)-3-([(dimethylamino)methylene]amino)-5*H*-pyrano[3,2-*d*][2]benzazepin-2(2*H*)-one (**17**).

A mixture of 0.24 g (0.5 mmole) of **11**, 20 ml of ethanol and 1 ml of concentrated sulfuric acid was heated to reflux for 1 hour. The dark reddish solution was poured onto 10% aqueous sodium carbonate and ice and was extracted with methylene chloride. The extracts were dried and evaporated and the residue was chromatographed over 7 g of silica gel using 50% of ethyl acetate in methylene chloride. The less polar **16** was crystallized from ethyl acetate/hexane to give 90 mg (48%) of yellow crystals with mp 238-239°; uv: λ sh 217-227 nm (ε = 28400) sh 265 (7500) max 367 (17000) sh 385 (15500); ir (chloroform): 3505, 3405 cm^{-1} (NH_2) 1710 (CO); pmr (deuteriochloroform): 4.1 ppm (broad s, 2, NH_2), 4.43 (broad s, 2, NH_2), 6.46 (s, 1, C_4-H), 7.1-7.7 (m, 6, aromatic H), 7.95 (d, 1, J = 8 Hz, C_{11}-H); ms: m/e 370 (M^+).

Anal. Calcd. for $C_{19}H_{12}Cl_2N_2O_2$: C, 61.47; H, 3.26; N, 7.55. Found: C, 61.22; H, 3.33; N, 7.44.

The more polar amidine **17** was crystallized from ethyl acetate/hexane to yield 75 mg (35%) of yellow crystals with mp *ca.* 200° dec; uv: λ sh 230 nm (ε = 28500), sh 268 (10500), max 396 (26700); ir (chloroform): 1708, 1690 cm^{-1} (CO), 1628, 1613 (C=N); pmr (deuteriochloroform): 3.02 (s, 6, NMe_2), 4.1 (broad s, 2, CH_2), 6.9 (s, 1, C_4-H), 7.1-7.7 (m, 6, aromatic H), 7.93 (d, 1, J = 8 Hz, C_{11}-H), 8.38 (s, 1, N-CH=N); ms: m/e 425 (M^+).

Anal. Calcd. for $C_{22}H_{17}Cl_2N_3O_3$: C, 61.98; H, 4.02; N, 9.86. Found: C, 62.02; H, 4.01; N, 9.76.

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