Synthesis of Pyridazino[1,6-*a*]benzimidazoles

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The synthesis of eight pyridazino[1,6-*a*]benzimidazoles by a novel synthetic route is described. This relatively unexplored heterocyclic ring system is readily accessible starting from benzoylpropionic acids and phenylhydrazines in five steps. The interactions of these compounds with the benzodiazepine receptor are briefly mentioned.

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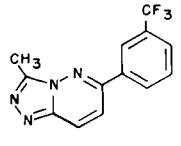
As part of a program in medicinal chemistry involved with the synthesis of novel heterocyclics and their interactions with the benzodiazepine receptor complex, we noticed with interest some common structural features that existed between the triazolopyridazines of Lederle [1] such as CL 218872 **1** and the β-carbolines originally reported by Braestrup [2], such as β-CCE **2**. Both of these structural classes have been reported to be competitive inhibitors of diazepam at the benzodiazepine receptor. A comparison of these two compounds along with a proposed structural model for compounds that interact with the benzodiazepine receptor [3] led to the design of pyridazinobenzimidazoles **3** as possible compounds to be synthesized and studied in the [3*H*]diazepam binding assay [4].

The only pyridazino[1,6-*a*]benzimidazoles which were reported in the literature were the tetrahydro compound **4** and a hydroxy compound **5** [5,6], both of which were prepared by synthetic routes which differ substantially from the synthesis reported in this paper.



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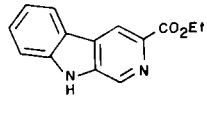

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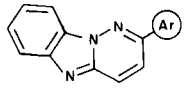

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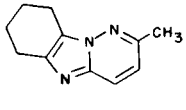

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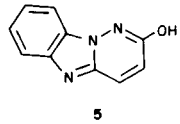
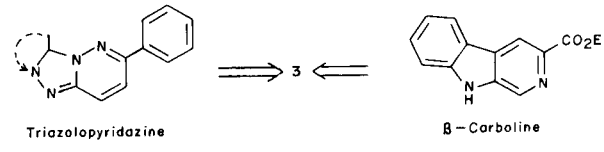


5

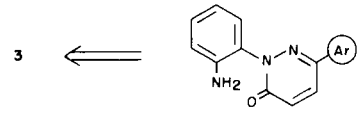
The structural similarities between CL 218872 and β-CCE can be seen by a comparison of the structures shown in Figure 1. Thus, by forming a ring as indicated by the dotted line and by removing one of the 5-membered ring nitrogens, a 6,5,6 ring system is created similar to the ring structure of β-CCE. The phenyl group is then in the same relative position as the ethyl ester group in β-CCE. A proposed structural model for ligands which interact with the benzodiazepine receptor (see reference 3 for details) also accommodates the pyridazinobenzimidazole ring system. Based on the above and the lack of many reported pyridazinobenzimidazoles in the literature, the synthesis of a series of pyridazinobenzimidazoles was undertaken.



Triazolopyridazine — 3 — β-Carboline

As a synthetic approach to this ring system, the cyclization of an amino group to an amide functionality seemed like an attractive possibility. Examples of an intermolecular cyclization of this type have been reported [7], but this reaction had not previously been attempted in an intramolecular fashion. Thus, in a retrosynthetic sense the intermediate of structure **6** was the target molecule.

Figure 1. Structural similarity of pyridazino[1,6-*a*]benzimidazoles, β-carbolines and triazolopyridazines.



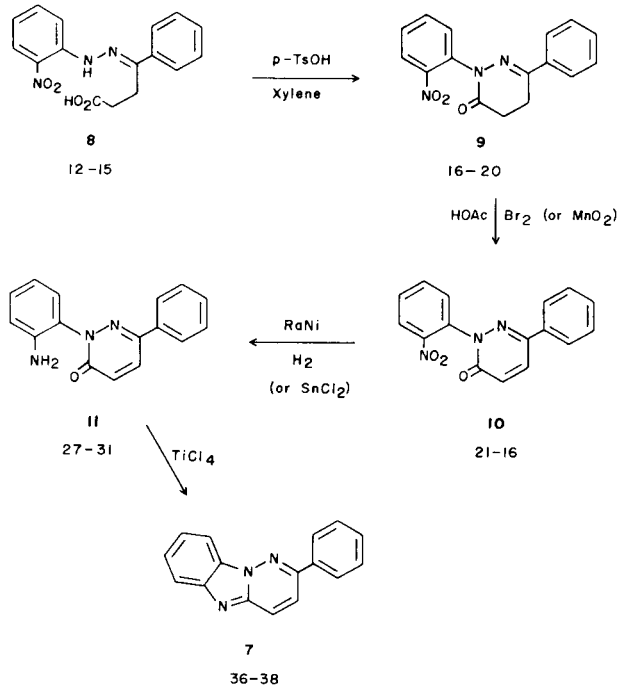
3 — 6

The synthesis of the unsubstituted compound 2-phenylpyridazino [1,6-*a*]benzimidazole **7** is outlined in Scheme I. The hydrazone **8** was prepared by the condensation of 2-nitrophenylhydrazine and 3-benzoylpropionic acid. Acid catalyzed cyclization of **8** led to the dihydropyridazinone **9**, which was oxidized to give the unsaturated pyridazinone **10**. Reduction of the nitro group then gave the amino compound **11**, corresponding to the intermediate **6** discussed previously. The end product **7** was obtained by the titanium tetrachloride cyclization of **11**.

In a general sense, this synthetic approach allows for the preparation of a wide variety of pyridazinobenzimida-

zoles and depends only on the availability of the starting benzoylpropionic acid and phenylhydrazine.

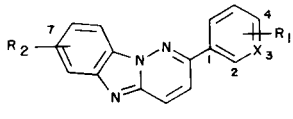
Scheme I



The pyridazinobenzimidazoles were tested in the [3*H*]diazepam binding assay [8] in order to determine if there was any interaction of these compounds with the benzodiazepine receptor complex [9]. As can be seen from the data listed in Table I, the most potent inhibitor of [3*H*]diazepam binding was the pyridine **35** with an IC_{50} = 24 nM. In subsequent *in vivo* pharmacological testing this compound did not show any activity. Subsequently, **35** was shown to be a weak antagonist [10] of diazepam. Although these compounds were weak in the binding assay, they nevertheless represent a novel class of compounds which interact with the benzodiazepine receptor.

Table I

Pyridazino[1,6-*a*]benzimidazoles [b]



Compound	R_1	R_2	X	[3*H*]Diazepam binding assay, IC_{50}, nM [a]
7	H	H	C	72
32	H	7-NH_2	C	56
33	H	7-Cl	C	150
34	3-CF_3	H	C	200
35	H	H	N	24
36	3-Cl	H	C	500
37	4-Cl	H	C	>1000
38	2-Cl	H	C	>1000

[a] For comparison, the IC_{50} for diazepam is 5 nM. [b] Details for the preparation of **7-38** are given in the Experimental.

EXPERIMENTAL

Melting points were determined either on a Thomas-Hoover capillary melting point apparatus or a hot stage apparatus, and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and HA-100 instruments and chemical shifts are reported in parts per million from internal tetramethyl silane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110 instruments, respectively. Anhydrous sodium sulfate or magnesium sulfate was used for drying of organic solutions.

2-Phenylpyridazino[1,6-*a*]benzimidazole (**7**).

After refluxing 4.0 g (0.014 mole) of **11** in 400 ml of xylene for 30 minutes, the mixture was cooled and 3 ml (0.027 mole) of titanium tetrachloride was added and the reaction was refluxed for 10 hours. After cooling the solvents were removed *in vacuo* and the residue was partitioned with methylene chloride and 3*N* ammonium hydroxide. The organics were dried and concentrated. Thin layer chromatography indicated that approximately 50% of starting material was present. The residue was dissolved in 400 ml of xylene and 4.0 ml of titanium tetrachloride was added. After refluxing for 12 hours, the mixture was cooled and poured over ice. The mixture was made basic with 3*N* ammonium hydroxide and the precipitate was collected by filtration. The layers were separated and the organics dried and concentrated. The residue and the previously collected precipitate were combined and chromatographed on florisil using methylene chloride, methylene chloride/ether (5:1), and finally ether as the eluent. The ether fractions were combined and concentrated and the residue crystallized from methylene chloride/ether/petroleum ether to give 3.2 g (94%) of **7** as off-white rods, mp 127-28°; ms m/e 245 (M+); nmr (deuteriochloroform): δ 7.38-8.31 (m, 11H, aromatics).

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.143; H, 4.71; N, 17.19.

γ-[(2-Nitrophenyl)hydrazono]phenylbutanoic Acid (**8**).

A mixture of 2.0 g (0.01 mole) of 3-benzoylpropionic acid, 2.0 g (0.013 mole) of 2-nitrophenylhydrazine, and 25 ml of ethanol was stirred and refluxed for 4 hours. After cooling, the solvent was removed *in vacuo*. The residue was crystallized from ether/petroleum ether to give 3.0 g of **8** (86%). The analytical sample was obtained as red prisms from the same solvent mixture, mp 136-140°; ir (potassium bromide): 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.18; H, 4.77; N, 13.27.

4,5-Dihydro-2-(2-nitrophenyl)-6-phenyl-3(2*H*)-pyridazinone (**9**).

A mixture of 0.5 g (0.0016 mole) of **8**, 20 mg of *p*-toluene sulfonic acid, and 50 ml of xylene was stirred at reflux under a Dean-Stark trap for 18 hours. The solvent was removed *in vacuo* and the residue dissolved in methylene chloride, which was washed with dilute ammonium hydroxide. The organic layer was dried and concentrated. The residue was purified by thick layer chromatography using methylene chloride/ethyl acetate (10:1) as the developing agent. The product (Rf = 0.7) was recovered and crystallized from methanol to give 0.25 g (53%) of **9** as off-white rods, mp 99-102°; ir (chloroform): 1692 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.70-3.25 (complex multiplet, 4H, CH_2CH_2) 7.34-8.06 (m, 9H, aromatics).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.10; H, 4.64; N, 14.40.

2-(2-Nitrophenyl)-6-phenyl-3(2*H*)-pyridazinone (**10**).

To a solution of 1.4 g (0.0047 mole) of **9** in 23 ml of glacial acetic acid was added 0.3 ml of a solution of 0.33 ml (0.0062 mole) of bromine in 2.5

ml of acetic acid. The mixture was heated on a steam bath and the remainder of the bromine/acetic acid was added over 10 minutes. After heating for one hour the mixture was cooled and concentrated *in vacuo*. The residue was partitioned between methylene chloride and 3*N* ammonium hydroxide. The organics were dried and concentrated. Crystallization from a mixture of ether/methylene chloride/petroleum ether gave 1.1 g (79%) of **10** as yellow prisms, mp 111-113°; ir (chloroform): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.00-8.10 (m, 11H), aromatics).

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.47; H, 3.84; N, 14.36.

2-(2-Aminophenyl)-6-phenyl-3(2*H*)-pyridazinone (**11**).

A mixture of 0.7 g (0.0024 mole) of **10**, one teaspoon of Raney nickel, 15 ml of tetrahydrofuran, and 35 ml of ethanol was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen was complete (approximately 20 minutes). The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was crystallized from methylene chloride/methanol to give 0.5 g (79%) of **11** as colorless needles, mp 183-186°; ir (chloroform): 1674 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.94 (broad s, 2H, NH_2), 6.82-7.80 (m, 11H, aromatics).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.99; H, 4.71; N, 15.84.

γ-[(2-Nitrophenyl)hydrazono]-3-pyridylbutanoic acid (**12**).

A mixture of 1.5 g (0.0085 mole) of δ-oxo-3-pyridylbutanoic acid [11], 1.3 g (0.0085 mole) of *o*-nitrophenylhydrazine and 30 ml of ethanol was refluxed for 5 hours, cooled and filtered. The solid was recrystallized from methylene chloride/methanol to give 1.8 g (67%) of **12** as orange rods, mp 184-188°.

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.00; H, 4.55; N, 17.83.

γ-[2,4-Dinitrophenyl)hydrazono]phenylbutanoic Acid (**13**).

A mixture of 4.5 g (0.025 mole) of 3-benzoylpropionic acid, 5.5 g (0.025 mole) of 2,4-dinitrophenylhydrazine, 100 mg of *p*-toluenesulfonic acid, and 100 ml of xylene was refluxed under a Dean-Stark trap overnight and then concentrated to dryness. The residue was triturated with hot methylene chloride, cooled and filtered to give 5.1 g (57%) of **13**. The analytical sample was obtained as orange needles from methylene chloride/methanol, mp 192-194°; ms: m/e 358 (M+).

Anal. Calcd. for $C_{16}H_{14}N_4O_6$: C, 53.63; H, 3.94; N, 15.64. Found: C, 53.62; H, 4.03; N, 15.49.

γ-(2-Nitrophenylhydrazono)-3-(trifluoromethyl)phenylbutanoic acid (**14**).

A mixture of 1.8 g (0.0073 mole) of 3-(3-trifluoromethyl)benzoylpropionic acid [12], 1.1 g (0.0073 mole) of 2-nitrophenylhydrazine, and 40 ml of ethanol was refluxed for 5 hours, cooled and concentrated *in vacuo*. The residue was crystallized from methylene chloride/methanol/petroleum ether to give 1.0 g (36%) of **14** as yellow rods, mp 190-192°.

Anal. Calcd. for $C_{17}H_{14}F_3N_3O_4$: C, 53.69; H, 3.45; N, 11.05. Found: C, 53.34; H, 3.65; N, 11.09.

γ-[(2-Nitrophenyl)hydrazono]-3-chlorophenylbutanoic Acid Ethyl Ester (**15**).

A solution of 5 g (0.0149 mole) of γ-cyano-γ-(*m*-chlorophenyl)-4-morpholinylbutanoic acid ethyl ester [13], 2.55 g (0.167 mole) of 2-nitrophenylhydrazine, and 100 ml of xylene was heated to reflux and then approximately 50 ml of xylene was removed by distillation. After cooling, the reaction mixture was diluted with ether and water. The layers were separated and the organic phase dried and concentrated *in vacuo*. The residue was triturated with hexane and the solids were collected by filtration to give 3.35 g (60%) of **15**. The analytical sample was prepared by recrystallization from ether/hexane to give **15** as red plates, mp 110-112°; ir (chloroform): 3330 (NH) and 1733 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.21 (t, J = 7 Hz, 3H, CH_3), 2.66 (t, J = 7 Hz, 2H, CH_2), 3.14 (t, J = 7 Hz, 2H, CH_2), 4.15 (q, J = 7 Hz, 2H, CH_2), 6.78-8.24 (m, 8H, aromatics).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_4$: C, 57.53; H, 4.83; N, 11.18. Found: C, 57.49; H, 4.76; N, 11.51.

4,5-Dihydro-2-(2,4-dinitrophenyl)-6-phenyl-3(2*H*)-pyridazinone (**16**).

A mixture of 1.0 g (0.0028 mole) of **13** and 10 ml of polyphosphoric acid was heated at 110° for 1.5 hours. After cooling, ice was added and the reaction made basic with 3*N* ammonium hydroxide followed by extraction with methylene chloride. The organic phase was dried and concentrated. The residue was crystallized from methylene chloride/ether to give 0.3 g (32%) of **16** as yellow needles, mp 215-217°; ms: m/e 340 (M+); ir (chloroform): 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{12}N_4O_5$: C, 56.47; H, 3.55; N, 16.46. Found: C, 56.33; H, 3.51; N, 16.26.

4,5-Dihydro-2-(2-nitrophenyl)-6-[3-(trifluoromethyl)phenyl]-3(2*H*)-pyridazinone (**17**).

A solution of 0.4 g (0.0011 mole) of **14** and 25 mg of *p*-toluenesulfonic acid in 40 ml of xylene was refluxed for 3 hours, cooled and concentrated. The residue was purified by thick layer chromatography using methylene chloride/ether (10:1) as the eluent. The product was recovered and crystallized from methylene chloride/ether/petroleum ether to give 0.2 g (25%) of **17** as pale yellow prisms, mp 117-118°; ir (chloroform): 1696 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.72-3.08 (complex multiplets, 4H, CH_2CH_2).

Anal. Calcd. for $C_{17}H_{12}F_3N_3O_3$: C, 56.20; H, 3.33; N, 11.57. Found: C, 56.03; H, 3.36; N, 11.31.

4,5-Dihydro-2-(2-nitrophenyl)-6-(3-pyridyl)-3(2*H*)-pyridazinone (**18**).

A mixture of 6.0 g (0.0127 mole) of **12** and 30 ml of polyphosphoric acid was heated at 110° for 90 minutes and then cooled and poured over ice.

The reaction was made basic with 3*N* ammonium hydroxide and extracted with methylene chloride. The organics were dried and concentrated. The residue was chromatographed on florisil using methylene chloride, ether and finally ethyl acetate as the eluent. The ether and ethyl acetate fractions were combined and concentrated. The residue was crystallized from methylene chloride/ether/petroleum ether to give 1.5 g (39%) of **18**. The analytical sample was obtained as colorless plates from the same solvent mixture, mp 138-140°; ms: m/e 296 (M+); ir (chloroform): 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.69; H, 3.92; N, 18.65.

6-(3-Chlorophenyl)-4,5-dihydro-2-(2-nitrophenyl)-3(2*H*)-pyridazinone (**19**).

To 11 ml of concentrated sulfuric acid was added, in portions, 2.25 g (0.006 mole) of **15**. After heating on a steam bath for 20 minutes, the reaction was cooled to room temperature. After pouring over ice and making basic with ammonium hydroxide, the mixture was extracted with methylene chloride. The organics were dried and concentrated *in vacuo*. The residue was dissolved in 50 ml of ether and concentrated on a steam bath to a volume of approximately 20 ml. The solids were collected by filtration to give 0.7 g (35%) of **19**. The analytical sample was prepared by recrystallization from ethanol/methylene chloride to give off-white plates, mp 119-120°; ir (chloroform): 1697 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.68 and 3.14 (complex multiplet, 4H, CH_2CH_2).

Anal. Calcd. for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.20; H, 3.50; N, 12.59.

6-(4-Chlorophenyl)-4,5-dihydro-2-(2-nitrophenyl)-3(2*H*)-pyridazinone (**20**).

A mixture of 0.2 g (0.001 mole) of 3-(*p*-chlorobenzoyl)propionic acid [13] 0.17 g (0.0011 mole) of 2-nitrophenylhydrazine, 10 ml of xylene, and 40 mg of *p*-toluenesulfonic acid was stirred and refluxed for one hour. The mixture was cooled and evaporated *in vacuo*. The residue was purified by thick layer chromatography in methylene chloride to give 0.15 g (45%) of product. The analytical sample was prepared by recrystallization from ethanol to give pale yellow prisms, mp 109-110°; ir

(chloroform): 1697 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.77 (m, 4H, CH_2CH_2), 7.26-8.08 (m, 8H, aromatics).

Anal. Calcd. for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.22; H, 3.57; N, 12.66.

2-(2,4-Dinitrophenyl)-6-phenyl-3(2*H*)-pyridazinone (**21**).

To a solution of 1.0 g (0.0029 mole) of **16** in 16 ml of acetic acid was added 0.15 ml of a solution of 0.2 ml (0.0038 mole) of bromine in 1.5 ml of acetic acid. The mixture was heated on a steam bath and the remainder of the bromine/acetic acid was added over 15 minutes. After heating for 2 hours the reaction was concentrated and the residue partitioned between cold dilute ammonium hydroxide and methylene chloride. The aqueous phase was extracted, methylene chloride and the organics were combined, dried, and concentrated. The residue was crystallized from methylene chloride/ether to give 0.4 g (41%) of **16** as yellow needles, mp 206-208°; ms: m/e 338 (M+); ir (chloroform): 1682 cm^{-1} (C=O); nmr (DMSO-d_6): δ 7.17-8.84 (m, 10H, aromatics).

Anal. Calcd. for $C_{16}H_{10}N_4O_5$: C, 56.81; H, 2.98; N, 16.56. Found: C, 56.57; H, 2.99; N, 16.60.

2-(2-Nitrophenyl)-6-[(3-trifluoromethyl)phenyl]-3(2*H*)-pyridazinone (**22**).

A mixture of 0.8 g (0.0022 mole) of **17**, 1.6 g of activated manganese dioxide, and 30 ml of toluene was refluxed overnight and filtered hot. The solids were washed with tetrahydrofuran/methylene chloride and the filtrates concentrated. The residue was purified by thick layer chromatography using methylene chloride/ether (5:1) as the eluent. The band eluting with a Rf of 0.5 was recovered and the product recrystallized from methylene chloride/petroleum ether to give 0.3 g (38%) of **22** as colorless prisms, mp 132-133°; ms: m/e 361 (M+); ir (chloroform): 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{10}F_3N_3O_3$: C, 56.52; H, 2.79; N, 11.63. Found: C, 56.33; H, 2.69; N, 11.62.

2-(2-Nitrophenyl)-6-(3-pyridyl)-3(2*H*)-pyridazinone (**23**).

A mixture of 5.0 g (0.017 mole) of **18**, 10 g of activated manganese dioxide and 50 ml of toluene was refluxed for 7 hours. The reaction was cooled and filtered to remove the manganese salts which were washed with hot methylene chloride. The filtrates were concentrated and the residue was crystallized from methylene chloride/ether to give 4.5 g (90%) of **23** as pale orange rods, mp 148-151°; ir (potassium bromide): 1675 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{10}N_4O_3$: C, 61.22; H, 3.43; N, 19.04. Found: C, 61.03; H, 3.35; N, 18.98.

6-(3-Chlorophenyl)-2-(nitrophenyl)-3(2*H*)-pyridazinone (**24**).

To a solution of 4 g (0.012 mole) of **19** in 60 ml of glacial acetic acid was added 0.5 ml of a solution of 2.13 g (0.013 mole) of bromine in 5 ml of acetic acid. The mixture was heated on a steam bath and the remainder of the bromine/acetic acid solution was added dropwise. After heating for 30 minutes, the mixture was cooled and concentrated *in vacuo*. The residue was covered with water and allowed to stand. After 48 hours, the solid was collected by filtration and washed with water and air-dried to give 3.77 g (96%) of **24**. Recrystallization from ethanol/methylene chloride gave the analytical sample as pale yellow prisms, mp 130-132°; ir (chloroform): 1678 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.08-8.20 (m, 10H, aromatics).

Anal. Calcd. for $C_{16}H_{10}ClN_3O_3$: C, 58.64; H, 3.08; N, 12.81. Found: C, 58.50; H, 2.94; N, 12.68.

6-(4-Chlorophenyl)-2-(2-nitrophenyl)-3(2*H*)-pyridazinone (**25**).

To 3 g of **20** in 45 ml of glacial acetic acid was added 0.5 ml of a solution of 0.5 ml of bromine in 3.5 ml of acetic acid. The mixture was heated on a steam bath and the remainder of the bromine/acetic acid solution was added over 10 minutes. After heating for 30 minutes the mixture was cooled and concentrated *in vacuo*. The residue was covered with water and allowed to stand overnight. The solid was collected by filtration and washed with water. The solid was dissolved in methylene chloride and dried over sodium sulfate. The methylene chloride was removed *in vacuo* to give 2.6 g (88%) of **25** as pale yellow prisms. An analytical sample was prepared by recrystallization from methylene chloride/ethanol, mp 149-151°; ms: m/e 327 (M+); ir (chloroform(: 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.10-8.18 (m, 10H, aromatics).

Anal. Calcd. for $C_{16}H_{10}ClN_3O_3$: C, 58.64; H, 3.08; N, 12.81. Found: C, 58.70; H, 3.35; N, 12.99.

6-(2-Chlorophenyl)-2-(2-nitrophenyl)-3(2*H*)-pyridazinone (**26**).

A mixture of 11 g (0.052 mole) of 3-(2-chlorobenzoyl)propionic acid [13], 8.25 g (0.054 mole) of 2-nitrophenylhydrazine and 460 ml of xylene was stirred and refluxed for 1 hour. The xylene was removed *in vacuo* to leave 11.6 g of γ-(2-nitrophenylhydrazono)-2-chlorophenylbutanoic acid as a dark red gum which was used crude in the next step. To the 11.6 g of gum was added 60 ml of sulfuric acid and the mixture stirred for 1.5 hours. After pouring over ice the mixture was extracted with methylene chloride. The organics were dried and concentrated to give ~ 12 g of 4,5-dihydro-2-(2-nitrophenyl)-6-[2-(chlorophenyl)]-3(2*H*)-pyridazinone as a gum which was used without purification. To a solution of 2 g (0.006 mole) of the crude gum in 30 ml of glacial acetic acid was added 0.25 ml of a solution of 0.33 ml of bromine in 2.5 ml of acetic acid. The mixture was heated to reflux and the remainder of the bromine/acetic acid was added dropwise. After refluxing for 30 minutes the mixture was concentrated *in vacuo*. After standing, the residue slowly crystallized and yielded 1.96 g (100%) of **26** as a brown solid. The analytical sample was obtained as brown prisms by recrystallization from methylene chloride/ethanol, mp 169-171°; ir (chloroform) 1678 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.06-8.14 (m, 10H, aromatics).

Anal. Calcd. for $C_{16}H_{10}ClN_3O_3$: C, 58.64; H, 3.08; N, 12.81. Found: C, 58.64; H, 3.11; N, 12.68.

2-(2,4-Diaminophenyl)-6-phenyl-3(2*H*)-pyridazinone (**27**).

A mixture of 0.4 g (0.0012 mole) of **21**, one teaspoon of Raney nickel, 20 ml of tetrahydrofuran, and 40 ml of ethanol was hydrogenated at atmospheric pressure until the uptake of hydrogen was complete (0.5 hour). The catalyst was removed by filtration and washed with methylene chloride. The filtrates were concentrated and the residue crystallized from methylene chloride/ether to give 0.1 g (30%) of **27** as green-yellow prisms, mp 200-202 dec; ir (potassium bromide): 1665 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.24; N, 20.13. Found: C, 68.82; H, 5.24; N, 19.87.

2-(2-Aminophenyl)-6-[3-(trifluoromethyl)phenyl]-3(2*H*)-pyridazinone (**28**).

To a solution of 0.8 g (0.0022 mole) of **22** in 20 ml of ethanol was added a solution of 1.5 g stannous chloride dihydrate in 6 ml of concentrated hydrochloric acid. The mixture was stirred at room temperature for 5 hours and an additional 1.0 g of stannous chloride was added and stirring continued for 12 hours. Water was added and then 10*N* sodium hydroxide until the reaction was basic. After extracting with methylene chloride the organics were combined, dried, and concentrated. The residue was dissolved in a small amount of ethyl acetate and filtered through florisil. The filtrates were concentrated and the residue was crystallized from methylene chloride/ether/petroleum ether to give 0.5 g (69%) of **28** as off-white prisms, mp 156-158°; ms: m/e 331 (M+); ir (chloroform): 1665 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{12}F_3N_3O$: C, 61.63; H, 3.65; N, 12.68. Found: C, 61.64; H, 3.56; N, 12.43.

2-(2-Aminophenyl)-6-(3-pyridyl)-3(2*H*)-pyridazinone (**29**).

A mixture of 25 g (0.085 mole) of **23**, 1.5 teaspoons of Raney nickel, 1.5 ℓ of tetrahydrofuran, and 300 ml of ethanol was hydrogenated at atmospheric pressure until the uptake of hydrogen was complete (9 hours). The catalyst was removed by filtration and washed well with warm methylene chloride/ethanol. The filtrates were concentrated to a small volume, cooled and the precipitate was collected by filtration to give 15 g (67%) of **29**. The analytical sample was prepared by recrystallization from methanol, mp 196-198°; ir (potassium bromide): 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 67.99; H, 4.44; N, 20.94.

2-(2-Aminophenyl)-6-(3-chlorophenyl-3(2*H*)-pyridazinone (**30**).

A mixture of 3.27 g (0.01 mole) of **24**, 2 teaspoons of Raney nickel, 36 ml of tetrahydrofuran, and 70 ml of ethanol was hydrogenated at room temperature in a Parr apparatus until the uptake of hydrogen was complete (approximately 15 minutes). The mixture as diluted with methylene chloride and filtered to remove the catalyst. The filtrate was concentrated *in vacuo* and the residue stirred with petroleum ether (bp 30-60). The product was collected by filtration to yield 2.7 g (91%). Trituation with ether gave 2.5 g (85%) of **30** as off-white crystals. Recrystallization from ethanol/methylene chloride gave the analytical sample as off-white needles, mp 184-185°; ir (chloroform): 1668 cm^{-1} (C=O); nmr (deuteriochloroform): δ 6.81-7.85 (m, 10H, aromatics), and 3.94 (broad s, 2H, NH_2).

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.45; H, 4.02; N, 14.02.

2-(2-Aminophenyl)-6-(4-chlorophenyl)-3(2*H*)-pyridazinone (**31**).

A mixture of 3.1 g (0.0095 mole) of **25**, 1 teaspoon of Raney nickel, 25 ml of tetrahydrofuran, and 50 ml of ethanol was hydrogenated in a Parr hydrogenator until the uptake of hydrogen was complete (one hour). The catalyst was removed by filtration and the filtrates were concentrated. The residue was tritiated with petroleum ether (bp 30-60°), and the solids were collected by filtration to give 1.86 g (66%) of **31** as off-white needles. Recrystallization from methylene chloride/methanol gave the analytical sample, mp 213-216; ir (chloroform): 3420-3320 (OH), 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 6.81-7.84 (m, 10H, aromatics), 3.80-4.00 (bs, 2H, NH_2).

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.50; H, 3.87; N, 14.28.

2-Phenylpyridazino[1,6-*a*]benzimidazol-7-amine Dihydrochloride 1 Molar Methanol Solvate (**32**).

A mixture of 1.0 g (0.0036 mole) of **27**, 1.0 ml of titanium tetrachloride, and 50 ml of xylene was refluxed under a Dean-Stark trap for 4 hours. After cooling, ice was added followed by 3*N* ammonium hydroxide until the mixture was basic. Following extraction with methylene chloride, the organics were combined, dried and concentrated. The residue was filtered through a small amount of florisil using ethyl acetate/ethanol (10:1) as the eluent. The solvents were removed *in vacuo* and the residue was treated with methanolic hydrochloric acid to form the salt which was precipitated by the addition of ether. The solid was collected and crystallized from methanol to give 0.15 g (12%) of **32** as yellow rods, mp 193-197 dec.

Anal. Calcd. for $C_{16}H_{12}N_4 \cdot 2HCl \cdot CH_3OH$: C, 55.89; H, 4.97; N, 15.34. Found: C, 55.69; H, 4.78; N, 15.51.

7-Chloro-2-phenylpyridazino[1,6-*a*]benzimidazole (**33**).

To a solution of 5.0 g (0.014 mole) of **32** in 50 ml of acetic acid and 100 ml of 3*N* hydrochloric acid, cooled in an ice bath, was added, dropwise, a solution of 1.04 g (0.015 mole) of sodium nitrite in 10 ml of water. After 10 minutes the reaction mixture was added dropwise to a solution of 5.4 g (0.055 mole) of cuprous chloride in 50 ml of concentrated hydrochloric acid. The mixture was allowed to come to room temperature over 2-3 hours and then concentrated ammonium hydroxide was added until basic. The reaction mixture was extracted well with methylene chloride which was dried and concentrated *in vacuo*. The residue was dissolved in a small amount of methylene chloride and filtered through florisil. The florisil was washed with ether and then ethyl acetate. The filtrates were concentrated and the residue crystallized from methylene chloride/methanol to give 2.0 g (52%) of **33** as pale yellow rods, mp 199-203°; ms: m/e 279 (M+).

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.54; H, 3.50; N, 15.04.

2-[3-(Trifluoromethyl)phenyl]pyridazino[1,6-*a*]benzimidazole (**34**).

A mixture of 11.3 g (0.034 mole) of **28**, 11 g (0.056 mole) of *p*-toluenesulfonic acid, and 440 ml of xylene was refluxed for 90 minutes under a Dean-Stark trap. The reaction was cooled and washed with 3*N* ammonium hydroxide. The organics were dried and concentrated. The residue was crystallized from ether/petroleum ether to give 10.2 g (95%) of product as off-white needles, mp 157-160°; ms: m/e 313 (M+).

Anal. Calcd. for $C_{17}H_{10}F_3N_3$: C, 65.18; H, 3.22; N, 13.41. Found: C, 65.34; H, 3.13; N, 13.26.

2-(3-Pyridyl)pyridazino[1,6-*a*]benzimidazole (**35**).

A mixture of 13 g (0.044 mole) of **29**, 13 g (0.068 mole) of *p*-toluenesulfonic acid and 500 ml of toluene was refluxed for 24 hours under a Dean-Stark trap. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and 3*N* ammonium hydroxide. The organic layer was dried and concentrated. The residue was chromatographed on florisil using methylene chloride/ether (4:1), ether and finally ethyl acetate as the eluent. The methylene chloride/ether fraction gave 1.5 g of a mixture of starting material and product. The ether fraction gave 4 g of product and the ethyl acetate fraction gave 1 g of product. They were combined and recrystallized from methylene chloride/ether to give 5.6 g (52%) of product, mp 186-188°; ms: m/e 246 (M+).

Anal. Calcd. for $C_{15}H_{10}N_4$: C, 73.16; H, 4.09; N, 22.75. Found: C, 72.66; H, 4.02; N, 22.25.

2-(3-Chlorophenyl)pyridazino[1,6-*a*]benzimidazole (**36**).

A solution of 2 g (0.0067 mole) of **30**, 2 ml (0.0179 mole) of titanium tetrachloride and 200 ml of xylene was stirred and refluxed overnight. The reaction mixture was cooled, poured over ice and made basic with 3*N* ammonium hydroxide. After adding 300 ml of water, the mixture was extracted with methylene chloride. The organics were dried and concentrated *in vacuo* to give an oil which crystallized on standing. The solid was collected to give 1.75 g (94%) of **36**. The analytical sample was obtained as tan needles by recrystallization from methylene chloride/-hexane, mp 111-113°; nmr (deuteriochloroform): δ 7.40-8.31 (m, 10H, aromatics.

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.68; H, 3.63; N, 14.99.

2-(4-Chlorophenyl)pyridazino[1,6-*a*]benzimidazole (**37**).

To a solution of 1.5 g (0.005 mole) of **31** in 150 ml of xylene was added 1.5 ml (0.013 mole) of titanium tetrachloride and the resulting mixture was stirred and refluxed overnight, protecting the reaction from moisture by the use of a drying tube. After cooling to room temperature, the reaction was poured over ice and allowed to stand. After making basic with 3*N* ammonium hydroxide, the product was extracted with methylene chloride which was dried and removed *in vacuo*. The residue was crystallized from methylene chloride/hexane to give 1.27 g of **37** in two crops, mp 135-137°; ms: m/e 279 (M+); nmr (deuteriochloroform): δ 7.38-8.26 (m, 10H, aromatics).

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.55; H, 3.58; N, 14.88.

2-(2-Chlorophenyl)pyridazino[1,6-*a*]benzimidazole (**38**).

A solution of 4.4 g (0.015 mole) of **26** in 440 ml of xylene was stirred and refluxed under a Dean-Stark trap for 0.5 hour and then cooled to room temperature. The Dean-Stark trap was removed and 4.4 ml (0.039 mole) of titanium tetrachloride was added and the mixture refluxed overnight. After cooling, the reaction mixture was poured over ice and made basic with ammonium hydroxide. Water (500 ml) and methylene chloride (500 ml) were added and the mixture stirred for 2 hours. The layers were separated and the organic phase dried and concentrated to give 2.85 g (69%) of crude **38**. The analytical sample was prepared by recrystallization from methylene chloride/hexane and obtained as tan needles, mp 163-165°; ir (chloroform): no carbonyl; nmr (deuteriochloroform): δ 7.36-8.28 (m, 10H, aromatics).

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.55; H, 3.46; N, 14.91.

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