(s, 1 H), 7.50 (m, 2 H), 7.80 (complex d, 1 H), 8.32 (complex d, 1 H).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.08; H, 5.87; N, 6.16.

1,2-Dimethoxynaphthalene-4-acetic acid was produced from the cyano compound (5.54 g) by heating to reflux in a solution of 25 g of KOH in 35 mL of water and 50 mL of methanol for 24 h. The cooled solution was filtered, diluted with water, and acidified with dilute HCl. After the solution was cooled in the refrigerator, the precipitated acid was collected and washed with water, and air-dried, 4.21 g, mp 156–158 °C. Recrystallization from ethyl acetate with charcoaling gave 3.09 g of nearly colorless prisms, mp 158.5–161 °C. A small sample was crystallized several time from benzene for analysis: mp 157–159 °C; mass spectrum, *m/e* 246, 231, 201, 189, 185, 157, 144, 128, 115; NMR (100 MHz) δ 3.80 (br s, 8 H), 7.03 (s, 1 H), 7.23 (m, 2 H), 7.70 (br d, 1 H), 7.97 (br d, 1 H).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.77; H, 5.80.

Methyl 1,2-dimethoxynaphthalene-4-acetate (13) was prepared from the above acid (2.76 g) by treatment of its suspension in ether with the diazomethane solution[8] prepared from 4.50 g of nitrosomethylurea. The acid went into solution slowly and after 10 min the excess diazomethane was destroyed by addition of acetic acid dropwise. The ether was washed with water and brine, filtered through anhydrous Na_2SO_4, concentrated, and pumped out to give 2.98 g of very pale yellow viscous oil: IR strong absorbance at 1724 cm^{-1}, inter alia; mass spectrum, *m/e* 260, 245, 201, 157; NMR (100 MHz) δ 3.70 (s, 3 H), 4.08 (s with some fine structure, 8 H), 7.35 (s, 1 H), 7.53 (m, 2 H), 8.04 (complex d, 1 H), 8.28 (complex d, 1 H).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 68.96; H, 6.26.

Action of [*p*-(Dimethylamino)phenyl]lithium on 13. 1,2-Dimethoxy-4-[2,2-bis[*p*-(dimethylamino)phenyl]vinyl]-naphthalene (14). To the lithium derivative prepared from 173 mg of lithium and 2.00 g of *p*-bromo-*N,N*-dimethylaniline in ether was added a solution of 1.00 g of methyl ester **13** in 15 m*l* of benzene. A dark brown color was produced at once. The solution was heated to reflux for 3 h and allowed to stand overnight. The ether benzene solution was extracted 4 times with 10% HCl, and the extracts were made basic with dilute KOH and extracted 4 times with CH_2Cl_2. The extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated to give 1.58 g of deep blue-green oil or glass smelling of *N,N*-dimethylaniline.

The ether-benzene solution on concentration gave 0.686 g of brown oily residue, which was refluxed with methanolic KOH and a little water for 15 min, diluted, and filtered, and the filtrate was acidified to give 390 mg of crude 1,2-dimethoxy-4-naphthaleneacetic acid, mp 150–154 °C, corresponding to 415 mg of starting material **13**.

The deep blue-green glass obtained above was heated briefly to boiling in glacial acetic acid (deep blue color), diluted with water, made basic with dilute KOH, and extracted 4 times with CH_2Cl_2. The deep amethyst-purple extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated to give 1.48 g of deep green-black oil or glass smelling of *N,N*-dimethylaniline.

Chromatography of this material on alumina gave a total of 393 mg of crude **14** as a yellow crystalline solid. Recrystallization from benzene yielded 336 mg, mp 168–169 °C (33% on the basis of amount of **13** utilized). Several further crystallizations from benzene gave bright yellow prisms: mp 168.5–170 °C; mass spectrum, *m/e* 452, 437, 421, 393, 377, 365, 350, 322, 307, 292, 264, 249, 202, 188, 145, 121; NMR (400 MHz) δ 2.90 (s, 6 H), 3.00 (s, 6 H), 3.50 (s, 3 H), 3.94 (s, 3 H), 6.57 (AB), 7.01 (*J* = 8.0 Hz, 4 H), 6.72 (AB), 7.36 (*J* = 8.4 Hz, 4 H), 6.93 (s, 1 H), 7.23 (s, 1 H), 7.35 (t, 1 H), 7.46 (t, 1 H), 8.12 (d of d, 2 H).

Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.96; H, 7.14; N, 6.13.

Reductive Methylation of 2 (14). A solution of 422 mg of **2** in 25 mL of tetrahydrofuran, freshly distilled from sodium benzophenone ketyl was hydrogenated over 197 mg of $PdCl_2$ on C (10%). Ninety-seven percent of hydrogen (theoretical) was taken up over 40 min. The catalyst was removed by filtration under N_2 with the aid of diatomaceous earth, and the light yellow filtrate was treated with a solution of trimethylphenylammonium ethoxide prepared from 1.23 g of trimethylphenylammonium tosylate and freshly prepared sodium ethoxide solution (169 mg of Na) followed by filtration.

The mixture was heated under a stream of N_2 in a bath maintained at 110 °C for 5.5 h. By 1.5 h essentially all the solvents had evaporated. The cooled, orange-brown solid residue was steam-distilled until no more *N,N*-dimethylaniline came over (odor), cooled, made basic, and extracted 5 times with CH_2Cl_2. The extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated to give 332 mg of a green-black residue which crystallized readily. It was chromatographed on a 30 × 30 mm column of Al_2O_3 to remove dark color. Elution with ethyl acetate–CH_2Cl_2 and crystallization from benzene–absolute alcohol gave 234 mg of bright yellow crystalline material, mp 168.5–169.5 °C. Its mixture melting point with **14** prepared from **13** by the action of [*p*-(dimethylamino)phenyl]lithium was 168.5–170 °C, and NMR and IR spectra were indistinguishable from those of that sample.

Acknowledgment. I am deeply grateful to Mr. Joseph Wright of the Research Laboratories of the Eastman Kodak Co., who determined and interpreted many of the mass spectra reported herein, and to James Schultz and Henry DeQuasie for determining others of the mass spectra. I am also indebted to Drs. Michael Roberts and David Miller and to Yukio Kuroda, Pawel Fludzinski, Richard Nugent, and Daniel Mantell for the 400-Mz NMR spectra reported. It is a pleasure to acknowledge several helpful discussions with Dr. George Fawaz some years ago. The generous support of the Hoffman-La Roche Foundation was of very great help.

Registry No. 2, 79971-22-5; 2-azine, 79971-23-6; **3**, 79971-24-7; **4**, 79971-25-8; **5**, 70313-13-2; **6**, 79971-26-9; 6-carbinol, 79972-39-7; **7**, 79971-27-0; **8**, 79971-28-1; **9**, 72735-91-2; **10**, 79971-29-2; **11**, 7474-90-0; **12**, 79971-30-5; **13**, 79971-31-6; **14**, 79971-32-7; 1,1-dianisylethylene, 4356-69-8; 1,4-dimethoxynaphthalene-2-acetic acid, 79971-33-8; [*p*-(dimethylamino)phenyl]lithium, 13190-50-6; 2-(dimethylamino)-5-[*p*-(dimethylamino)phenyl]-7,12-dimethoxybenz[*a*]anthracene, 79971-34-9; *p*-bromoanisole, 104-92-7; 2,7,12-trimethoxy-5-(*p*-anisyl)benz[*a*]anthracene, 79971-35-0; 1,2-dimethoxy-4-(cyanomethyl)naphthalene, 79971-36-1; 4-(cyanomethyl)-1,2-naphthoquinone, 79971-37-2; 1,2-dimethoxynaphthalene-4-acetic acid, 79971-38-3.

Convenient and Regioselective Synthesis of Substituted 2,3,4,5-Tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazoles

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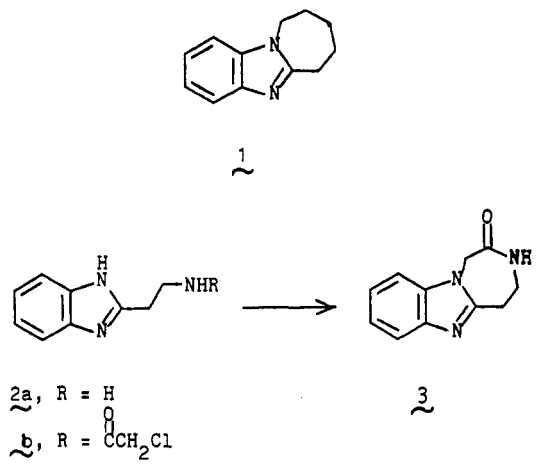
Detailed computer graphic analysis aimed at elucidating structural parameters required for binding to the serotonin receptor suggested that appropriately substituted 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazoles (**10**) would be capable of such interactions. This report describes a convenient and regioselective synthetic procedure for preparing derivatives of this novel ring system.

Initial attempts to obtain the parent member of this series paralleled the work of DeSelms,[1] who synthesized the carbocyclic analogue **1**. This route is shown in Scheme I for lactam **3**. Attempted cyclization of chloro amide **2b** under a variety of conditions, including those of DeSelms, gave unacceptable yields of **3**. The highest yield, 12%, was

(1) DeSelms, R. C. *J. Org. Chem.* **1962**, *27*, 2165.

0022-3263/82/1947-0582$01.25/0

Scheme I



obtained through cyclization of **2b** with *t*-BuONa in *t*-BuOH. low yields and the inherent lack of regioselectivity of this approach prompted a search for a more efficient procedure for the regioselective synthesis of nuclear substituted derivatives of this ring system. The details of the resulting method are depicted in Scheme II.

Treatment of readily available *o*-chloronitrobenzenes **4** with 2-aminoethanol according to the procedure of Clarke and Moorehouse[2] afforded the corresponding *o*-nitroanilines **5**. Reduction of the nitro function in **5**, either catalytically or chemically with $Na_2S_2O_4$, gave substituted *o*-phenylenediamines **6** in which the amino groups were selectively differentiated with respect to other nuclear substituents. Although **6** could be isolated and purified, it was generally more expedient to carry the crude product forward in order to avoid autoxidation reactions. Condensation of **6** with 3-aminopropionic acid in 6 N HCl resulted in smooth conversion to benzimidazoles **7**.[3] No benzimidazoles were formed under these reaction conditions, however, when either 3-chloropropionic acid or 3-hydroxypropionic acid were substituted for the amino acid.

Although cyclodehydration of **7a** to **10a** could be effected directly with triphenylphosphine and diethyl azodicarboxylate,[4] the yield of this conversion, 15%, was too low to be of synthetic value. Other attempts at direct cyclization also failed. Therefore, alternate procedures for ring closure were explored. After protection of the primary amine in **7a** as its trifluoroacetamide, the hydroxyl function was converted to either the corresponding benzenesulfonate or iodide. Attempted cyclization of these compounds with KH in THF resulted only in elimination to afford the 1-vinylbenzimidazole derivative as determined by NMR.

The cyclization procedure chosen, although somewhat more circuitous, proved to be efficient. Following protection of the primary amine in **7** as the Boc derivative, the hydroxyl group was converted to the corresponding tosylate. This tosylation proved to be surprisingly lethargic, requiring a reaction temperature of 50 °C for 2 h to effect complete conversion of **8a**. Prolonged (18 h) heating of **8c** with TsCl in pyridine at 50 °C resulted in the clean transformation to the chloride **9c**, probably via chloride displacement of the intermediate tosylate. Deprotection of **9** with trifluoroacetic acid at 0 °C, followed by cyclization to **10** in refluxing aqueous 2-propanol containing excess K_2CO_3 was accomplished without isolation of intermediates. The overall yield of **10a** from **7a** was 64%.

Radioligand binding studies revealed that compounds **10a** and **10c** do bind competitively to serotonin receptors, albeit with moderate to low affinity. Compound **10a** is the most potent ligand in this series, displacing specifically bound [^{3}H]serotonin and [^{3}H]LSD from synaptasomal membranes with K_i's of 8.7×10^{-7} and 3.0×10^{-6} M, respectively. Further pharmacological characterization of **10a** showed that it is a weak serotonin agonist, causing head twitch activity in mice and hyperthermia in rabbits. More detailed biological results will be reported in due course.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were determined on a Varian EM-390 spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed in these laboratories.

2-[2-(2-Chloroacetamido)ethyl]benzimidazole (2b) and 3-(2-Chloroacetyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazol-5-one. A solution of redistilled chloroacetyl chloride (5.01 g, 44.4 mmol) in 30 mL of dry EtOAc was added over 1 h to a vigorously stirred mixture of 2-(2-aminoethyl)-benzimidazole dihydrochloride (**2a**; 3.39 g, 14.5 mmol),[3] anhydrous K_2CO_3 (20.6 g), 100 mL of EtOAc, and 30 mL of H_2O at room temperature. After the mixture was stirred at room temperature for 3 h, the EtOAc layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed over 250 g of silica gel (particle size 0.040–0.063 mm). Elution with 5% 2-propanol–95% CH_2Cl_2 gave 600 mg (14.9%) of the chloroacetamide of **3**, mp 268–275 °C dec (darkens at 225 °C). An analytical sample with an unchanged melting point was obtained by recrystallization from EtOAc–hexane: ^{1}H NMR (Me_2SO-d_6) δ 3.4 (t, 2 H, CH_2), 4.6 (t, 2 H, CH_2), 4.9 (s, 2 H, CH_2Cl), 5.4 (s, 2 H, CH_2CO), 7.2–7.9 (m, 4 H, aromatic); mass spectrum, *m/e* 277.

Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36; N, 15.13. Found: C, 56.56; H, 4.43; N, 14.77.

Further elution with 10% 2-propanol–90% CH_2Cl_2 gave 2.4 g (70%) of **2b**, homogeneous by TLC (10% MeOH–90% $CHCl_3$, silica gel), R_f 0.7. Recrystallization from EtOH–H_2O gave 1.45 g of analytically pure chloroamide: mp 221–223 °C dec (with partial melting and resolidifying at 171–175 °C); ^{1}H NMR (Me_2SO-d_6) δ 3.0 (t, 2 H, CH_2), 3.6 (m, 2 H, CH_2N), 4.1 (s, 2 H, CH_2Cl), 7.1 (m, 2 H, aromatic), 7.6 (m, 2 H, aromatic), 8.5 (br t, 1 H, NH); mass spectrum, *m/e* 237.

Anal. Calcd for $C_{11}H_{12}ClN_3O$: C, 55.58; H, 5.09; N, 17.68. Found: C, 55.91; H, 5.37; N, 17.43.

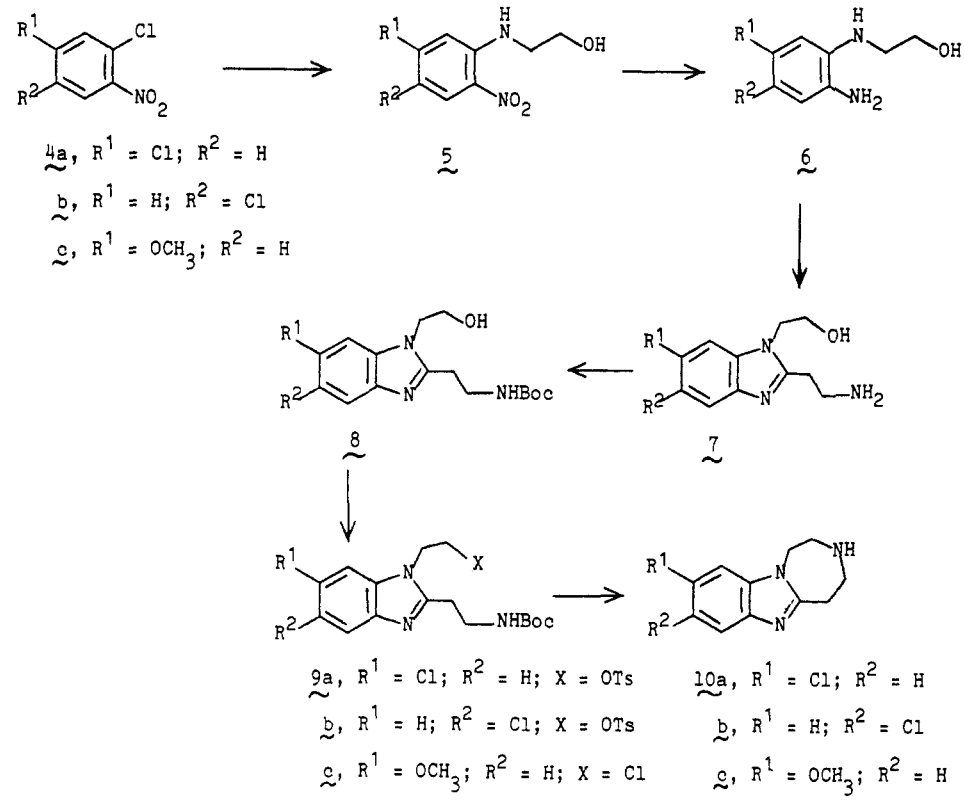
2,3,4,5-Tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazol-4-one (3). Solid 2-[2-(2-chloroacetamido)ethyl]benzimidazole (1.34 g, 5.64 mmol) was added to a solution of sodium *tert*-butoxide in 50 mL dry *tert*-butyl alcohol (prepared by adding 274 mg, 5.70 mmol, of 50% NaH–mineral oil to the *tert*-butyl alcohol and stirring at 90 °C until reaction was complete) at 50 °C, and the reaction mixture stirred at 50 °C for 5 h. After the addition of 0.5 mL of HOAc, the *tert*-butyl alcohol was removed under reduced pressure. The crude product was extracted into EtOAc, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed over 40 g of silica gel (particle size 0.040–0.063 mm). Elution with 7% MeOH–CH_2Cl_2 gave **3**: 130 mg (11.5%); mp 227–228 °C dec (shrinks at 220 °C). Recrystallization from EtOH–EtOAc–hexane gave an analytical sample: mp 229–230 °C dec, (shrinks at 227 °C); ^{1}H NMR (Me_2SO-d_6) δ 3.2–3.4 (m, 3 H, CH_2 and NH, 1 H exchangeable with D_2O), 3.5–3.8 (m, 2 H, CH_2), 5.0 (s, 2 H, CH_2CO), 7.1–7.3 (m, 2 H, aromatic), 7.5–7.7 (m, 2 H, aromatic), 8.3 (br t, 1 H, NH, exchangeable with D_2O); mass spectrum, *m/e* 201.

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.51; N, 20.88. Found: C, 65.68; H, 5.57; N, 21.03.

4-Chloro-2-[(2-hydroxyethyl)amino]aniline (6a). Sodium hydrosulfite (16.1 g) was added over 10 min to a stirred solution of 5-chloro-*N*-(2-hydroxyethyl)-2-nitroaniline[2] (6.70 g, 30.9 mmol)

(2) Clarke, P.; Moorehouse, A. *J. Chem. Soc.* **1963**, 4763.
(3) Cescon, L.; Day, A. *J. Org. Chem.* **1962**, *27*, 581.
(4) Carlock, J. T.; Mack, M. P. *Tetrahedron Lett.* **1978**, 5153.

Scheme II



in 250 mL of 50% EtOH–H_2O. After the mixture was stirred at reflux for 15 min, EtOH was removed under reduced pressure, and the aqueous solution was basified with 40% NaOH. The product was extracted into Et_2O, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated to 3.1 g (53.7%) of **6a**, mp 97.0–99.0 °C (lit.[2] mp 105 °C).

2-(2-Aminoethyl)-6-chloro-1-(2-hydroxyethyl)benzimidazole Dihydrochloride Hemihydrate (7a). By use of the procedure of Cescon and Day,[3] a mixture of **6a** (26 g, 0.14 mol) and 3-aminopropionic acid (18.6 g, 0.21 mol) in 265 mL of 6 N HCl was heated at reflux for 24 h. After the mixture was concentrated under reduced pressure, the solution was basified with 40% NaOH and extracted with chloroform (5 × 500 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in MeOH and treated with excess anhydrous EtOH–HCl solution. Addition of EtOAc precipitated 26.1 g (58%) of product as the dihydrochloride hemihydrate, mp 196–200 °C dec.

Anal. Calcd for $C_{11}H_{14}ClN_3O{\cdot}2HCl{\cdot}0.5H_2O$: C, 41.07; H, 5.48; N, 13.06. Found: C, 41.29; H, 5.30; N, 12.66.

2-(2-Aminoethyl)-5-chloro-1-(2-hydroxyethyl)benzimidazole Dihydrochloride (7b). A slurry of sodium hydrosulfite (48.8 g, 0.28 mol) in 100 mL of H_2O was added over 0.5 h to a stirred solution of 4-chloro-*N*-(2-hydroxyethyl)-2-nitroaniline[5] (**5b**; 19.6 g, 0.09 mol) in 500 mL of 40% aqueous EtOH. After the mixture was heated at reflux for 30 min, EtOH was removed under reduced pressure. The crude 5-chloro-2-[(2-hydroxyethyl)amino]aniline (**6b**; 15 g, 89%) was filtered and added to a solution of 3-aminopropionic acid (10.7 g, 0.12 mol) in 150 mL of 6 N HCl. After being refluxed for 24 h, the reaction was basified with 40% NaOH and extracted with $CHCl_3$. The organic extract was dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOH and acidified with ethanolic HCl. The crude product was filtered and recrystallized from EtOH to afford 11 g (44%) of an analytical sample of **7b**: mp 128–130 °C dec; ^1H NMR (Me_2SO-d_6) δ 3.3–4 (m, 6 H), 4.62 (m, 2 H), 7.59 (dd, 1 H, J_{AB} = 2 Hz, J_{AC} = 9 Hz), 7.88 (d, 1 H, J = 2 Hz), 8.02 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{11}H_{14}ClN_3O{\cdot}2HCl$: C, 42.26; H, 5.16; N, 13.46. Found: C, 42.20; H, 5.20; N, 13.33.

(5) Prepared by the method of Clarke and Moorehouse[2] in 76% yield.

2-(2-Aminomethyl)-1-(2-hydroxyethyl)-6-methoxybenzimidazole Dihydrochloride Hemihydrate (7c). A suspension of *N*-(2-hydroxyethyl)-5-methoxy-2-nitroaniline[2] (19.2 g, 0.09 mol) in 200 mL of anhydrous EtOH was hydrogenated at 50 psi of H_2 at 25 °C with 4.5 g of 10% Pd/C catalyst until the theoretical amount of H_2 was absorbed (3 h). The catalyst was filtered and washed with 3 N HCl. The filtrate was concentrated to dryness and the residue taken up in 200 mL of 6 N HCl. To this solution was added 3-aminopropionic acid (12.0 g, 0.135 mol) and the reaction refluxed for 24 h. After cooling, the reaction mixture was made basic with 40% NaOH and concentrated to dryness. The solid residue was extracted thoroughly with 10% MeOH/$CHCl_3$. Evaporation of the solvent yielded a solid which was triturated with $CHCl_3$ (to separate the product from a small amount of sodium β-alaninate). The $CHCl_3$ was then evaporated and replaced by MeOH. Acidification with ethanolic HCl followed by addition of Et_2O caused the product to separate as tiny needles. Recrystallization from MeOH/EtOH yielded 6.0 g (22% overall) of analytically pure **7c**: ^1H NMR (Me_2SO-d_6) δ 3.3–3.8 (m, 6 H), 3.81 (s, 3 H), 4.5 (m, 2 H), 7.11 (dd, 1 H, J = 2, 9 Hz), 7.53 (d, 1 H, J = 2 Hz), 7.62 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{12}H_{17}N_3O_2{\cdot}2HCl{\cdot}0.5H_2O$: C, 45.43; H, 6.36; N, 13.25. Found: C, 45.75; H, 6.39; N, 13.11.

2-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-6-chloro-1-(2-hydroxyethyl)benzimidazole (8a). To a slurry of **7a** (1.0 g, 3.1 mmol) in 15 mL of DMF was added triethylamine (0.66, 6.5 mmol) followed after 5 min by di-*tert*-butyl dicarbonate (0.74 g, 3.34 mmol). After being stirred 3 h at 25 °C, the reaction mixture was diluted with 80 mL of water and extracted with EtOAc. The organic layer was dried ($CaSO_4$) and concentrated to yield 1.0 g (95%) of **8a** which was homogeneous by TLC (silica gel, 10% MeOH/$CHCl_3$). Recrystallization from chloroform/hexane afforded an analytical sample: mp 168–170 °C; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 2.89 (t, 2 H, J = 6 Hz), 3.49 (dt, 2 H, $J^1 = J^2$ = 6 Hz), 3.88 (t, 2 H, J = 5 Hz), 4.12 (t, 2 H, J = 5 Hz), 5.21 (m, 1 H), 7.07 (dd, 1 H, J = 2, 9 Hz), 7.20 (d, 1 H, J = 2 Hz), 7.39 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{16}H_{22}ClN_3O_3$: C, 56.55; H, 6.52; H, 12.37. Found: C, 56.47; H, 6.79; N, 12.35.

2-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-5-chloro-1-(2-hydroxyethyl)benzimidazole (8b). This compound was prepared in the same manner as **8a** to afford, in 95% yield, the desired

product which was homogeneous by TLC (10% MeOH/$CHCl_3$): mp 109–112 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.98 (t, 2 H, J = 7 Hz), 3.54 (dt, 2 H, $J^1 = J^2$ = 7 Hz), 3.98 (t, 2 H, J = 5 Hz), 4.23 (t, 2 H, J = 5 Hz), 5.33 (br t, 1 H), 7.2–7.3 (m, 2 H), 7.40 (d, 1 H, J = 1.5 Hz).

Anal. Calcd for $C_{16}H_{22}ClN_3O_5$: C, 56.55; H, 6.53; N, 12.37. Found: C, 56.35; H, 6.62; N, 12.35.

2-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-1-(2-hydroxyethyl)-6-methoxybenzimidazole (8c). This compound was prepared in the same manner as for **8a** to afford in 81% yield the desired product which was homogeneous by TLC (10% MeOH/$CHCl_3$): mp 132 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.84 (t, 2 H, J = 6 Hz), 3.49 (dd, 2 H, $J^1 = J^2$ = 6 Hz), 3.82 (s, 3 H), 3.9–4.1 (m, 2 H), 4.1–4.3 (m, 2 H), 6.8–6.9 (m, 2 H), 7.41 (dd, 1 H, J = 9, 2 Hz).

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.73; H, 7.70; N, 12.34.

2-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-6-chloro-1-[2-(*p*-toluenesulfonyloxy)ethyl]benzimidazole (9a). A solution of **8a** (1.5 g, 4.46 mmol) and *p*-toluenesulfonyl chloride (1.0 g, 5.5 mmol) in 7.5 mL of dry pyridine was treated at 50 °C for 2 h. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic extracts were dried ($CaSO_4$) and concentrated. The remaining pyridine was removed by azeotroping with toluene under reduced pressure. The crude product, 1.6 g (70%), was obtained as a white solid which was homogeneous by TLC (silica gel, 10% MeOH/$CHCl_3$) and was used without further purification: ^1H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 2.28 (s, 3 H), 3.01 (t, 2 H, J = 6 Hz), 3.62 (br t, 2 H, J = 6 Hz), 3.73 (t, 2 H, J = 6 Hz), 4.34 (t, 2 H, J = 6 Hz), 5.51 (br t, 1 H), 7.2–7.6 (m, 5 H), 7.55–7.8 (m, 2 H).

2-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-1-(2-chloroethyl)-6-methoxybenzimidazole (9c). A solution of **8c** (4.0 g, 11.9 mmol) and TsCl (2.73 g, 14.3 mmol) in 10 mL of dry pyridine was heated at 50 °C for 18 h. The reaction was then diluted with CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ followed by brine. After being dried (Na_2SO_4), the organic extracts were concentrated in vacuo. The residue was taken up in toluene and reconcentrated. This procedure was repeated to remove traces of remaining pyridine. Recrystallization of the residue from butyl chloride yielded **9c**: 2.8 g (66%); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 3.05 (t, 2 H, J = 6 Hz), 3.6–3.8 (m, 4 H), 3.88 (s, 3 H), 4.42 (t, 2 H, J = 6 Hz), 5.4 (br s, 1 H), 6.79 (d, 1 H, J = 2 Hz), 6.97 (dd, 1 H, J = 2, 9 Hz), 7.62 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{17}H_{24}N_3ClO_3$: C, 57.70; H, 6.83; N, 11.88. Found: C, 57.31; H, 6.89; N, 11.51.

8-Chloro-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazole Dihydrochloride (10a). A solution of **9a** (1.5 g, 3.0 mmol) in 20 mL of trifluoroacetic acid (TFA) was prepared at 0 °C. After the mixture was stirred at that temperature for 1 h, the TFA was removed in vacuo, and the residue was dissolved in 100 mL of 20% aqueous 2-propanol containing 3.0 g of K_2CO_3. This mixture was refluxed 2 h, cooled, and concentrated. The resulting solid was partitioned between CH_2Cl_2 and water. After the organic phase was dried ($CaSO_4$), the solvent was evaporated to afford the product as a white solid. This solid was dissolved in 15 mL of 2-propanol and acidified with ethanolic HCl. The colorless crystals which separated were filtered, washed with 2-propanol, and dried to yield 0.85 g (96%) of the dihydrochloride salt **10a**: mp 318 °C dec; ^1H NMR (Me_2SO-d_6/D_2O) δ 3.6 (m, 6 H), 4.8 (m, 2 H), 7.56 (dd, 1 H, J = 8, 2 Hz), 7.79 (d, 1 H, J = 8 Hz), 8.01 (d, 1 H, J = 2 Hz).

Anal. Calcd for $C_{11}H_{12}ClN_3 \cdot 2HCl$: C, 44.84; H, 4.79; N, 14.26. Found: C, 44.80; H, 4.74; N, 14.16.

9-Chloro-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazole Dihydrochloride (10b). Treatment of **8b** with TsCl as described for **9a** yielded the crude tosylate **9b**. This material was directly deprotected and cyclized by the procedure used to prepare **10a**, affording **10b** in 45% overall yield from **8b**: mp 290–292 °C dec; ^1H NMR (Me_2SO-d_6) δ 3.3–3.8 (m, 6 H), 4.8–5.0 (m, 2 H), 7.57 (dd, 1 H, J = 9, 2 Hz), 7.91 (d, 1 H, J = 2 Hz), 7.94 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{11}H_{12}ClN_3 \cdot 2HCl$: C, 44.84; H, 4.79; N, 14.26. Found: C, 44.88; H, 4.83; N, 14.27.

8-Methoxy-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]benzimidazole Dihydrochloride Hemihydrate (10c). Deprotection and cyclization of **9c** by the procedure described for the preparation of **10a** afforded **10c**: 62% yield; mp 289–293 °C dec; ^1H NMR (Me_2SO-d_6) δ 3.4–3.8 (m, 6 H), 3.88 (s, 3 H), 4.9 (m, 2 H), 7.15 (dd, 1 H, J = 9, 2 Hz), 7.62 (d, 1 H, J = 2 Hz), 7.70 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{12}H_{15}N_3O \cdot 2HCl \cdot 0.5H_2O$: C, 48.17; H, 6.06; N, 14.05. Found: C, 48.41; H, 6.00; N, 13.79.

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Registry No. 2a, 4499-07-4; **2b**, 80028-68-8; **3**, 80028-69-9; **3** chloroacetamide, 80028-70-2; **5a**, 50610-29-2; **5b**, 59320-13-7; **5c**, 78213-34-0; **6a**, 63387-85-9; **6b**, 33141-10-5; **6c**, 79858-71-2; **7a**, 78056-08-3; **7b**, 80028-71-3; **7c**, 80028-72-4; **8a**, 78056-10-7; **8b**, 80028-73-5; **8c**, 80028-74-6; **9a**, 78056-11-8; **9b**, 80028-75-7; **9c**, 80028-76-8; **10a**, 78056-12-9; **10b**, 80028-77-9; **10c**, 80028-78-0; 3-aminopropionic acid, 107-95-9; di-*tert*-butyl dicarbonate, 24424-99-5.

Pyrimido[4,5-*c*]pyridazines. 4. Cyclizations with α-Keto Acids

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In this report we describe the cyclization behavior of 6-(1-alkylhydrazino)isocytosines (**1**) with four α-keto acids in refluxing water. Most of our findings were unexpected in view of the information contained in earlier papers.

We reported previously[1] that reactions of 6-(1-alkylhydrazino)isocytosines (**1**) with a variety of simple α-keto esters (**2**) in refluxing water produce the highly insoluble pyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones (**3**, Scheme I) in good yields (51–87%). With the nonalkylated analogue **1** (R^1 = H) and methyl pyruvate we isolated only the hydrazone **4** which appeared to be resistant to pyrimidopyridazine formation under the reaction conditions or in the presence of acidic or basic catalysts.

The failure of **4** to cyclize was not surprising in view of Pfleiderer's earlier study of the chemistry of 1,3-dimethyl-6-hydrazinouracil with simple α-keto acids and esters.[2] Reaction with methyl pyruvate in refluxing water proceeded only to the hydrazone **5a** which showed no tendency to cyclize. Furthermore, an attempted ring closure with refluxing aqueous bicarbonate effected only ester cleavage to the stable hydrazone **5b**. A similar reaction with oxomalonic acid stopped at the hydrazone stage (compound **6**), although cyclization to a pyrimido[4,5-*c*]pyridazine did occur with the corresponding diethyl ester.

In contrast with Pfleiderer's experience with the stable hydrazones **5b** and **6**, we now report that pyruvic acid and phenylglyoxylic acid react rapidly with **1a** (Scheme II) to give the known[1] pyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones **3a** and **3b**, respectively, in isolated yields virtually identical with those from the corresponding α-keto ester cyclizations. Furthermore, unlike the ethyl ester of phenylpyruvic acid which cyclized readily (in methanol) with **1a** to give pyrimidopyridazine **3c**, phenyl- and (*p*-hydroxyphenyl)pyruvic *acids* cyclized rapidly with **1a** and

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(2) Pfleiderer, W.; Ferch, H. *Justus Liebigs Ann. Chem.* **1958**, *615*, 48.

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