2-Benzazepines. 7. Synthesis of Pyrimido[5,4-*d*][2]benzazepines [1]

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Two novel syntheses of pyrimido[5,4-*d*][2]benzazepines are described. The first synthesis started with 3-phenylphthalide which in three steps was converted to a functionalized pyrimidine which was cyclized to give the 2-benzazepine ring system. The second approach used *o*-benzoylbenzoic acid methyl ester as the starting material, which in four steps was converted to a functionalized pyrimidine which was cyclized to give a 2-benzazepine. Pyrimido[5,4-*d*][2]benzazepines have been found to have activity in standard central nervous system (CNS) pharmacological tests.

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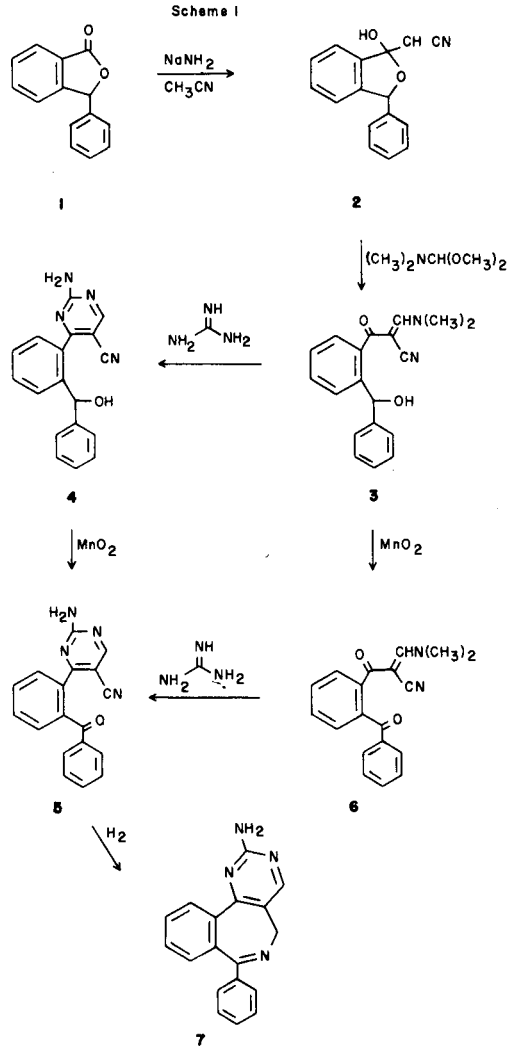
Earlier reports [1] from these laboratories have described the synthesis of various 2-benzazepines and their potential utility as central nervous system (CNS) active compounds, comparable in biological activity to diazepam. We now report two alternate syntheses of pyrimido[5,4-*d*][2]-benzazepines which involved the construction of a suitably functionalized pyrimidine which was cyclized to give the 2-benzazepine ring system.

The first synthesis (see Scheme I) started with 3-phenylphthalide, **1**, [2] which was condensed with the anion of acetonitrile to give the hydroxyisobenzofuran **2**. Treatment of **2** with dimethylformamide dimethylacetal yielded **3** which was obtained as an oil and was used without further purification. Condensation of **3** with guanidine gave the pyrimido compound **4** which was oxidized with manganese dioxide to give **5**. Alternatively, **3** could first be oxidized with manganese dioxide to give the ketone **6** which yielded **5** when treated with guanidine. The yields were slightly higher in the latter case, but extensive process work was not carried out for any of the reactions described. Hydrogenation of **5** using Raney nickel as catalyst resulted in reduction of the nitrile function and ring closure to give the 2-benzazepine **7**. Although this process from phthalides to 2-benzazepines was not studied in detail, in principle, a variety of pyrimido-2-benzazepines could be prepared by the proper choice of substituted phthalides and amidines.

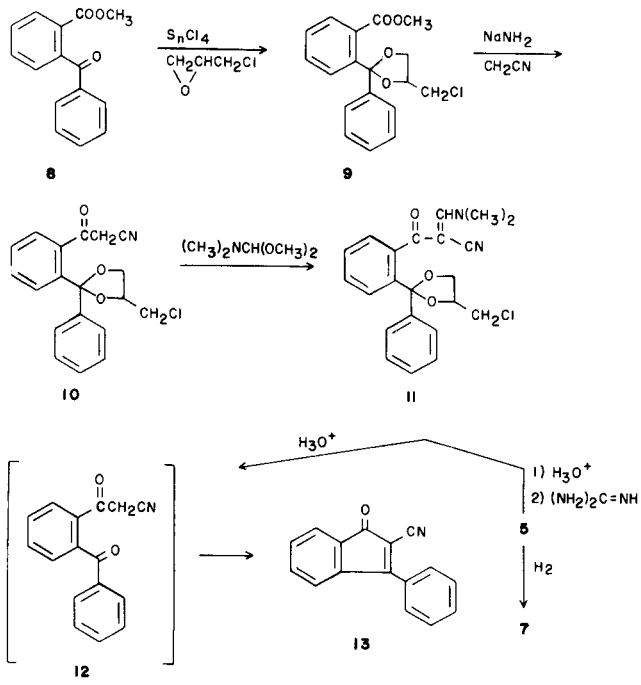
Scheme I



The second approach to pyrimido-2-benzazepines (see Scheme II) started with the known [3] methyl ester (**8**) of *o*-benzoylbenzoic acid. This approach was convergent with the first synthesis and led to the common intermediate **5**. Ketalization of **8** was accomplished by a modification of the published procedure [4] for the ketalization of crotonaldehyde using epichlorohydrin and stannic chloride. Attempts to ketalize **8** using ethylene glycol and acid catalysis were not successful. The ketal **9** was condensed with the anion of acetonitrile to give the keto-nitrile **10** which was obtained as an oil and was used directly in the next step. The keto-nitrile **10** was treated with dimethylformamide dimethylacetal to give **11**. The pyrimidine **5** was prepared in two steps by hydrolyzing the ketal with acid followed by treatment with guanidine. In addition to the pyrimidine **5**, a by-product which was characterized as the indene derivative **13** was also isolated from the reaction

mixture. This by-product probably arises *via* hydrogenation and elimination of *N,N*-dimethylformamide to give the diketone **12** which cyclizes to **13**, although this mechanism was not proven by further study. Hydrogenation of **5** over Raney nickel as a catalyst gave the pyrimido[2]benzazepine **7**, as in the previous synthesis.

Scheme II



EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137 instrument; mass spectra were determined on a CEC-110B instrument; nuclear magnetic resonance spectra were determined on either a Varian A-60 or HA-100 spectrometer, using internal tetramethylsilane as a standard. Aromatic protons are not reported but in all cases were observed as complex multiplets and integrated for the correct number of protons. Anhydrous sodium sulfate or magnesium sulfate was used for drying of organic solutions.

1,3-Dihydro-1-hydroxy-3-phenylisobenzofuran-1-acetonitrile (**2**).

Ammonia (80 ml) was condensed into a flask and then a small piece of sodium and a few crystals of ferric nitrate were added with stirring. Over a 20 minute period 1.6 g (0.0718 mole) of sodium was added and after stirring for 15 minutes, 3.7 ml (0.0718 mole) of acetonitrile was added dropwise (10 minutes). After stirring for 5 minutes a solution of 5.0 g (0.0239 mole) of 3-phenylphthalide, **1**, in 20 ml of acetonitrile was added over 5 minutes. After 2 hours, 20 ml of ether was added and the ammonia was allowed to evaporate. The reaction mixture was partitioned between dichloromethane (100 ml) and water (75 ml). The layers were separated and the aqueous layer was adjusted to *p*H 8 with concentrated hydrochloric acid and extracted with 100 ml of dichloromethane. The aqueous layer was then acidified with a concentrated hydrochloric acid and extracted with 100 ml of dichloromethane.

The first dichloromethane extract gave upon evaporation and recrystallization of the residue from dichloromethane/petroleum ether, 1.5 g of **2** as white needles, mp 143-148°. The extraction at *p*H 8 gave an additional 0.3 g of product. The extraction after acidifying the aqueous phase, gave 0.5 g of recovered starting material. The yield of **2**, based upon recovered starting material, was 33%. Compound **2** was obtained as white needles from dichloromethane/petroleum ether, mp 143-148°; ir (chloroform): 3570 (OH), 2250 cm^{-1} (CN); nmr (DMSO-d_6): δ 7.40 (s, 1H, OH), 6.09 (s, H, CH), 3.18, 3.14 (d, 2H, CH_2).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.16; H, 5.35; N, 5.38.

3-(2-Benzhydrylphenyl)-2-[(dimethylamino)methylene]-3-oxopropanenitrile (**3**).

A solution of 2.0 g (7.97 mmoles) of **2** in 8.0 ml of *N,N*-dimethylformamide dimethylacetal was allowed to stand for 18 hours and then evaporated to dryness. The residue was triturated with ice water which was decanted and the oil was partitioned bytween 50 ml of dichloromethane and 40 ml of water. The organic layer was dried and evaporated to give 2.4 g of oil which was about 90% pure by thin layer chromatography. The crude oil was used directly without further purification.

2-Amino-4-(2-benzhydrylphenyl)pyrimidine-5-carbonitrile (**4**).

To a solution of 1.3 g (3.82 mmoles) of crude **3** (*ca.* 90% pure) in methanol was added 2.3 g (12.7 mmoles) of guanidine carbonate and 1.4 g (25.5 mmoles) of sodium methoxide. The reaction was stirred for 18 hours, evaporated, and the residue partitioned between 75 ml of dichloromethane and 50 ml of water. The aqueous solution was adjusted to approximately *p*H 8 with 3 *N* hydrochloric acid, the phases separated and the aqueous layer extracted with 75 ml of dichloromethane. The organic layers were dried, concentrated and the product purified by development on five silica gel thick layer plates in ethyl acetate/dichloromethane (2:1). The band which had an Rf of 0.7 was removed and the product recovered by crystallization from dichloromethane/petroleum ether followed by recrystallization from methanol/ether/petroleum ether, bp 36-60°, to give 0.3 g (25%) of **4** as white rods; mp 165-168°; ir (potassium bromide): 3325, 3180 (NH_2), 2215 cm^{-1} (CN); nmr (DMSO-d_6): δ 8.50 (s, 1H, =CH), 7.40 (s, 2H, NH_2), 6.02, 5.96 (d, 1H, OH), 5.68, 5.62 (d, 1H, CH).

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.55; H, 4.52; N, 18.53.

2-Amino-4-(2-benzoylphenyl)pyrimidine-5-carbonitrile (**5**) (from **4**).

A solution of 0.1 g (0.331 moles) of **4** in 30 ml of dichloromethane was refluxed and stirred with 0.4 g of activated manganese dioxide for 2 hours. The solids were filtered, washed with methanol and the filtrates were evaporated to dryness. The oil was dissolved in dichloromethane and filtered through 10 g of Florisil, and eluted with 150 ml of ether. The solution was concentrated to a small volume, cooled, and filtered to give 60 mg (60%) of **5** as white prisms, mp 197-199°. A mixed mp of 197-200° was obtained with a sample prepared according to reference [1]. Compound **5** showed: ir (potassium bromide): 3380, 3315, 3195, 3150 (NH_2), 2220 (CN), 1660 cm^{-1} (C=O); nmr (DMSO-d_6): δ 8.38 (s, 1H, CH); ms: m/e 330 (M^+).

3-(2-Benzoylphenyl)-2-[(dimethylamino)methylene]-3-oxopropanenitrile (**6**).

A solution of 0.4 g (1.18 mmoles) of **3** (90% pure) in 30 ml of dichloromethane was refluxed and stirred with 2.0 g of activated manganese dioxide for 3 hours. The solid was filtered, washed with ethyl acetate and the filtrates were concentrated. The residue was developed on 3 silica gel thick layer plates in dichloromethane/ether (5:1), and the band at Rf 0.7 was removed. The product was purified by crystallization from ether and recrystallized from dichloromethane/ether to give 0.2 g (50%) of **6** as white prisms, mp 138-141°; ir (potassium bromide): 2195 (CN), 1660 cm^{-1} (C=O); nmr (DMSO-d_6): δ 3.31, 3.22 (2s, 6H, 2 × CCH_3).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.92; H, 5.27; N, 9.25.

2-Amino-4-(benzoylphenyll)pyrimidine-5-carbonitrile (**5**) (from **6**).

To a solution of 50 mg (0.164 mmoles) of **6** in 4 ml of methanol was added 90 mg (0.493 mmoles) of guanidine carbonate and 53 mg (0.986

mmoles) of sodium methoxide. The reaction was stirred for 6 hours, partitioned between 50 ml of dichloromethane and 30 ml of water. The layers were separated, and the organic phase dried and evaporated. The solid was crystallized from methanol to give 25 mg (50%) of white prisms, mp 195-199°. A mixed melting point of 197-200° was obtained with a sample prepared according to the procedure outlined in Scheme II.

7-Phenyl-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-amine (**7**).

A soluton of 3.1 g (10.3 mmoles) of **5** in 60 ml of glacial acetic acid was treated with 1 teaspoon of Raney nickel [5] and then hydrogenated for 8.5 hours. The reaction was filtered through celite, and evaporated. The filtrate was partitioned between 50 ml of dichloromethane and 30 ml of dilute ammonium hydroxide, and the organic layer was dried with sodium sulfate and evaporated. The resulting oil was refluxed in 75 ml of methanol for 15 minutes, evaporated and dissolved in 100 ml of dichloromethane. This was treated with 3 g of activated manganese dioxide [6], and then refluxed and stirred for 30 minutes. The fraction was filtered, concentrated and chromatographed over 100 g of Florisil. The column was eluted with 300 ml of dichloromethane, 500 ml of ether and 1.5 ℓ of ethyl acetate. The ethyl acetate fraction was evaporated, and the oil was crystallized from ether and recrystallized from dichloromethane/ether to give 0.6 g of **7** as white rods, mp 239-242°. The filtrates and the ether fraction from the column were evaporated and developed on silica gel thick layer plates in ethyl accetate/methanol (20:1) to give an additional 0.3 g of **8** for a total yield of 31%. An analytical sample was recrystallized from ether to give white prisms, mp 201-205° which reset to from rods, mp 240-243°; ir (potassium bromide): 3320, 3190 cm^{-1} (NH_3); mass spectrum m/e 286 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_4$: C, 75.51; H, 4.93; N, 19.57. Found: C, 75.70; H, 5.01; N, 19.30.

2-[(4-Chloromethyl)-2-phenyl-1,3-dioxolan-2-yl]benzoic Acid Methyl Ester (**9**).

To a solution of 33 g (0.138 mole) of **8** in 200 ml of dry carbon tetrachloride was added 10.1 ml (0.13 mole) of 1-chloro-2,3-epoxypropane. The reaction was cooled in an ice bath and a solution of 1.5 ml (0.013 mole) of stannic chloride in 10 ml of carbon tetrachloride was added with stirring over a 20 minute period. The reaction was allowed to stand over the weekend, and then the same quantities of 1-chloro-2,3-epoxypropane and stannic chloride were added. After 18 hours, the reaction was cooled in an ice bath and neutralized with concentrated ammonium hydroxide. The precipitate was collected and washed with dichloromethane and the combined filtrates were washed with 150 ml of water, dried with sodium sulfate and evaporated. The resulting oil was dissolved in 100 ml of dichloromethane and chromatographed through 500 g of neutral alumina. Elution with 3 ℓ of dichloromethane gave 20 g (41%) of **9** as an oil which was about 95% pure by tlc. Crystallization and recrystallization of a small sample from ether/petroleum ether, bp 30-30°, gave white rods, mp 90-91°; ir (chloroform): 1725 cm^{-1} (C=O); nmr (DMSO-d_6): δ 3.64 (s, 3H, CH_3), 3.68-4.00 (m, 4H, $2CH_2$), 4.10-4.34 (m, 1H, CH) and 7.18-7.60 (m, 9H, aromatics).

Anal. Calcd. for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15. Found: C, 65.01; H, 5.09.

2-[4-(Chloromethyl)-2-phenyl-1,3-dioxalan-2-yl]-α-[(dimethylamino)methylene]-β-oxobenzenepropanenitrile (**11**).

To a stirring solution of 75 ml of liquid ammonia was added a small piece of sodium and a few crystals of ferric nitrate. A total of 1.15 g (50.2 mmoles) of sodium was added over a 20 minute period, and after 5 minutes a solution of 2.9 ml (50 mmoles) of acetonitrile in 10 ml of ether was added dropwise. A solution of 6.6 g (19.8 mmoles) of **9** in 40 ml of ether was added dropwise, and after 2 hours 100 ml of ether was added and the ammonia was allowed to evaporate. About 100 g of ice was added to the reaction, which was then acidified with acetic acid, followed by neutralization with a saturated solution of sodium bicarbonate. The water layer was separated and extracted once more with ether. The combined ether layers were washed with 100 ml of water, dried and evaporated. The oil was dissolved in 15 ml of dichloromethane and filtered through 100 g of Florisil. Elution with dichloromethane, and evaporation gave 1.5 g of **10** which was used without further purification.

A solution of 20 g (0.0585 mole) of **10** (prepared as in the above procedure) in 75 ml of *N,N*-dimethylformamide dimethylacetal was refluxed and stirred for 90 minutes, and evaporated to dryness. The oil was triturated with ice water which was decanted, and the residue was partitioned between 150 ml of dichloromethane and 150 ml of water. The organic layer was dried with sodium sulfate, concentrated, and filtered through 150 g of Florisil. The column was eluted with ether, the solution was evaporated and the resulting oil was crystallized from ethanol to give 10 g of **11**. A sample was recrystallized from dichloromethane/ether to give white prisms, mp 107-110°; ir (chloroform): 2200 (CN), 1663 cm^{-1} (C=O); nmr (DMSO-d_6): δ 3.14 (s, 3H, NCH_3), 3.25, 3.28 (d, 3H, NCH_3), 3.64 (q, J = 16, 2H, CH_2Cl), 3.78-4.14 (m, 2H, CH_2O), 4.15-4.43 (m, 1H, CHO) and 7.00-7.54 (m, 10H, aromatics and =CH); ms: m/e 396 (M^+).

Anal. Calcd. for $C_{22}H_{21}ClN_2O_3$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.52; H, 5.35; N, 7.11.

2-Amino-4-(2-benzoylphenyl)pyrimidine-5-carbonitrile (**5**) and 1-Oxo-3-phenyl-1*H*-indene-2-carbonitrile (**13**).

To a solution of 2.0 g (5.04 mmoles) of **11** in 10 ml of dichloromethane was added 10 ml of methanol and 2 ml (19.2 mmoles) of 9.6 *N* ethanolic hydrogen chloride. After 90 minutes, the solvent was evaporated and the oil was partitioned between 50 ml of dichloromethane and 30 ml of a saturated sodium bicarbonate solution. The organic layer was dried with sodium sulfate and evaporated. The 1.5 g of oil obtained was dissolved in 30 ml of methanol, and 1.5 g (8.33 mmoles) of guanidine carbonate was added. The solution was stirred for 90 minutes and then refluxed for 2 hours. The reaction was evaporated and then partitioned between 50 ml of dichloromethane and 30 ml of dilute ammonium hydroxide. The organic layer was dried with sodium sulfate and filtered through 50 g of Florisil. The column was eluted with dichloromethane (200 ml) and then ether (300 ml). The dichloromethane fraction was evaporated, crystallized and then recrystallized from dichloromethane/petroleum ether, bp 30-60°, to give 0.4 g (33%) of **13** as yellow rods, mp 173-175°; ir (chloroform): 2225 (CN), 1723 cm^{-1} (C=O); ms: m/e 231 (M^+).

Anal. Calcd. for $C_{16}H_9NO$: C, 83.10; H, 3.92; N, 6.06. Found; C, 82.83; H, 3.91; N, 5.90.

The ether fraction was evaporated and recrystallized from dichloromethane/petroleum ether, bp 30-60°, to give 0.6 g (40%) of **5**, mp 195-199°. An analytical sample was recrystallized from methanol to give off-white prisms, mp 197-200°; ir (potassium bromide): 3380, 3310, 3150 (NH_2), 2220 (CN), 1663 cm^{-1} (C=O); ms: m/e 300 (M^+).

Anal. Calcd. for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 71.74; H, 4.00; N, 18.67.

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REFERENCES AND NOTES

[1] For the previous paper in this series see: E. J. Trybulski, R. I. Fryer, E. Reeder, A. Walser and J. Blount, in press. For alternate synthesis of pyrimido[2]benzazepines see: E. J. Trybulski, L. E. Benjamin, Sr., J. V. Earley, R. I. Fryer, N. W. Gilman, E. Reeder, A. Walser, A. B. Davidson, W. D. Horst, J. Sepinwall, R. O'Brien and W. Dairman, in press.

[2] 3-Phenylphthalide was prepared from *o*-benzoylbenzoic acid according to the literature procedure: G. R. Risinger and J. A. Thompson, *Rec. Trav. Chim.*, **82**, 801 (1963).

[3] M. S. Newman and S. Hishida, *J. Am. Chem. Soc.*, **84**, 3582 (1962).

[4] G. Willfand, *Chem. Ber.*, **74B**, 145 (1941).

[5] A high activity grade Raney Nickel similar to type 28 was used.

[6] The crude product was treated with manganese dioxide in order to oxidize any dihydroprimidines which might have formed during the hydrogenation.