Synthesis of 1-Amino-5-phenyl-4,5-dihydro-3*H*-2-benzazepines and the Isomeric 2-Amino-1-benzazepines

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The title amidines (**1** and **2**) were synthesized. A synthesis of lactam **10** free of isomeric **4** is described. An interesting rate difference in displacement of thiomethyl ether intermediates **5** and **11** with amines was observed.

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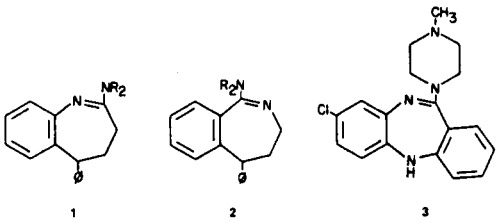
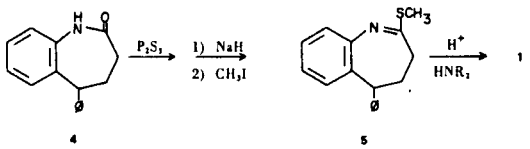
In a search for novel neuroleptic agents, amidines **1** and **2** were chosen as target structures based on their similarity to clozapine (**3**), a clinically useful agent (1).



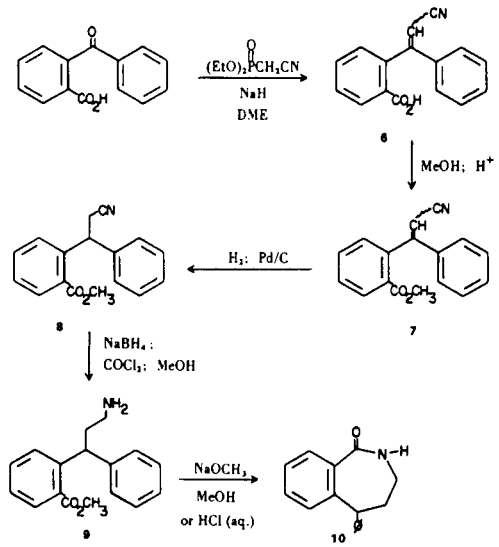
The synthesis of **1** *via* displacement of thiomethyl ether **5** with various secondary amines (see Table I) is described in Scheme I. The requisite lactam (**4**) is readily prepared by a Beckman rearrangement of the oxime of 4-phenyl-1-tetralone (2).

Scheme I



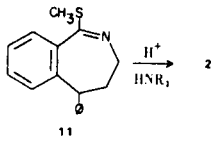
The isomeric lactam (**10**) has only been isolated in minute quantity by separation from the mixture of these lactams after a Schmidt reaction of 4-phenyl-1-tetralone (3,4). Consequently, a more practical synthesis was devised and carried out as described in Scheme II.

Scheme II



A Wittig reaction of benzophenone-2-carboxylic acid with a large excess of diethyl cyanomethylphosphate and sodium hydride in dimethoxyethane led to **6** as a 80:20, presumed E to Z, mixture. Experimental expedience called for esterification of **6** prior to catalytic hydrogenation. Selective reduction of the nitrile **8** was accomplished with a mixture of sodium borohydride and cobaltous chloride (5). The resultant aminoester (**9**) was refluxed with sodium methoxide in methanol for 90 hours or treated with aqueous acid at room temperature to effect cyclization. Lactam **10** had physical characteristics identical to those reported previously (3).

Amidine **2** was obtained in a series of reactions similar to those described in Scheme I. Lactam **10** was converted to a thiolactam. Subsequent treatment with sodium hydride followed by iodomethane yielded thiomethyl ether **11**.

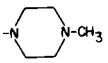
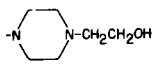
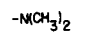
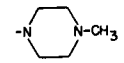
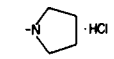


Interestingly, the displacement reactions of **5** and **11** with amines were very different in rate. Thus treatment of **5** with excess dimethyl amine and a catalytic amount of glacial acetic acid at ambient temperature led to complete conversion in 18 hours. On the other hand, **11** was refluxed with a large excess of *N*-methylpiperazine and acetic acid catalyst in chloroform for 11 days and only partial reaction was detected by thin layer chromatography. When greater than an equivalent of acetic acid relative to amine was added, the reaction was complete after 20 hours of additional reflux.

This type of rate phenomenon has been observed in a number of systems in these laboratories. The mechanistic possibilities for this displacement reaction are numerous and to discriminate between them solely on the basis of the above observation is tenuous.

Unfortunately all of the amines listed in the table were devoid of any significant activity in the central nervous system.

Table I

Compound	Amine	Recrystallization Solvent M.p.	Calcd. for: Theory Found
1a		ethyl acetate 105-106.5°	$C_{21}H_{25}N_3$ C, 78.96; H, 7.89; N, 13.16 C, 79.06; H, 8.02; N, 13.02
1b		Skelly B 151-152°	$C_{22}H_{27}N_3O$ C, 75.61; H, 7.79; N, 12.03 C, 75.70; H, 7.83; N, 11.91
1c		cyclohexane 143.5-145°	$C_{20}H_{22}N_2$ C, 82.72; H, 7.64; N, 9.65 C, 82.60; H, 7.60; N, 9.68
1d		ethyl acetate 135-136°	$C_{18}H_{20}N_2$ C, 81.77; H, 7.63; N, 10.60 C, 81.37; H, 7.66; N, 10.64
2a		acetonitrile 108.5-111°	$C_{21}H_{25}N_3$ C, 78.96; H, 7.89; N, 13.16 C, 79.20; H, 7.91; N, 13.27
2b		251-256° dec.	$C_{20}H_{23}N_2Cl$ C, 73.50; H, 7.09; N, 8.57 C, 73.52; H, 7.22; N, 8.56

EXPERIMENTAL

All melting points were obtained with a Thomas Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian T-60 instrument.

1-Cyano-2,2-diphenylethene-2′-carboxylic Acid (**6**).

Diethyl cyanomethylphosphate (35 g., 198 mmoles) in 50 ml. of dimethoxyethane (DME) was added dropwise over a 10 minute period to a cooled (0°), stirred suspension of sodium hydride (9 g., 57% in oil; 210 mmoles) in 100 ml. of DME under a nitrogen atmosphere. The resultant mixture was allowed to warm to room temperature and stirred an additional 2 hours before benzophenone-2-carboxylic acid (15 g., 66 mmoles) in 100 ml. of DME was added. The mixture was heated under reflux for 65 hours. It was diluted with water and washed three times with methylene chloride before it was acidified with the addition of concentrated hydrochloric acid. It was then extracted with three portions of methylene chloride (600 ml. total). These combined organic extracts were washed with water (3X) and brine, dried over magnesium sulfate and concentrated to yield 7 g. (42%) of white solid. A sample was recrystallized from ether, m.p. 183-189°; nmr (deuteriochloroform, TMS): δ 5.55 (s, olefinic Z isomer), 6.0 (s, olefinic, E isomer), 7.2-8.5 (m, aromatic). The ratio of olefinic singlets indicated a 80:20, E to Z, mixture.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.08; H, 4.45; N, 5.62. Found: C, 76.76; H, 4.56; N, 5.35.

Methyl 1-Cyano-2,2-diphenylethene-2′-carboxylate (**7**).

To a solution of carboxylic acid **6** (6.9 g.) in 200 ml. of methanol was added 2 ml. of concentrated sulfuric acid. The solution was heated under reflux for 48 hours before it was diluted with an equal volume of water and extracted with ether (2X). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated to yield 7.0 g. (96%) of tan solid, m.p. 110-118°; nmr (deuteriochloroform, TMS): δ 3.55 (s, methyl, Z isomer), 3.6 (s, methyl, E isomer), 5.5 (s, olefinic, Z isomer), 5.9 (s, olefinic, E isomer), 7.2-8.2 (m, aromatic).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.53; H, 4.90; N, 5.03.

Methyl 1-Cyano-2,2-diphenylethane-2′-carboxylate (**8**).

A solution of alkene **7** (7.0 g.) with a suspension of 10% palladium on carbon (1.4 g.) in 300 ml. of methanol was hydrogenated in a Paar shaker at 60 psi for 24 hours. The solution was filtered and concentrated to yield 6.9 g. (98%) of pale yellow oil; nmr (deuteriochloroform, TMS): δ 3.0 (d J = 7, 2H, methylene), 3.75 (s, 3H, methyl), 5.45 (t J = 7, 1H, methine), 7.0-8.0 (m, 9H, aromatic).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.86; H, 5.92; N, 5.01.

Methyl 1-Amino-3,3-diphenylpropane-2′-carboxylate (**9**).

Cobaltous chloride hexahydrate (12.5 g., 52.4 mmoles) was added to a stirred solution of the nitrile **8** (6.9 g., 26.2 mmoles) in 250 ml. of 4:1 methanol-benzene. Then the mixture was cooled to 0° and sodium borohydride (9.9 g., 262 mmoles) added. The resultant dark solution was allowed to warm to room temperature and stirred 3.5 hours before the addition of 250 ml. of 3*N* hydrochloric acid. After an additional 1.5 hours the mixture was concentrated on a rotary evaporator and basified with concentrated ammonium hydroxide. This was extracted with ether (3X). The ether layers were combined, washed with water and brine, dried with magnesium sulfate, and concentrated to yield 5.67 g. (81%) of colorless oil; nmr (deuteriochloroform, TMS): δ 1.4 (s, 2H, $-NH_2$), 2.15 (m, 2H, methylene), 2.7 (m, 2H, $-CH_2NH_2$), 3.8 (s, 3H, methyl), 5.1 (t J = 7, 1H, methine), 6.9-7.9 (m, 9H, aromatic).

5-Phenyl-4,5-dihydro-2-benzazepin-1-one (**10**).

Sodium methoxide (3.5 g.) was added to a stirred solution of aminoester **9** (5.67 g.) in 250 ml. of methanol. The resultant mixture was heated under reflux for 90 hours before it was poured into water and extracted three times with chloroform. These combined extracts were dried and concentrated to yield 5.1 g. of -

solid which after recrystallization from acetonitrile yielded a white solid, m.p. 227-229° (lit. 226-228°) (3).

Alternatively, the crude reaction mixture from the previous sodium borohydride reduction was allowed to sit overnight after treatment with 3*N* hydrochloric acid. The desired lactam (**10**) crystallized from solution and was isolated by vacuum filtration (44% from **8**).

5-Phenyl-4,5-dihydro-2-benzazepin-1-thione.

Lactam **10** (3.39 g., 14.3 mmoles) and phosphorus pentasulfide (3.33 g., 15 mmoles) were suspended in pyridine (30 ml.) and heated under reflux for one hour. The resultant orange-brown solution was dripped into 100 ml. of stirred water warmed to *ca.* 70°. Heating was continued for 2.5 hours before the solid suspension was isolated by filtration to yield 2.48 g. (m.p. 167-171°) and a second crop of 0.7 g. (total 88.5%).

Anal. Calcd. for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53. Found: C, 75.93; H, 5.99; N, 5.74.

1-Thiomethyl-5-phenyl-4,5-dihydro-2-benzazepin-1-ene (**11**).

Sodium hydirde (1.1 g. of 57% in oil; 26 mmoles) was added to a stirred suspension of the thioamide (3.2 g., 12.7 mmoles) in 50 ml. of benzene. The resultant mixture was heated under reflux for 1.5 hours before it was allowed to cool slightly and methyl iodide (2.7 g., 19 mmoles) in 15 ml. of benzene was added through the condenser. After an additional 2 hours of reflux, the mixture was filtered and the filtrate concentrated to yield 3.92 g. of clear yellow oil which was used without further purification.

Anal. Calcd. for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24; S, 11.99. Found: C, 76.50; H, 6.43; N, 5.65; S, 12.13.

1-*N*-Methylpiperazino-5-phenyl-4,5-dihydro-2-benzazepine (**2a**).

N-Methylpiperazine (8 ml.) and glacial acetic acid (3 ml.) were added to a stirred solution of thioether **11** (3.92 g.) in chloroform. The solution was heated under reflux for 11 days but thin layer chromatography indicated mostly starting material with a small amount of product. An additional 8 ml. of the amine and 9 ml. of acetic acid were added and reflux continued. After 18 hours only a trace of starting material remained but heating was continued for a total of 42 hours. It was then allowed to cool and carefully added to 200 ml. of concentrated ammonium hydroxide in a separatory funnel. The aqueous layer was extracted with two additional portions of chloroform. The combined organic layers were washed with concentrated ammonium hydroxide, water, and brine, dried with magnesium sulfate and concentrated to yield 4 g. of viscous yellow oil. This was redissolved in benzene and extracted with three portions (250 ml. total) of 20% acetic acid solution. The combined acid extracts were washed with benzene (3X) and then basified with 200 ml. concentrated ammonium hydroxide and finally extracted three times with chloroform. The combined chloroform layers were dried and concentrated to yield 3.45 g. of pale yellow glass which was recrystallized from acetonitrile to yield 1.6 g. (40% from crude thiolactam) of white solid, m.p. 108.5-111°.

2-Amino-5-phenyl-4,5-dihydro-1-benzazepine (Typical Procedure).

The crude thiomethylether **5** (4.48 g.), *N*-methylpiperazine (9 ml.), and glacial acetic acid (2 ml.) were dissolved in chloroform and heated under reflux for 16 hours. The mixture was concentrated on a rotary evaporator and then partitioned between benzene and water. The benzene layer was washed with water (2X) before it was extracted with two 125 ml. portions of 20% aqueous acetic acid. The acidic extracts were combined and washed with benzene (3X) before basification with 250 ml. of concentrated ammonium hydroxide. It was then extracted with benzene (3X). These organic fractions were combined, dried with brine and magnesium sulfate and concentrated *in vacuo* to yield 3.1 g. of yellow oil. Crystallization from ethyl acetate yielded 1.8 g. (38% from crude thiolactam) of pale yellow prisms, m.p. 105-106.5°.

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