Synthesis of 4,5-Dihydro-4-phenyl-3*H*-1,3,4-benzotriazepines

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Several 4,5-dihydro-4-phenyl-3*H*-1,3,4-benzotriazepines were synthesized by conversion of 1-[(2-nitrophenyl)methyl]-1-phenylhydrazine to either 1-[(2-aminophenyl)methyl]-1-phenylhydrazine or 1-[(2-aminophenyl)-methyl]-2-methyl-1-phenylhydrazine. Ring closure of these intermediates with triethyl orthoacetate or triethyl orthopropionate gave the title compounds in overall yields of 40-60%.

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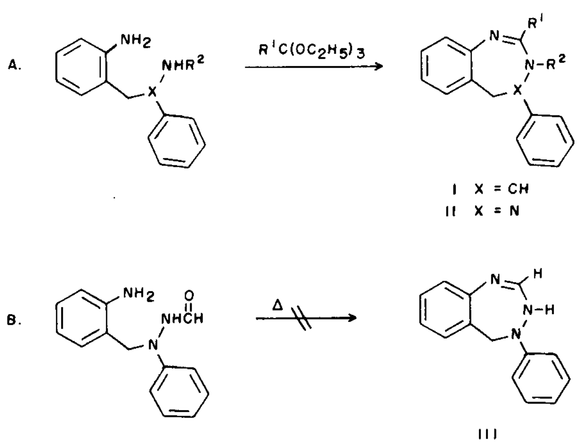
We recently reported the synthesis and biological evaluation of 4,5-dihydro-4-aryl-3*H*-1,3-benzodiazepines (Scheme I,I) as potential central nervous system and antihypertensive agents [1-3]. From this work (±)-4,5-dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3-benzodiazepine (I, R^1 = R^2 = CH_3, HRP 543) was selected for clinical development based on a favorable spectrum of biological properties including potent, antidepressant-like activity [1]. As an attempt to further modify the profile of biological activity, the isosteric replacement of the C-4 methine group of I with nitrogen was proposed and the synthesis of several 4,5-dihydro-4-phenyl-3*H*-1,3,4-benzotriazepines II was investigated.

A survey of the literature revealed that an unsuccessful attempt to prepare 4,5-dihydro-4-phenyl-3*H*-1,3,4-benzotriazepine (III) was reported by Paal and Bodewig [4]. The failure of their synthesis could be attributed to the harsh conditions employed for the formation of the triazepine ring by a thermally induced intramolecular cyclization of 1-[(2-aminophenyl)methyl]-2-formyl-1-phenylhydrazine (Scheme I, Path B). Based on our experience with 1,3-benzodiazepines (Path A, X = CH), we believed that modification of the Paal and Bodewig approach by ring closure of 1-[(2-aminophenyl)methyl]-1-phenylhydrazine derivatives with ortho esters under mild conditions would afford the 1,3,4-benzotriazepines for our investigation (Path A, X = N).

Scheme I

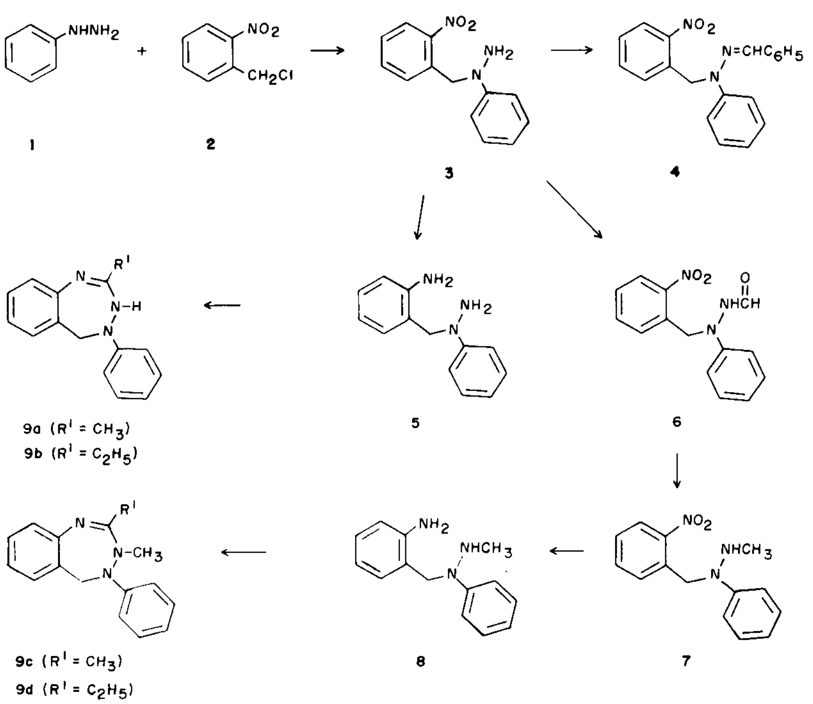


As outlined in Scheme II, phenylhydrazine (**1**) and 2-nitrobenzyl chloride (**2**) were condensed as described [4] to give 1-[(2-nitrophenyl)methyl]-1-phenylhydrazine (**3**). The original structure proof for **3** was based on reduction to 1-[(2-aminophenyl)methyl]-1-phenylhydrazine (**5**), and a vaguely described comparison of **5** with purportedly the same material prepared earlier by Busch [5] *via* an alternative route. Due to this indirect, vaguely described structure proof, the unsymmetrical structure of **3** was confirmed by ^{15}N-nmr and, in a more classical sense, by conversion of **3** to the benzylidine derivative **4**. With respect to the ^{15}N-nmr study, only two singlets were observed in the proton decoupled spectrum of **3**. These singlets represent the hydrazine nitrogens since the nitro group nitrogen has a very long T_1 value and is not visible under the conditions employed. When ^1H-^{15}N coupling was permitted, the peak to lower field remained as a singlet while the peak to higher field was significantly reduced in intensity. The downfield singlet represents a nitrogen bearing no protons and this is compatible only with the unsymmetrically disubstituted structure proposed for **3**.

Reduction of **3** with iron-hydrochloric acid afforded **5** which was readily cyclized with either triethyl orthoacetate or triethyl orthopropionate to provide benzotriazepines **9a** and **9b**, respectively. For the synthesis of the potentially more significant 3-methyl analogues, **3** was refluxed with formic acid to give 2-formyl-1-[(2-nitrophenyl)methyl]-1-phenylhydrazine (**6**) which was reduced with borane-methyl sulfide to afford 2-methyl-1-[(2-nitrophenyl)methyl]-1-phenylhydrazine (**7**). Similar reduction of the nitro group of **7** and cyclization with ortho esters gave **8** and **9c,d**, respectively.

Benzotriazepines **9a-d** were evaluated biologically in a battery of assays including the tetrabenazine-induced ptosis model [6] to detect antidepressant-like properties. None of these 1,3,4-benzotriazepines displayed significant potency in this model ($ED_{50} > 20$ mg/kg, i.p.) suggesting little, if any, antidepressant-like activity is associated with these compounds.

Scheme II



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds are supported by their ir (Pye Unicam SP3-200), ^{1}H nmr (JEOL C60HL or FX60; tetramethylsilane was the internal standard), and ms (Finnigan 4023) spectra. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL and results are within ±0.4% of the theoretical values unless otherwise noted. Generally, reactions were conducted under a dry nitrogen atmosphere. Yields were not optimized.

1-(2-Nitrophenyl)-1-phenylhydrazine (**3**).

A stirred suspension of phenylhydrazine (21.6 g, 0.2 mole), 2-nitrobenzylchloride (17.2 g, 0.1 mole) and absolute ethanol (80 ml) was refluxed for one hour with exclusion of moisture. During this time a red color developed and a crystalline precipitate formed. The hot mixture was decanted into a beaker containing 1 ℓ of a warm (50°) buffer solution prepared from glacial acetic acid (6.0 g, 0.1 mole) and sodium acetate trihydrate (13.6 g, 0.1 mole). The mixture was thoroughly stirred and a lower phase red oil separated. After cooling to 30°, the aqueous phase was decanted and the oil was dissolved in ether (500 ml). The dried (sodium sulfate) organic phase was filtered and treated with ethereal hydrogen chloride. The resultant precipitate was collected and washed several times with ether until the filtrate was almost colorless. The filter cake was treated with 2.5 *N* sodium hydroxide solution (300 ml) and the miture was extracted with methylene chloride (300 ml). The dried (sodium sulfate) organic phase was filtered and concentrated to a red oil which was dissolved in hot 95% ethanol (40 ml). After stirring for two hours at ambient temperature, the crystalline precipitate was collected to afford 10.7 g (44%) of **3** as bright yellow crystals, mp 66.5-70° (lit [4], 72°); ^{1}H-nmr (deuteriochloroform): δ 3.82 (br s, 2H, NH_2), 5.06 (s, 2H, CH_2), 6.6-7.8 (m, 8H, aromatic), 8.0-8.36 (m, 1H, aromatic); ir (chloroform): 1345 and 1525 cm^{-1} (NO_2); ms (CI/CH_4): 244 (MH$^+$, 100%); ^{15}N-nmr (JEOL FX90Q, deuteriochloroform): See text.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.38; N, 17.27. Found: C, 64.16; H, 5.22; N, 17.23.

1-[(2-Nitrophenyl)methyl]-1-phenylhydrazine Benzaldehyde Hydrazone (**4**).

A warm stirred mixture of **3** (4.0 g, 0.016 mole) and 95% ethanol (80 ml) was treated dropwise with benzaldehyde (4.0 ml). After several hours, the crystalline precipitate was collected and recrystallized from absolute ethanol to afford 2.8 g (52%) of **4** as yellow crystals, mp 135-137°; ^{1}H-nmr (deuteriochloroform): δ 5.60 (s, 2H, CH_2), 6.80-7.90 (m, 13H, aromatic), 8.20-8.80 (m, 2H, CH and aromatic); ir (chloroform): 3025, 1590, 1560, 1520, 1395, 1350, 1340, 1160, 1150, 960, 950, 880, 850 cm^{-1}; ms (CI/CH_4): 332 (MH$^+$, 80%).

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.15; H, 5.14; N, 12.59.

1-[(2-Aminophenyl)methyl]-1-phenylhydrazine (**5**).

A stirred mixture of **3** (25 g, 0.12 mole), iron powder (67 g, 1.2 g-atom; Mallinckrodt, reduced, electrolytic), 95% ethanol (300 ml) and water (75 ml) was treated with concentrated hydrochloric acid (2 ml). After refluxing for 0.5 hour, Celite was added and the mixture was filtered. The filter cake was washed with 95% ethanol and the combined filtrate was concentrated. The aqueous residue was basified with sodium hydroxide and extracted with ether. The dried (sodium sulfate) organic phase was filtered and evaporated to dryness, and the residue was recrystallized from 95% ethanol to give 16.1 g (63%) of **5** as almost colorless crystals, mp 95-97° (lit [4], 102°); ^{1}H-nmr (deuteriochloroform-deuterium oxide ex.): δ 4.45 (s, 2H, CH_2), 6.70-7.70 (m, 9H, aromatic); ms (CI/CH_4): 214 (MH$^+$, 83%). The material was utilized for subsequent syntheses without further purification.

2-Formyl-1-[(2-nitrophenyl)methyl]-1-phenylhydrazine (**6**).

A stirred solution of **3** (48.7 g, 0.2 mole) and 97% formic acid (200 ml) was refluxed for 4 hours, cooled and concentrated on a rotary evaporator. A solution of residue and methylene chloride (1.5 ℓ) was washed with 2.5 *N* sodium hydroxide solution, dried (sodium sulfate), filtered and evaporated to dryness. Recrystallization of the residue from 95% ethanol gave 44 g (82%) of **6** as yellow crystals, mp 140-142.5° (lit [4], 141-142°); ^{1}H-nmr (deuteriochloroform/DMSO-d_6; apparent mixture of 3 conformers at ambient temperature): δ 4.98 and 5.12 (two s, ratio 1:1.5, CH_2), 6.64-8.48 (m, 10H, NH and aromatic), 9.28, 9.46, 9.76 (three s, ratio 1.5:1:3.5, CHO); ir (potassium bromide): 1670 cm^{-1} (C=O), 1350 and 1515 cm^{-1} (NO_2); ms (CI/CH_4): 272 (MH$^+$, 100%).

2-Methyl-1-[(2-nitrophenyl)methyl]-1-phenylhydrazine Hydrochloride (7).

A solution of **6** (30 g, 0.11 mole) and sieve dried tetrahydrofuran (1 ℓ) was treated dropwise with 1 *M* borane-methyl sulfide in dichloromethane (333 ml), maintaining the temperature below 25°. After stirring overnight at ambient temperature, the mixture was treated with excess ethereal hydrogen chloride and then basified with 2.5 *N* sodium hydroxide solution. After concentration to remove the ether and tetrahydrofuran, the residue was extracted with ether. The organic phase was washed with water, dried (sodium sulfate), filtered and evaporated to afford a red oil (28 g) which was purified by hplc (Waters Associates, Prep LC/System 500, silica gel, eluted with toluene, 250 ml/minute flow rate). Concentration of the appropriate fractions gave 20 g (71%) of a yellow solid which was converted to the hydrochloride salt and recrystallized from absolute ethanol-ether to afford **7**, mp 169-172°; ^{1}H-nmr (deuteriochloroform/DMSO-d_6): δ 2.78 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 7.2-8.25 (m, 8H, aromatic), 8.35-8.70 (m, 1H, aromatic); ir (potassium bromide): 3450 (br), 3000-2300 (br), 1535, 1495, 1460, 1380, 1350, 1150, 780, 760, 740, 700 cm^{-1}; ms: m/e (%) 257 (M$^{+\cdot}$, 8), 121 (100), 77 (23).

Anal. Calcd. for $C_{14}H_{16}ClN_3O_2$: C, 57.24; H, 5.49; N, 14.30. Found: C, 57.01; H, 5.12; N, 14.02.

4,5-Dihydro-2-ethyl-4-phenyl-3*H*-1,3,4-benzotriazepine Hydrochloride (9b).

A mixture of **5** (3.75 g, 0.018 mole), triethyl orthopropionate (19 g, 0.11 mole) and glacial acetic acid (6.8 ml) was converted under conditions as described for the preparation of **9a** to afford **9b** (4.75 g as the crude hydrochloride salt). Recrystallization from absolute ethanol gave 2.0 g (40%) of **9b**, mp 236-239°; ^{1}H-nmr (DMSO-d_6): δ 1.48 (t, J = 7.5 Hz, 3H, CH_2CH_3), 3.05 (q, J = 7.5 Hz, 2H, CH_2CH_3), 5.08 (s, 2H, CH_2), 6.5-8.0 (m, 9H, aromatic); ir (potassium bromide): 3425, 3200-2400 (br), 1630, 1600, 1580, 1500, 1450, 750 cm^{-1}; ms (CI/CH_4): 252 (MH$^+$, 100%).

Anal. Calcd. for $C_{16}H_{18}ClN_3$: C, 66.78; H, 6.30; N, 14.60. Found: C, 66.46; H, 6.39; N, 14.26.

1-[(2-Aminophenyl)methyl]-2-methyl-1-phenylhydrazine (8).

A mixture of **7** (30.8 g, 0.12 mole, free base) was reduced with iron-hydrochloric acid as described for the preparation of **5**. The crude oil (25 g) was triturated with isopropyl ether and hexane to give a yellow solid. Recrystallization from 2-propanol-hexane afforded 15.7 g (58%) of **8** as colorless crystals, mp 57-59°; ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 6.50-7.50 (m, 9H, aromatic); ir (chloroform): 3450, 3350, 3150-2800 (br), 1620, 1600, 1500, 1460, 1350, 1295 cm^{-1}; ms: m/e (%): 227 (M$^{+\cdot}$, 39), 121 (61), 106 (100), 77 (59), 43 (40).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 73.98; H, 7.54; N, 18.48. Found: C, 74.06; H, 7.46; N, 18.56.

4,5-Dihydro-2-methyl-4-phenyl-3*H*-1,3,4-benzotriazepine Hydrochloride (9a).

A stirred mixture of **5** (2.5 g, 0.012 mole), triethyl orthoacetate (11.7 g, 0.072 mole) and glacial acetic acid (4.5 ml) was refluxed for 3.5 hours, concentrated and the residue partitioned between 2.5 *N* sodium hydroxide solution and ether. The organic phase was washed with water, dried (sodium sulfate), filtered and treated with ethereal hydrogen chloride. Recrystallization of the precipitate from absolute ethanol-ether gave 2.0 g (61%) of **9a**, mp 244-247°; ^{1}H-nmr (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 6.63-7.80 (m, 9H, aromatic); ir (potassium bromide): 3600-2300 (br), 1630, 1595, 1585, 1490, 1445, 1240, 1210, 1190, 1040, 940, 880, 840, 785, 745, 685, 625 cm^{-1}; ms (CI/CH_4): 238 (MH$^+$, 100%).

Anal. Calcd. for $C_{15}H_{16}ClN_3$: C, 65.82; H, 5.90; N, 15.37. Found: C, 66.13; H, 5.92; N, 15.15.

4,5-Dihydro-2,3-dimethyl-4-phenyl-3*H*-1,3,4-benzotriazepine Hydrochloride (9c).

A solution of **8** (3.5 g, 0.015 mole), triethyl orthoacetate (4.9 g, 0.03 mole) and acetonitrile (40 ml) was acidified with ethereal hydrogen chloride. After refluxing for 5.5 hours, the mixture was concentrated and the residue was partitioned between 2.5 *N* sodium hydroxide solution and ether. The organic phase was washed with water, dried (sodium sulfate), filtered and treated with ethereal hydrogen chloride to give 2.6 g (60%) of **9c** as a colorless solid, mp 274-277°. Final purification was effected by trituration of the solid with hot acetonitrile; ^{1}H-nmr (trifluoroacetic acid): δ 2.88 (s, 3H, C-CH_3), 3.78 (s, 3H, N-CH_3), 5.08 (s, 2H, CH_2), 6.55-7.88 (m, 9H, aromatic); ir (potassium bromide): 3450, 3000-2400 (br), 1615, 1600, 1580, 1500, 760 cm^{-1}; ms m/e (%): 251 (M$^{+\cdot}$, 27), 131 (73), 130 (100), 89 (47), 77 (87).

Anal. Calcd. for $C_{16}H_{18}ClN_3$: C, 66.78; H, 6.30; N, 14.60. Found: C, 66.90; H, 6.33; N, 14.40.

4,5-Dihydro-2-ethyl-3-methyl-4-phenyl-3*H*-1,3,4-benzotriazepine Hydrochloride (9d).

A mixture of **8** (3.5 g, 0.15 mole), triethyl orthopropionate (5.43 g, 0.031 mole) and acetonitrile (40 ml) was converted under conditions as described for the preparation of **9c** to afford **9d** (2.0 g, 43%, precipitated from ether with ethereal hydrogen chloride), mp 126-130°; ^{1}H-nmr (DMSO-d_6): δ 1.43 (t, J = 7.5 Hz, 3H, CH_2CH_3), 3.15 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.58 (s, 3H, N-CH_3), 5.15 (br s, 2H, CH_2), 6.6-8.0 (m, 9H, aromatic); ir (potassium bromide): 3425, 3000-2300 (br), 1605, 1590, 1565, 1490, 1450, 745 cm^{-1}; ms (CI/CH_4): 266 (MH$^+$, 100%).

Anal. Calcd. for $C_{17}H_{20}ClN_3$: C, 67.65; H, 6.68; N, 13.92. Found: C, 67.79; H, 6.66; N, 13.55.

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