Synthesis of Novel Substituted Spirohydantoins

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Received February 4, 1992

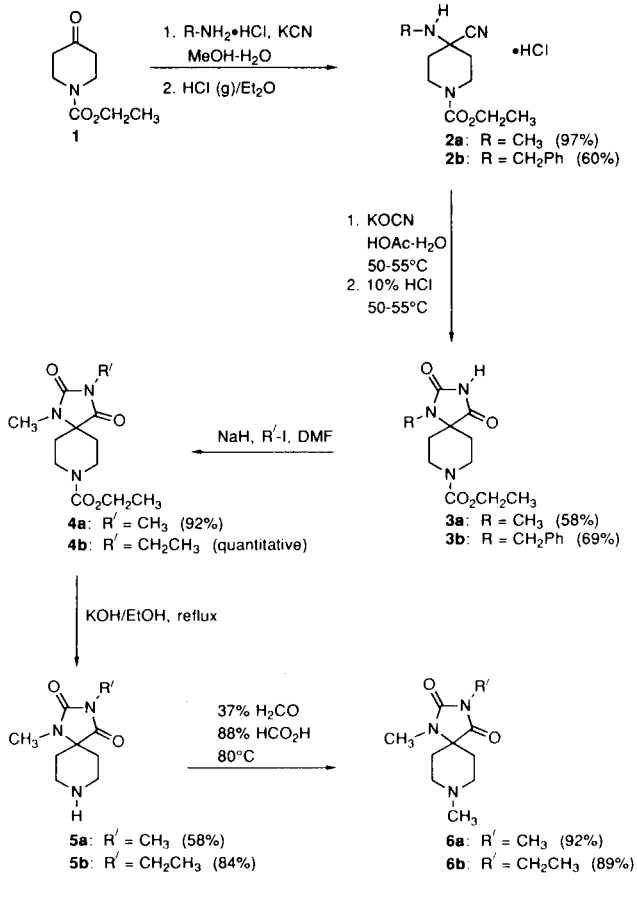
The synthesis of novel *N*-1-alkylspirohydantoins (1-alkyl-1,3,8-triazaspiro[4.5]decanes) is reported. The key hydantoin intermediates **3** were prepared using standard hydantoin methodology. This synthesis allows for differential substitution of all three nitrogens.

J. Heterocyclic Chem., **29**, 847 (1992).

Introduction.

In connection with a program directed toward the development of novel central nervous system agents, a general method for the preparation of *N*-substituted spirocyclic hydantoins of type **5** and **6** (Scheme I) was required. Our analog strategy required that various alkyl substituents could be incorporated selectively at each of the three nitrogens present in these molecules.

Scheme I



Although synthetic strategies to produce hydantoins have been known for over a century [1,2], surprisingly few examples of hydantoins appended to a piperidine ring have been characterized previously [3,4a-d]. Some of these known piperidine hydantoins were prepared utilizing atypical methods for hydantoin formation and thus do not take advantage of the wealth of classical literature pertaining to the synthesis of hydantoins from carbonyl compounds [5,6]. Reported herein, as shown in Scheme I, are the syntheses of spirocyclic hydantoin piperidines **5** and **6**, which serve to illustrate the facile preparation of this series of compounds from commercially available 1-carboethoxy-4-piperidone **1**.

Results and Discussion.

Since selective *N*-1 alkylation of hydantoins is problematic due to the competing reactivity of the nitrogen at the 3-position [2,7-9], this substituent was incorporated during the initial modified Strecker reaction. As examples, methylamine and benzylamine gave the α-alkylaminonitriles **2a** and **2b**, which were isolated as their hydrochloride salts in good to excellent yields [10,11]. Completion of the hydantoin ring under modified Urech conditions afforded the key intermediates **3** which were isolated as analytically pure materials simply by filtration of the reaction mixtures [10,11]. *Via* this sequence multigram quantities of intermediates **3** were prepared easily.

Derivatives such as **3** are ideally suited for selective alkylation of the hydantoin nitrogen at the 3-position. In addition, the carboethoxy protecting group aids greatly in purification and is easily removed at the end of the synthesis. Formation of the anion of **3a** with sodium hydride followed by reaction with an alkyl halide proceeded smoothly to yield **4**. Deprotection of the piperidine nitrogen was accomplished by treatment with alcoholic potassium hydroxide heated to reflux. Some care needed to be exercised during the hydrolysis step, since prolonged reaction times resulted in decomposition of the desired product **5**. Careful monitoring of the reaction by thin layer chromatography minimized the formation of undesirable side products. Finally, substitution at the piperidine nitrogen was accomplished routinely by reductive *N*-methylation under Eschweiler-Clarke conditions [12] to produce the desired *N*-methylated and fully substituted products **6**.

In conclusion, we have demonstrated that this class of

spirohydantoins, the 1-alkyl-1,3,8-triazaspiro[4.5]decanes, can be easily prepared from readily available starting materials and that the substitution patterns on each of the three nitrogens can be controlled. Details regarding the interesting biologic activities of these compounds will be reported elsewhere.

EXPERIMENTAL

Unless noted, all reagents employed were purchased from commercial suppliers and used without further purification.

Melting points are uncorrected. Thin layer chromatography was performed using pre-coated Merck plates, silica gel 60 F_{254}, 0.25 mm thickness. Flash chromatography was carried out using Merck silica gel 60, 230-400 mesh. The pmr spectra were obtained on 300 MHz General Electric QE 300 and QZ 300 spectrometers. Low resolution mass spectra (DCl-NH_3) were obtained on Finnigan-MAT SSQ70 and Hewlett Packard 5985A spectrometers. Elemental analyses were performed by the Abbott Laboratories Analytical Research Department.

1-Carboethoxy-4-cyano-4-methylaminopiperidine Hydrochloride (**2a**).

Potassium cyanide (16.3 g, 0.250 mole) in water (32 ml) was added dropwise at a steady rate to a chilled (ice-water bath) solution of 1-carboethoxy-4-piperidone **1** (42.8 g, 0.250 mole) and methylamine hydrochloride (16.9 g, 0.250 mole) in 1:1 methanol-water (50 ml). The cooling bath was removed and the reaction mixture allowed to stir overnight at room temperature. Two clear layers formed. The reaction mixture was diluted with diethyl ether (100 ml) and water (150 ml), and the layers were separated. The aqueous phase was extracted further with diethyl ether (4 x 100 ml), then the combined organics were concentrated to a smaller volume (*ca.* 250 ml) and dried (sodium sulfate). The ethereal solution was treated with a saturated ethereal gaseous hydrochloric acid solution to afford the hydrochloride, which was filtered off under nitrogen and further triturated with diethyl ether, then dried *in vacuo* over phosphorus pentoxide to give a white powder (60 g, 97%), mp 129-132°; tlc (chloroform-methanol, 10:1) R_f 0.56; pmr (methanol-d_4): δ 1.27 (t, 3H, J = 8 Hz), 1.92 (td, 2H, J = 5, 13 Hz), 2.40 (d, 2H, J = 13 Hz), 2.91 (s, 3H), 3.09 (m, 2H), 4.15 (q, 2H, J = 8 Hz), 4.37 (d, 2H, J = 15 Hz); ms: (DCl-NH_3): m/z 229 $(M+NH_4)^+$.

Anal. Calcd. for $C_{10}H_{18}N_3O_2Cl$: C, 48.47; H, 7.34; N, 16.96. Found: C, 48.37; H, 7.37; N, 16.56.

8-Carboethoxy-1-methyl-1,3,8-triazaspiro[4.5]decane (**3a**).

To a solution of α-amino nitrile **2a** (10.0 g, 40.4 mmoles) in glacial acetic acid (30 ml) was added potassium cyanate (6.55 g, 80.7 mmoles) in water (10 ml) dropwise. The cloudy reaction mixture was heated in a 50° oil bath for 1 hour. The bath was removed. After it had cooled, the reaction mixture was poured into cold water (200 ml) and extracted with ethyl acetate (4 x 200 ml). The combined organics were dried (sodium sulfate) and concentrated (toluene azeotrope) to give an opaque yellow waxy solid (10.8 g). The solid was treated with 10% aqueous hydrochloric acid (40 ml) and heated in a 50° oil bath. After a few minutes the reaction mixture became homogeneous, and after a few more minutes white granular solid began to precipitate. After a total of 15 minutes the reaction mixture was allowed to cool and the solid was filtered off, rinsing with cold water. Drying *in vacuo* at 50° over phosphorus pentoxide gave a white granular solid (6.0 g, 58%), mp 203-206°; tlc (chloroform-methanol, 20:1) R_f 0.32; pmr (methanol-d_4): δ 1.27 (t, 3H, J = 7 Hz), 1.72 (d, 2H, J = 14 Hz), 1.94 (td, 2H, J = 5, 13 Hz), 2.79 (s, 2H), 3.52 (m, 2H), 4.11 (m, 2H), 4.14 (q, 2H, J = 7 Hz); ms: (DCl-NH_3) m/z 273 $(M+NH_4)^+$, 256 $(M+H)^+$.

Anal. Calcd. for $C_{11}H_{17}N_3O_4$: C, 51.74; H, 6.72; N, 16.46. Found: C, 51.99; H, 6.82; N, 16.55.

4-Benzylamino-1-carboethoxy-4-cyanopiperidine Hydrochloride (**2b**).

Potassium cyanide (6.52 g, 0.100 mole) in water (20 ml) was added dropwise, rapidly to a chilled (ice-water bath) solution of 1-carboethoxy-4-piperidone **1** (17.2 g, 0.100 mole) and benzylamine hydrochloride (14.4 g, 0.100 mole) in 1:1 methanol-water (30 ml). The cooling bath was removed and the cloudy two-phase reaction mixture was allowed to stir at room temperature. After 5 hours, tlc revealed that significant amounts of starting materials remained. Methanol (150 ml) was added to produce a homogeneous solution, which was allowed to stir overnight. Benzylamine still remained by tlc, so more ketone (0.2 eq) and cyanide (0.2 eq) in water (4 ml) were added. After 5 hours, the reaction mixture was concentrated to a small volume (*ca.* 50 ml) and partitioned between diethyl ether (100 ml) and water (100 ml). After separation, the aqueous phase was extracted further with ether (2 x 100 ml). The combined organics were dried (sodium sulfate) and filtered. The ethereal solution was diluted with ether (to 600 ml), then treated with a saturated ethereal gaseous hydrochloric acid solution to afford the hydrochloride, which was filtered off under nitrogen, washed with cold ether, and dried *in vacuo* over phosphorus pentoxide (32.1 g). Since this material contained a significant amount of benzylamine hydrochloride (pmr), the greater part of the sample (29.0 g) was recrystallized from methanol-diethyl ether to give small white needles (19.6 g, 60%), mp 154-157°; tlc (hexane-ethyl acetate, 1:1) R_f 0.47; pmr (methanol-d_4): δ 1.28 (t, 3H, J = 8 Hz), 2.03 (td, 2H, J = 5, 13 Hz), 2.49 (d, 2H, J = 13 Hz), 3.12 (m, 2H), 4.16 (q, 2H, J = 8 Hz), 4.40 (d, 2H, J = 14 Hz), 4.47 (s, 2H), 7.45-7.54 (c, 3H), 7.54-7.62 (c, 2H); ms: (DCl-NH_3) m/z 305 $(M+NH_4)^+$, 288 $(M+H)^+$, 261 $(M+H-HCN)^+$.

Anal. Calcd. for $C_{16}H_{22}N_3O_2Cl$: C, 59.33; H, 6.86; N, 12.98. Found: C, 59.34; H, 6.87; N, 12.91. (A small sample was recrystallized thrice to obtain this analysis.)

1-Benzyl-8-carboethoxy-1,3,8-triazaspiro[4.5]decane (**3b**).

To a suspension of α-amino nitrile **2b** (10.0 g, 30.9 mmoles) in glacial acetic acid (20 ml) was added potassium cyanate (5.01 g, 61.8 mmoles) in water (10 ml) dropwise. An exothermic reaction was observed, and the reaction mixture became clear. After subsiding, the reaction mixture was heated in a 55° oil bath for 45 minutes. The bath was removed. After it had cooled, the reaction mixture was poured into cold water (200 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organics were dried (sodium sulfate) and concentrated (toluene azeotrope) to give a very viscous, clear, colorless oil (11.3 g). This crude oil was treated with 10% aqueous hydrochloric acid (30 ml) using rapid, efficient stirring. Within a few minutes fine white solid began to precipitate, and the reaction mixture was heated in a 55° oil bath. The viscous starting material had dissolved within 10 minutes, and much more white solid had formed. After 15 minutes the heat source was removed and the thick white suspension was chilled (ice-water bath). The solid was filtered off, rinsing with

cold water, then dried *in vacuo* at 50° over phosphorus pentoxide to give a white granular solid (7.03 g, 69%), mp 191-195°; tlc (chloroform-methanol, 20:1) R_f 0.40; pmr (dimethyl sulfoxide-d_6): δ 1.16 (t, 3H, J = 7 Hz), 1.63 (d, 2H, J = 13 Hz), 1.74 (td, 2H, J = 5, 13 Hz), 3.32 (br s, 2H), 3.87 (d, 2H, J = 12 Hz), 4.01 (q, 2H, J = 7 Hz), 4.46 (s, 2H), 7.21-7.36 (c, 5H), 11.07 (s, 1H); ms: (DCl-NH_3) m/z 349 $(M+NH_4)^+$, 332 $(M+H)^+$.

Anal. Calcd. for $C_{17}H_{21}N_3O_4$: C, 61.61; H, 6.40; N, 12.68. Found: C, 61.72; H, 6.38; N, 13.05.

General Procedure for *N*-3 Alkylation of Hydantoin **3**.

To a solution of hydantoin **3a** (0.26 g, 1.0 mmole) in anhydrous *N,N*-dimethylformamide (1.75 ml) under nitrogen was added sodium hydride (72 mg, 3.0 mmoles) in one portion. After a few minutes the alkyl iodide (3.0 mmoles, filtered through basic alumina) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1.5-2.5 hours. After chilling in an ice-water bath, 10% aqueous citric acid (5 ml) was added and the mixture was allowed to stir until gas evolution ceased. This mixture was poured into additional citric acid solution (5 ml) and was extracted with ethyl acetate (3 x 20 ml). The combined organics were washed with brine, dried (sodium sulfate), and concentrated to afford a clear yellow oil. The crude oil was purified by flash chromatography on silica gel, eluting with 50-75% ethyl acetate/hexane (v/v), to give the products **4a** (0.25 g, 92%) and **4b** (0.29 g, quantitative).

8-Carboethoxy-1,3-dimethyl-1,3,8-triazaspiro[4.5]decane (**4a**).

This compound was obtained as a clear yellow oil, which formed yellow rosettes on refrigerator storage, mp 97-100°; tlc (ethyl acetate-hexane, 3:1) R_f 0.23; pmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7 Hz), 1.62 (d, 2H, J = 14 Hz), 1.87 (td, 2H, J = 5, 13 Hz), 2.84 (s, 3H), 3.02 (s, 3H), 3.55 (m, 2H), 4.16 (q, 2H, J = 7 Hz), 4.16 (m, 2H); ms: (DCl-NH_3) m/z 270 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.51; H, 7.12; N, 15.60. Found: C, 53.26; H, 7.12; N, 15.44.

8-Carboethoxy-3-ethyl-1-methyl-1,3,8-triazaspiro[4.5]decane (**4b**).

This compound was obtained as a clear pale yellow oil; tlc (ethyl acetate-hexane, 3:1) R_f 0.30; pmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz), 1.61 (d, 2H, J = 14 Hz), 1.87 (td, 2H, J = 5, 13 Hz), 2.83 (s, 3H), 3.54 (m, 2H), 3.56 (q, 2H, J = 7 Hz), 4.15 (m, 2H), 4.16 (q, 2H, J = 7 Hz); ms: (DCl-NH_3) m/z 301 $(M+NH_4)^+$, 284 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{21}N_3O_4$: C, 55.10; H, 7.48; N, 14.83. Found: C, 55.02; H, 7.43; N, 14.64.

1,3-Dimethyl-1,3,8-triazaspiro[4.5]decane (**5a**).

The hydantoin **4a** (0.50 g, 1.8 mmoles) was treated with a solution of 87% potassium hydroxide (0.84 g, 13 mmoles) in absolute ethanol (18 ml). The reaction mixture was heated to reflux for 24 hours. Longer reaction times were avoided, since complete degradation of desired product was observed in one case after 48 hours. The cooled reaction mixture was filtered and the collected solid was discarded. The filtrate was concentrated, dissolved in water (30-40 ml), and continuously extracted with ethyl acetate (*ca.* 150 ml) for 16 hours. The extract was concentrated, redissolved in dichloromethane, dried (sodium sulfate), and concentrated to give a clear yellow oil (0.49 g). The crude oil was purified by flash chromatography on silica gel, eluting with 5-9% methanol/chloroform (v/v), including 1% (v) 29% aqueous ammonium hydroxide, to afford a clear yellow oil (0.21 g, 58%), which formed white rosettes on refrigerator storage. To prepare an analytical sample, the free base in 3:1 diethyl ether-ethanol was treated with an ethereal oxalic acid solution to produce white precipitation, which was filtered off under nitrogen, rinsed with cold ether, and dried *in vacuo* over phosphorus pentoxide to give the oxalate, a white powder, mp 178-181°; tlc (chlorform-methanol, 7:1 + 2% (v) 29% aqueous ammonium hydroxide) R_f 0.32; pmr (methanol-d_4): δ 1.96 (d, 2H, J = 15 Hz), 2.28 (td, 2H, J = 5, 14 Hz), 2.89 (s, 3H), 2.98 (s, 3H), 3.47 (m, 2H), 3.68 (td, 2H, J = 3, 13 Hz); ms: (DCl-NH_3) m/z 215 $(M+NH_4)^+$, 198 $(M+H)^+$.

Anal. Calcd. for $C_{11}H_{17}N_3O_6 \cdot \frac{1}{4}H_2O$: C, 45.27; H, 6.06; N, 14.40. Found: C, 45.52; H, 5.97; N, 14.52.

3-Ethyl-1-methyl-1,3,8-triazaspiro[4.5]decane (**5b**).

The hydantoin **4b** (155 mg, 0.547 mmole) was treated with a solution of 87% potassium hydroxide (113 mg, 1.75 mmoles) in absolute ethanol (5.0 ml). The reaction mixture was heated to reflux for 4 hours, after which tlc revealed that starting material remained. More solid potassium hydroxide (105 mg, 1.63 mmoles) was added and reflux continued for 20 hours. The workup procedure used in the preparation of **5a** was repeated. Continuous extraction gave a clear pale yellow oil (0.13 g), which was purified by flash chromatography on silica gel to afford a clear, colorless oil (97 mg, 84%), which formed a white amorphous solid on refrigerator storage. The oxalate, a white powder, was prepared as an analytical sample, mp 202-204°; tlc (chloroform-methanol, 7:1 + 2% (v) 29% aqueous ammonium hydroxide) R_f 0.35; pmr (methanol-d_4): δ 1.17 (t, 3H, J = 7 Hz), 1.94 (d, 2H, J = 14 Hz), 2.28 (td, 2H, J = 5, 14 Hz), 2.88 (s, 3H), 3.46 (m, 2H), 3.53 (q, 2H, J = 7 Hz), 3.68 (td, 2H, J = 3, 13 Hz); ms: (DCl-NH_3) m/z 212 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{19}N_3O_6$: C, 47.83; H, 6.37; N, 13.95. Found: C, 48.10; H, 6.43; N, 13.87.

General Procedure for Reductive Alkylation of **5**.

To the spirohydantoin **5** (0.25 mmole) were added 88% aqueous formic acid (74 μl, 1.71 mmoles) and 37% aqueous formaldehyde (126 μl, 1.68 mmoles). The reaction mixture was heated in an 80° oil bath, which produced a homogeneous solution. After 2 hours the reaction mixture was diluted with water (5 ml), treated with 1.0 *M* hydrochloric acid (0.5 ml), and extracted with diethyl ether (2 x 5 ml). The acidic aqueous phase was chilled in an ice-water bath and treated with 2.0 *M* sodium hydroxide (1.0 ml), then continuously extracted with ethyl acetate (*ca.* 150 ml) overnight. The extract was concentrated, redissolved in dichloromethane, dried (sodium sulfate), and concentrated to give the crude material, which was purified by flash chromatography on silica gel, eluting with 5-9% methanol/chloroform (v/v), including ½% (v) 29% aqueous ammonium hydroxide, to give the products **6a** (49 mg, 92%) and **6b** (50 mg, 89%).

1,3,8-Trimethyl-1,3,8-triazaspiro[4.5]decane (**6a**).

This compound was obtained as an off-white flaky solid. To prepare an analytical sample, the free base in 2:1 diethyl ether-ethanol was treated with an ethereal oxalic acid solution to produce white flakes, which were filtered off under nitrogen, rinsed with cold ether, and dried *in vacuo* over phosphorus pentoxide to give the oxalate, a white powder, mp 208-210°; tlc (chloroform-methanol, 10:1 + 1% (v) 29% aqueous ammonium hydroxide) R_f

0.43; pmr (methanol-d_4): δ 1.98 (d, 2H, J = 15 Hz), 2.41 (td, 2H, J = 5, 14 Hz), 2.87 (s, 3H), 2.95 (s, 3H), 2.98 (s, 3H), 3.56 (m, 2H), 3.69 (td, 2H, J = 3, 13 Hz); ms: (DCl-NH_3) m/z 212 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{19}N_3O_6$: C, 47.83; H, 6.37; N, 13.95. Found: C, 47.66; H, 6.42; N, 13.68.

1,8-Dimethyl-3-ethyl-1,3,8-triazaspiro[4.5]decane (**6b**).

This compound was obtained as a clear yellow oil. The oxalate, a white powder, was prepared as an analytical sample, mp 118-121°; tlc (chloroform-methanol, 10:1 + 1% (v) 29% aqueous ammonium hydroxide) R_f 0.51; pmr (methanol-d_4): δ 1.18 (t, 3H, J = 7 Hz), 1.97 (d, 2H, J = 15 Hz), 2.40 (td, 2H, J = 5, 14 Hz), 2.87 (s, 3H), 2.95 (s, 3H), 3.53 (q, 2H, J = 7 Hz), 3.56 (m, 2H), 3.70 (td, 2H, J = 3, 13 Hz); ms: (DCl-NH_3) m/z 226 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{21}N_3O_6 \cdot \frac{1}{2}H_2O$: C, 48.13; H, 6.85; N, 12.96. Found: C, 48.30; H, 6.53; N, 12.81.

Acknowledgement.

The authors would like to thank Dr. Youe-Kong Shue and Professor Henry Rapoport for helpful discussions.

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