Chiral Aryl Sulfonyl Hydantoins as Hypoglycemic Agents
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Hydantoins, Antidiabetic Activity, NMR Data

Some novel chiral sulfonyl hydantoin derivatives 2a–e and 3a–e have been prepared. p-Toluenesulfonyl chloride on treatment with L-amino acids in presence of K2CO3/H2O yielded N-(p-toluenesulfonyl)-amino acids 1a–e which were cyclized in presence of NH4SCN / Ac2O to afford 1-(p-toluenesulfonyl)-5-substituted-2-thiohydantoins 2a–e. These compounds were oxidized with HNO3 to yield 1-(p-toluenesulfonyl)-5-substituted hydantoins 3a–e. The enantiomeric ratios of 3a–e were determined by 1H NMR spectroscopy using Eu(hfc)3. The antidiabetic activity of 3a–d has been determined.

Introduction

Besides biguanides and α-glucosidase inhibitors another class of oral hypoglycemic agents is seen in the market, the sulfonylureas. Tolbutamide, Glibenclamide, and Tolazamide are important drugs used for the treatment of non-insulin dependent diabetes mellitus. During the last two decades, literature is overloaded with the synthesis and antidiabetic activity of many acyclic aryl heterocyclic sulfonyl ureas. Little attention has been paid to cyclic urea derivatives.

Many researchers concentrated their attention to the synthesis of sulfonyl hydantoin derivatives [1–3]. It was proved that the arylsulfonyl group at 1-position of hydantoins greatly effects the physiochemical properties and intestinal absorption of the drugs, and they are much more active than those where the 3-position is substituted by arylsulfonyl group [4]. A number of aryl/heteroaryl sulfonyl hydantoin derivatives were prepared and tested against aldose reductase inhibitor and for treatment of glucose and galactose induced cataract. The synthesis of 3-arylsulfonyl hydantoins by coupling of corresponding sulfonyl chlorides with substituted hydantoins has been reported which on rearrangement in the presence of sodium hydride lead to 1-sulfonyl derivatives [5]. In the present work we report the synthesis of chiral 1-p-toluenesulfonyl hydantoins starting from the optically pure amino acids. The spectroscopy of the intermediate compounds and the final products is discussed. The enantiomeric ratios of compounds 3a–e have been determined by 1H NMR method using lanthanide shift reagent Eu(hfc)3. The antidiabetic activity of compounds 3a–e is also reported.

Results and Discussion

Syntheses

All the desired compounds 1a–e to 3a–e were synthesized using standard methods. N-(p-toluenesulfonyl) amino acids 1a–e were successfully prepared in 82–85% yield starting from p-toluenesulfonyl chloride and the respective L-amino acid [5, 6]. Surprisingly, only the NMR data of 1c have been reported before [6b, 6c] so that we include them in the Experimental Part. Novel thiohydantoin derivatives 2a–e were obtained under anhydrous conditions in 77–79% yield by treating the sulfonil amino acids 1a–e with NH4SCN in the presence of acetic anhydride and pyridine (Scheme 1) [7]. The NMR data (Experimental Part) meet the expectations; the assignment of C-2 and C-4 is based on well-known strong deshielings of thiocarbonyl carbons. On treatment with 50% (w/v) nitric acid, 2a–e were transformed into the corresponding novel (except 3d [8]) hydantoin...
derivatives 3a–e in 69–75% yield (Scheme 1) [7a]. Purification was mainly achieved by recrystallization using methanol or ethanol/water mixture. NMR spectra of various hydantoin derivatives have been reported, and the dependence of NMR parameters on various structural features were discussed [7a, 8, 9].

**Determination of the enantiomeric ratio of the hydantoin derivatives 3a–e using ¹H NMR spectroscopy in the presence of a chiral lanthanide shift reagent**

The enantiomeric ratio of compounds 3a–e was determined by ¹H NMR using the lanthanide shift reagent Eu(hfc)₃ (Aldrich). In most cases, ratios were found to be 70–76:30–34 although enantiomerically pure amino acids have been employed. It turned out that the temperature during the nitric acid reaction (2 to 3) has to be kept carefully below 100 °C and the reaction time should not exceed 2.5 hours to avoid total racemization.

**Antidiabetic activity**

INS-1 cells were grown in plastic culture or microwells for 4–6 days (half confluence: 1–2 × 10⁶ cells ml⁻¹) in RPMI medium supplemented with 10% (v/v) fetal calf serum, 100 U of penicillin ml⁻¹ and 0.1 mg of streptomycin ml⁻¹. Prior to the experiment cells were washed and incubated in Krebs-Ringer containing 10 mM HEPES and 0.5% bovine serum albumin (KRBH). To measure insulin secretion, half-confluent cells in microwells were incubated for 90 min at 37 °C in the aforementioned KRBH buffer. Insulin released into the medium was assayed with a radioimmunoassay using rat insulin (Novo Nordisk, Denmark) as a standard, porcin insulin as the labelled compound [(mono-¹²⁵I-Tyr A¹⁴)-porcine insulin; Hoechst, Table I. Effects of various compounds (3a–d) on insulin release from INS-1 cells in the presence of 5.6 mM glucose. The low glucose concentration (0.3 mM) and glibenclamide (= glyburide) served as negative and positive controls. INS-1 cells in multiwells were washed three times and incubated in KRBH-buffer for 90 minutes. The results are expressed as % secreted insulin at 5.6 mM glucose alone. Each value represents the mean (x) ± S. E. M. of experiments (n).
Germany] and insulin antibodies from Linco (U. S. A.).

Compounds 3a–d were dissolved in ethanol and tested for their antidiabetic activity in the presence of 5.6 mM glucose (Table I). It can be stated that compounds 3b and 3d possessed a clear inhibitory effect on insulin release at either 10⁻⁴ or 10⁻³ M concentration and thus showed no antidiabetic activity while compounds 3a and 3c exhibited antidiabetic activity only at lower concentrations. However, it requires further confirmatory evidence from in vivo studies in animal experiments in order to ascertain their margin of safety and freedom from undesirable toxic manifestation on vital functions in the host.

Experimental

The melting points were determined on a Gallenkamp digital melting point apparatus MFB-595–010M and are uncorrected. 'H and 13C NMR spectra were recorded on a Bruker AM-400 instrument (1H: 400.1 MHz and 13C: 100.6 MHz), and mass spectra on a Varian MAT CH-5 spectrometer. Solvents are noted in the Experimental Part. All chemical shifts are referenced to TMS. Optical rotations were determined on Jasco J-20A automatic recording spectropolarimeter.

General method for the preparation of N-(p-toluenesulphonyl) amino acids 1a–e

An equimolar mixture of potassium carbonate (0.01 mol) and an α-amino acid (0.01 mol) in water (50 ml) was heated at 60 °C for 30 minutes. To this mixture was added p-toluenesulphonyl chloride (0.01 mol) in dioxane (20 ml). The mixture was heated under reflux for 30 minutes. After cooling to room temperature the resultant solution was acidified with 2 N hydrochloric acid to a pH = 1–2. The precipitates obtained were filtered, washed with water and recrystallised from methanol.

N-(p-Toluenesulphonyl)glycine (1a)

M.p. 147 °C (lit. 147; 149–150 °C [5]). - Yield 85%.

1H NMR (CD3OD): δ = 3.70 (s, H-2), 5.40 (bs, NH), 7.35 (d, H-3”), 7.75 (d, H-2”). - 13C NMR (CD3OD): δ = 21.5 (Ar-CH3), 44.7 (C-2), 128.0 (C-2”), 130.6 (C-3”), 138.2 (C-1”), 144.7 (C-4”), 172.2 (C-1). - EI-MS, C9H14NOS (229), m/z (%): 229 (M+, 3); 225 (1), 185 (3), 184 (8), 156 (6), 155 (47), 92 (18), 91 (100), 90 (3), 89 (9).

N-(p-Toluenesulphonyl)alanine (1b)

M.p. 133 °C (lit. 132–133 °C [5]). - Yield 83%.

1H NMR (CD3OD): δ = 1.30 (d, H-1’), 2.40 (s, Ar-CH3), 3.90 (q, H-2), 5.10 (bs, NH), 7.35 (d, H-3”), 7.75 (d, H-2”). - 13C NMR (CD3OD): δ = 19.4 (C-1’) 21.4 (Ar-CH3), 52.6 (C-2”), 127.9 (C-2”), 130.6 (C-3”), 139.0 (C-1”), 144.6 (C-4”), 175.3 (C-1). - EI-MS, C10H18N3O4S (243), m/z (%): 243 (M+, 2), 242 (1), 199 (5), 198 (87), 189 (5), 183 (3), 178 (5), 155 (71), 106 (5), 96 (5), 91 (100), 79 (6). - [α]D²⁰ = -3.8° (MeOH).

N-(p-Toluenesulphonyl)phenylalanine (1c)

M.p. 134 °C (lit. 134–135 °C [5]). - Yield 83%.

1H NMR (CD3OD): δ = 2.40 (s, Ar-CH3), 2.85 and 3.05 (each dd, 2 H-1’), 4.00 (t, H-2), 4.90 (bs, NH), 7.00–7.30 (m, Ph), 7.35 (d, H-3”), 7.75 (d, H-2”). - EI-MS, C16H17N3O4S (319), m/z (%): 319 (M+, 1), 274 (5), 228 (10), 227 (1), 173 (10), 164 (2), 157 (3), 155 (48), 149 (3), 148 (25), 147 (3), 118 (5), 117 (4), 91 (100), 90 (3), 77 (6), 65 (21). - [α]D²⁰ = +63.9° (MeOH).

N-(p-Toluenesulphonyl)valine (1d)

M.p. 147 °C (lit. 147 °C [5]). - Yield 82%.

1H NMR (CD3OD): δ = 0.87 and 0.95 (each d, 2 H-3’), 2.40 (s, Ar-CH3), 3.50 (m, H-1’), 3.65 (d, H-2), 4.95 (bs, NH), 7.35 (d, H-3”), 7.75 (d, H-2”). - EI-MS, C12H17N3O4S (271), m/z (%): 271 (M+, 2), 228 (6), 227 (7), 226 (49), 173 (7), 157 (6), 156 (8), 155 (62), 139 (5), 92 (19), 91 (100). - [α]D²⁰ = +59° (MeOH).

N-(p-Toluenesulphonyl)leucine (1e)

M.p. 125 °C (lit. 121–122 °C [5]). - Yield 82%.

1H NMR (CD3OD): δ = 0.75 and 0.95 (each d, 2 H-3’), 1.45 (ddd, H-2’), 2.40 (s, Ar-CH3), 1.75 (m, H-1’), 3.80 (t, H-2), 4.95 (bs, NH), 7.35 (d, H-3”), 7.75 (d, H-2”). - EI-MS, C13H19N3O4S (285), m/z (%): 285 (M+, 2), 279 (1), 242 (3), 241 (8), 229 (5), 184 (14), 171 (5), 157 (3), 156 (6), 155 (64), 139 (4), 107 (4), 92 (14), 91 (100), 90 (4), 89 (8), 86 (8). - [α]D²⁰ = +21.0° (MeOH).

General method for the preparation of (p-toluenesulphonyl)-2-thiohydantoins 2a–e

A solution containing N-(p-toluenesulphonyl)-amino acid (2 mmol), NH4SCN (2.4 mmol) and acetic anhydride (4 mmol) in anhydrous pyridine (1 ml) was heated with stirring at 90 °C for 1 hour, then cooled to room temperature. Cold water (50 ml) was added to the solution and the mixture
was stirred for 1 h at room temperature. The precipitates were filtered off, washed with water to remove excess of pyridine and recrystallized from EtOH: H$_2$O (1:1).

**I-(p-Toluenesulphonyl)-2-thiohydantoin (2a)**

M.p. 270 °C. - Yield 78%. - $^1$H NMR (DMSO-d$_6$): $\delta$ = 2.40 (s, Ar-CH$_3$), 4.80 (s, H-5), 7.5 (d, H-$3^\prime$), 8.00 (d, H-2$^\prime$). 12.7 (bs, NH). - $^{13}$C NMR (DMSO-d$_6$): $\delta$ = 21.1 (Ar-CH$_3$), 54.1 (C-5), 128.8 and 129.5 (C-2/2$^\prime$), 133.9 (C-1$^\prime$), 145.5 (C-4$^\prime$), 169.8 (C-4), 180.6 (C-2). - EI-MS, C$_{10}$H$_{10}$N$_2$O$_3$S$_2$ (270), m/z (%): 270 (M$^+$, 1), 209 (4), 208 (11), 207 (57), 206 (52), 178 (8), 156 (4), 155 (4), 139 (5), 135 (7), 125 (5), 124 (9), 120 (20), 119 (5), 106 (10), 92 (12), 91 (100), 90 (4), 89 (9). C$_{10}$H$_{10}$N$_2$O$_3$S$_2$ (270): Calcd. C 44.70, H 3.65, N 10.40, S 23.53%; Found C 44.44, H 3.70, N 10.37, S 23.70%.

**I-(p-Toluenesulphonyl)-5-methyl-2-thiohydantoin (2b)**

M.p. 284 °C. - Yield 78%. - $^1$H NMR (acetone-d$_6$): $\delta$ = 1.70 (d, H-$1^\prime$), 2.45 (s, Ar-CH$_3$), 4.80 (q. (3), 249 (10), 248 (44), 247 (22), 208 (5), 207 (8), 206 (58), 205 (44), 193 (8), 192 (6), 162 (6), 160 (14), 156 (3), 155 (12), 150 (27), 146 (7), 139 (10), 128 (28), 124 (37), 123 (17), 119 (6), 118 (11), 97 (9), 96 (13), 93 (6), 92 (64), 91 (100), 90 (5), 89 (10). - [a]$_D^{390}$ = +51.3° (MeOH).

**I-(p-Toluenesulphonyl)-5-isobutyl-2-thiohydantoin (2c)**

M.p. 294 °C. - Yield 58%. - $^1$H NMR (acetone-d$_6$): $\delta$ = 1.70 (d, H-$1^\prime$), 2.45 (s, Ar-CH$_3$), 4.60 (s, H-5), 7.45 (d, H-3$^\prime$), 8.05 (d, H-2$^\prime$). - EI-MS, C$_{14}$H$_{18}$N$_2$O$_4$S (310), m/z (%): 310 (M$^+$, 2), 263 (5), 262 (23), 261 (4), 221 (5), 220 (16), 219 (100), 207 (23), 205 (4), 170 (4), 155 (10), 124 (29), 118 (4). - [a]$_D^{390}$ = +32.1° (MeOH).

$C_{14}H_{18}N_2O_4S$ (326): Calcd. C 51.53, H 5.52, N 19.58, S 19.63; Found C 51.23, H 5.60, N 19.80, S 19.53%.

**General procedure for the preparation of I-(p-toluenesulphonyl)-2-thiohydantoins (3a–e)**

To 1-(p-toluenesulphonyl)-2-thiohydantoins (5 mmol) was added 50% (w/v) nitric acid (20 ml), and the mixture was heated with stirring on a boiling water bath for 30 minutes, and 60% (w/v) nitric acid (10 ml) was added again. Then, the reaction mixture was heated with stirring on a boiling water bath for 2 hours. The resultant solution was then cooled, evaporated and treated with ice-cooled water. The precipitates formed were filtered, washed successively with water, methanol and dichloromethane and recrystallized from ethanol / water.

**I-(p-Toluenesulphonyl)-2-hydantoin (3a)**

M.p. 268 °C. - Yield 75%. - $^1$H NMR (acetone-d$_6$): $\delta$ = 2.40 (s, Ar-CH$_3$), 4.60 (s, H-5), 7.50 (d, H-3$^\prime$), 8.00 (d, H-2$^\prime$), 11.7 (bs, NH). - $^{13}$C NMR (DMSO-d$_6$): $\delta$ = 21.1 (Ar-CH$_3$), 54.2 (C-5), 127.8 (C-2$^\prime$), 129.4 (C-3$^\prime$), 134.8 (C-1$^\prime$), 145.4 (C-4$^\prime$), 152.8 (C-2), 170.2 (C-4). - EI-MS, C$_{10}$H$_{10}$N$_2$O$_4$S (254), m/z (%): 254 (M$^+$, 31), 253 (29), 252 (19), 251 (18), 250 (18), 190 (12), 184 (10), 172 (5), 156 (5), 155 (13), 119 (5), 91 (100). C$_{10}$H$_{10}$N$_2$O$_4$S (254): Calcd. C 47.24, H 3.93, N 11.02, S 12.59; Found C 47.29, H 3.89, N 10.96, S 12.65%.

**I-(p-Toluenesulphonyl)-5-methyl-2-hydantoin (3b)**

M.p. 254 °C. - Yield 69%. - $^1$H NMR (acetone-d$_6$): $\delta$ = 1.70 (d, H-1$^\prime$), 2.45 (s, Ar-CH$_3$), 4.80 (q.
H-5), 7.50 (d, H-3''), 8.00 (d, H-2''), 10.4 (bs, NH). - $^{13}$C NMR (DMSO-d$_6$): $\delta$ = 17.9 (C-1'), 21.5 (Ar-CH$_3$), 59.8 (C-5), 129.1 and 130.5 (C-2'/3'), 136.8 (C-1'), 146.2 (C-4'), 153.0 (C-2), 172.3 (C-4). - EI-MS, C$_{13}$H$_{16}$N$_2$O$_4$S (296), $m/z$ (%): 296 (M$^+$, 1), 254 (5), 232 (45), 191 (6), 190 (40), 189 (9), 156 (24), 155 (27), 146 (5), 139 (7), 137 (6), 118 (6), 108 (8), 100 (4), 99 (36), 91 (100), 90 (8). C$_{17}$H$_{16}$N$_2$O$_4$S (344): Calcd. C 59.30, H 4.65, N 8.13, S 9.30; Found C 58.99, H 4.75, N 8.02, S 9.35%.

1-(p-Toluenesulphonyl)-5-isobutyl-2-hydantoin (3e)

M.p. 176–177 °C. - Yield 71%. - $^1$H NMR (acetone-d$_6$): (3 = 0.95-1.05 (m, H-3'), 2.05-2.25 (m, H-l'), 2.45 (s, Ar-CH$_3$), 4.85 (dd, H-5), 7.50 (d, H-3''), 8.00 (d, H-2''), 13.0 (bs, NH). - $^{13}$C NMR (DMSO-d$_6$): (3 = 21.6 (Ar-CH$_3$), 22.2 and 23.8 (C-3'), 24.8 (C-2'), 41.0 (C-1'), 62.49 (C-5), 129.2 and 130.6 (C-2'/3'), 136.7 (C-1'), 146.4 (C-4'), 153.3 (C-2), 172.1 (C-4). - EI-MS, C$_{14}$H$_{18}$N$_2$O$_4$S (310), $m/z$ (%): 310 (M$^+$, 1), 255 (3), 247 (3), 203 (52), 190 (10), 155 (38), 139 (4), 127 (4), 108 (11), 107 (3), 91 (100), 90 (5), 89 (5), C$_{14}$H$_{18}$N$_2$O$_4$S (310). Calcd. C 54.19, H 5.80, N 9.03, S 10.32; Found C 54.03, H 5.89, N 9.23, S 10.25%.

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