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N-치환된 Nortropane Spirohydantoin 유도체의 합성

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A series of tropane and nortropane 3-spiro-5'-hydantoins showed anticonvulsant activity against pentylenetetrazol-induced convulsions in mice and antiarrhythmic activity in rabbit previously treated with ouabain.1-4 As a part of our study on the improvement of anticonvulsant, here we report the synthesis of corresponding N-substituted nortropane spirohydantoins by using N-substituted nortropinones. Already we reported the synthesis of N-substituted nortropinones derived from the reaction of amine, 2,5-dimethoxytetrahydrofuran and acetonedicarboxylic acid.5

N-Substituted nortropane spirohydantoins (3a-e) were respectively synthesized by the reactions of N-substituted nortropinones (2a-e, 0.01 mol) in ethanol (10 ml) with potassium cyanide (0.015 mol) and ammonium carbonate (0.03 mol) in water (Scheme 1). The reaction mixture was heated at 60°C in a sealed ampule for reaction time as shown in Table 1. After cooling, the product precipitated solid was removed by filtration. The mother liquor was concentrated (~50%) under reduced pressure and cooled, and the resulting solid was collected and combined with the first product obtained (Table 1). The hydantoin was washed with cold water three times (3 × 15 ml). The yield, mp, IR and 1H NMR of the products 3a-e are summarized in footnote.6 The formation of N-phenylnortropane spirohydantoin5 (isolated yield, 14%), N-(p-fluorophenyl)nortropane spirohydantoin (isolated yield, 61%), and N-(p-t-butylphenyl)nortropane spirohydantoin (isolated yield, 63%) were only confirmed by GC-Mass spectra.

Structural assignments of 3 were established based on 1H NMR spectral data. For example, in

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Scheme 1.
the case of 3a, H-1' and H-3' of spirohydantoin ring appear δ 10.63 and δ 8.09, respectively. The signals of the H-1 and H-5 clearly indicate δ 3.06. And the signals of the H$_2$-a and H$_2$-a are seen at δ 1.45 and at δ 2.12, respectively. The difference of 0.7 ppm was produced by the field effect due to the magnetic anisotropy of the C-4' carbonyl group. Methyl protons of N-8 clearly appear at δ 2.20 and the C-6 and C-7 methylene protons are seen at δ 1.87. Mass spectrum of 3a showed molecular ion peaks at m/z 209 (27%). The elemental analysis were also well matched with theoretical values.

The structures of all other products were confirmed by the same manner as the 3a. The biological studies of these compounds are in progress and will be reported in future.

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REFERENCES


6. Tropane spirohydantoin$^3$ 3a: Yield 56%; mp 220°C; $^1$H NMR (DMSO-d$_6$): δ 80.63 (s, NH, 1H), 8.09 (s, NH, 1H), 3.06 (s, C$_{ch}$), 2H, (J(W$_{2}$) = 9 Hz), 2.20 (s, NCH$_3$, 3H), 2.12-2.10 (m, C$_{ch}$, 2H), 1.90-1.85 (m, C$_{ch}$, 4H), 1.46-1.39 (dd, C$_{mn}$, C$_{mn}$, 2H); Mass, m/z (rel. intensity %): 209 (27), 181 (6), 152 (13), 110 (10), 96 (36), 82 (100), 68 (6); IR (v, KBr, cm$^{-1}$): 3258.8, 2954.7, 2832.7. 1718.3. Anal. Calcd. for C$_{24}$H$_{24}$N$_{2}$O$_{2}$: C, 57.40; H, 7.23; N, 20.08 Found C, 57.32; H, 7.18; N, 20.38%.

N-Isopropyltropane spirohydantoin$^3$ 3b: Yield 76%; mp 233°C; $^1$H NMR (DMSO-d$_6$): δ 80.64 (s, NH, 1H), 8.10 (s, NH, 1H), 3.54-3.44 (s, C$_{ch}$, C$_{ch}$, 2H, (J(W$_{2}$) = 9 Hz), 2.87-2.75 (m, C$_{ch}$, 1H), 2.22-2.09 (dd, C$_{ch}$, C$_{ch}$, 2H), 1.92-1.84 (m, C$_{ch}$, C$_{ch}$, 4H), 1.35-1.20 (m, C$_{ch}$, C$_{ch}$, 2H), 1.06-1.04 (d, C$_{ch}$, 6H); Mass, m/z (rel. intensity %): 237 (20), 222 (100), 124 (18), 110 (35), 97 (8), 83 (21), 68 (23), 54 (8). Anal. Calcd. for C$_{35}$H$_{35}$N$_{2}$O$_{5}$: C, 60.74; H, 8.07; N, 17.71 Found C, 60.52; H, 7.84; N, 18.08%.

N-Carboethoxytropane spirohydantoin$^3$ 3c: Yield 77%; mp 271°C; $^1$H NMR (DMSO-d$_6$): δ 80.79 (s, NH, 1H), 8.37 (s, NH, 1H), 4.16 (s, C$_{ch}$, C$_{ch}$, 2H, (J(W$_{2}$) = 9 Hz), 4.09-4.02 (q, OCH$_3$, 2H), 2.12-2.09 (m, C$_{ch}$, C$_{ch}$, 2H, 2.06-2.01 (m, C$_{ch}$, C$_{ch}$, 2H), 2) 1.22-1.15 (t, C$_{ch}$, 3H); Mass, m/z (rel. intensity %): 267 (16), 194 (11), 154 (79), 140 (55), 96 (10), 82 (69), 68 (100), 54 (29); IR (v, KBr, cm$^{-1}$): 3419.2, 3149.2, 2954.1, 1708.6. Anal. Calcd. for C$_{35}$H$_{35}$N$_{2}$O$_{5}$: C, 53.92; H, 6.41; N, 15.72 Found C, 54.12; H, 6.59; N, 15.87%.

N-Fururyltropane spirohydantoin$^3$ 3d: Yield 87%; mp 272°C; $^1$H NMR (DMSO-d$_6$): δ 80.67 (s, NH, 1H), 8.15 (s, NH, 1H), 7.55 (s, aromatic, 1H), 6.37-6.24 (dd, aromatic, 2H), 3.60 (s, C$_{ch}$, C$_{ch}$, 2H, (J(W$_{2}$) = 9 Hz), 3.22-3.18 (m, C$_{ch}$, 2H), 2.18-2.11 (dd, C$_{ch}$, C$_{ch}$, 2H), 2.09-1.91 (t, C$_{ch}$, C$_{ch}$, 4H), 1.51-1.44 (m, C$_{ch}$, C$_{ch}$, 2H); Mass, m/z (rel. intensity %):
275 (22), 163 (38), 148 (15), 122 (30), 81 (100), 68 (12), 53 (20). Anal. Calcd. for C_{16}H_{19}N_{3}O_{3}: C, 61.08; H, 6.22; N, 15.26. Found C, 61.35; H, 5.97; N, 15.55%.

N-(p-Methoxyphenyl)nortropane spirohydantoin 3e: Yields 70%; mp. 380°C (dec.); $^1$H NMR (DMSO-d$_6$): $\delta$10.63 (s, NH, 1H), 8.27 (s, NH, 1H), 6.83-6.70 (q, aromatic, 4H), 4.18 (s, CH$_3$C$_6$H$_4$, 2H, J \(W_{1/2}=9.5 Hz\)), 3.68 (s, OCH$_3$, 3H), 2.26-2.18 (dd, C$_{3b}$, C$_{4b}$, 2H), 2.12-1.90 (m, C$_{3a}$, C$_{4a}$, 4H), 1.42-1.35 (d, C$_{2a}$, C$_{2b}$ 2H); Mass, m/z (rel. intensity %): 301 (73), 281 (41), 272 (13), 207 (100), 193 (20), 147 (17), 91 (24), 82 (38), 73 (26). Anal. Calcd. for C$_{16}$H$_{19}$N$_{3}$O$_{3}$: C, 63.77; H, 6.36; N, 13.94. Found C, 64.13; H 5.99; N 14.24%.