Journal of the Korean Chemical Society
1999, *Vol. 43, No. 1*
Printed in the Republic of Korea

단 신

N-치환된 Nortropane Spirohydantoin 유도체의 합성

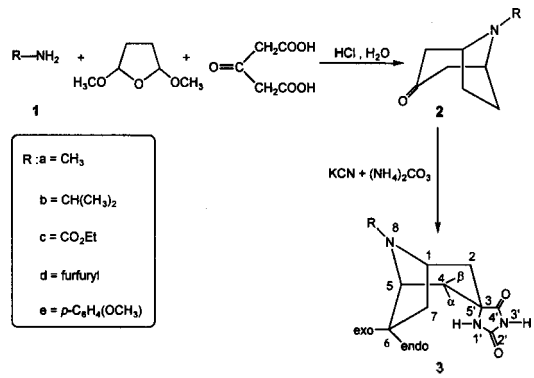
鄭大一* · 朴鍾勳 · 朴七星 · 金侖瑛 · 鄭斗熙 · 金實植' · 朴敏洙"
동아대학교 자연과학대학 화학과
'동아대학교병원 산업의학과
"경성대학교 약학대학 약학과
(1998. 8. 5 접수)

Synthesis of *N*-substituted Nortropane Spirohydantoin Derivatives

Dai-Il Jung*, Jong-Hoon Park, Chil-Sung Park, Yun-Young Kim, Doo-Hee Jung
In-Shik Kim', and Min-Soo Park"
Department of Chemistry, Dong-A University, Pusan 604-714, Korea
'Dong-A University Hospital, Pusan 602-715, Korea
"Department of Pharmacy, Kyungsung University, Pusan 608-736, Korea
(Received August 5, 1998)

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]



Scheme 1.

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 filteration. 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 ^{1}H NMR of the products **3a~e** are summarized in footnote.[6] The formation of *N*-phenylnortropane spirohydantoin[3] (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 ^{1}H NMR spectral data. For example, in

Table 1. Physical data of *N*-substituted tropinones 2 and *N*-substituted nortropane spirohydantoins 3

N-substituted Tropinones 2	Reaction time (h)	Yield (%)	*N*-substituted nortropane spirohydantoins 3	Reaction time (h)	Yield (%)
a	8	54	**a**	14	56
b	6	50	**b**	20	76
c	8	58	**c**	18	77
d	12	31	**d**	26	87
e	6	70	**e**	14	70

the case of **3a**, H-1' and H-3' of spirohydantion ring appear δ10.63 and δ8.09, respectively. The signals of the H-1 and H-5 clearly indicate δ3.06. And the signals of the $H_{2,4\alpha}$ and $H_{2,4\beta}$ are seen at δ1.45 and at δ2.12, 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 δ2.20 and the C-6 and C-7 methylene protons are seen at δ1.87. 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.

Acknowledgement. This work was supported in part by a grant of Dong-A University (1998) and in part by a grant of the 97' Good Health R& D Project (HMP-96-D-1-0001), Ministry of Health and Welfare.

REFERENCES

1. Trigo, G. G.; Martinez, M. *Pharm. Mediterr.* **1974**, *10*, 643.
2. Sacristan, A. G.; Illera, M.; Sancher, F. S. *Arch. Farmacol. Toxicol.* **1977**, *3*, 57.
3. Trigo, G. G.; Martinez, M.; Gâlvez, E. *J. of Pharm. Sci.* **1981**, *70*, 87.
4. Izquierdo, M. L.; Gâlvez, E.; Burgos, C.; Florencio, F. *J. Heterocyclic Chem.* **1988**, *25*, 419.
5. Jung, D. I.; Park, J. H.; Roh, S. A.; Lee, Y. K.; Park, Y. M.; Kim, I. S.; Jeong, I. S.; Park, M. S. *J. Kor. Chem. Soc.* **1997**, *4*, 1, 414.

6. **Tropane spirohydantoin**[3] **3a**: Yield 56%; mp. 220°C; ^{1}H NMR (DMSO-d_6): δ10.63 (s, NH, 1H), 8.09 (s, NH, 1H), 3.06 (s, C_{1H}, C_{5H}, 2H, J(W½)= 9Hz), 2.20 (s, NCH_3, 3H), 2.12-2.10 (m, $C_{2\beta}$, $C_{4\beta}$, 2H), 1.90-1.85 (m, C_{6H}, C_{7H}, 4H), 1.46-1.39 (dd, $C_{2\alpha}$, $C_{4\alpha}$, 2H); Mass, m/z (rel. intensity %): 209 (27), 181 (6), 152 (13), 110 (10), 96 (36), 82 (100), 68 (6); IR (*ν*, KBr, cm^{-1}): 3258.8, 2954.7, 2832.7, 1718.3. *Anal. Calcd.* for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08 Found C, 57.32; H, 7.18; N 20.38%.

***N*-Isopropylnortropane spirohydantoin**[3] **3b**: Yield 76%; mp. 233°C; ^{1}H NMR (DMSO-d_6): δ10.64 (s, NH, 1H), 8.10 (s, NH, 1H), 3.54-3.42 (s, C_{1H}, C_{5H}, 2H, J(W½)=9Hz), 2.87-2.75 (m, C_{9H}, 1H), 2.22-2.09 (dd, $C_{2\beta}$, $C_{4\beta}$, 2H), 1.92-1.84 (m, C_{6H}, C_{7H}, 4H), 1.35-1.20 (m, $C_{2\alpha}$, $C_{4\alpha}$, 2H), 1.06-1.04 (d, CH_3, 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 $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71 Found C, 60.52; H, 7.84; N, 18.08%.

***N*-Carboethoxynortropane spirohydantoin 3c**: Yield 77%; mp. 271°C; ^{1}H NMR (DMSO-d_6): δ10.79 (s, NH, 1H), 8.37 (s, NH, 1H), 4.16 (s, C_{1H}, C_{5H}, 2H, J(W½)=9Hz), 4.09-4.02 (q, OCH_2, 2H), 2.12-2.09 (m, $C_{2\beta}$, $C_{4\beta}$, 2H), 2.06-2.01 (m, C_{6H}, C_{7H}, 4H), 2.00-1.90 (m, $C_{2\alpha}$, $C_{4\alpha}$, 2H), 1.22-1.15 (t, CH_3, 3H); Mass, m/z (rel. intensity %): 267 (16), 194 (11), 154 (79), 140 (55), 96 (10), 82 (69), 68 (100), 54 (29); IR (*ν*, KBr, cm^{-1}): 3375.9, 3149.2, 2985.1, 1708.6, *Anal. Calcd.* for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72 Found C, 54.12; H, 6.50; N, 15.87%.

***N*-Furfurylnortropane spirohydantoin 3d**: Yield 87%; mp. 272°C; ^{1}H NMR (DMSO-d_6): δ10.67 (s, NH, 1H), 8.15 (s, NH, 1H), 7.55 (s, aromatic, 1H), 6.37-6.24 (dd, aromatic, 2H), 3.60 (s, C_{1H}, C_{5H}, 2H, J(W½)=9Hz), 3.22-3.18 (m, CH_2, 2H), 2.18-2.11 (dd, $C_{2\beta}$, $C_{4\beta}$, 2H) 2.09-1.91 (t, C_{6H}, C_{7H}, 4H), 1.51-1.44 (m, $C_{2\alpha}$, $C_{4\alpha}$, 2H); Mass, m/z (rel. intensity %):

275 (22), 163 (38), 148 (15), 122 (30), 81 (100), 68 (12), 53 (20). *Anal. Calcd.* for $C_{14}H_{17}N_3O_3$: 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): δ10.63 (s, NH, 1H), 8.27 (s, NH, 1H), 6.83-6.70 (q, aromatic, 4H), 4.18 (s, C_{1H}, C_{5H}, 2H, J ($W_{1/2}$)=9.5Hz), 3.68 (s, OCH_3, 3H), 2.26-2.18 (dd, $C_{2\beta}$, $C_{4\beta}$, 2H), 2.12-1.92 (m, C_{6H}, C_{7H}, 4H), 1.42-1.35 (d, $C_{2\alpha}$, $C_{4\alpha}$, 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 $C_{16}H_{19}N_3O_3$: C, 63.77; H 6.36; N, 13.94 Found C, 64.13; H 5.99; N 14.24%.