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A Study on the Synthesis of Nortropinone Derivatives

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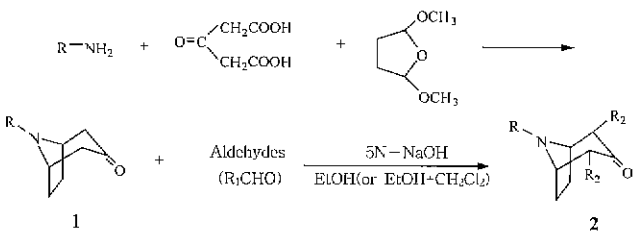
Abstract 2,4-Disubstituted nortropinone derivatives anticipated anticonvulsant activity were respectively synthesized by the reaction of *N*-substituted nortropinones, ethanol, 5*N*-NaOH and benzaldehyde (R_1CHO)

Key words: Nortropinone, anti-convulsant activity, aldol condensation

Introduction

Tropane alkaloids have received a great deal of attention because of their remarkable pharmaceutical significance. [1-4] Therefore a variety of synthetic approaches to tropane alkaloids have been investigated. Especially, a series of tropane showed anticonvulsant activity against pentylenetetrazol-induced convulsions in mice and antiarrhythmic activity in rabbit previously treated with ouabain. [5-8]



1 2

As a part of our study on the improvement of anti-convulsant, herein we first report the synthesis of corresponding 2,4-disubstituted nortropinones by aldol condensation from *N*-substituted nortropinones. Already we reported the synthesis of *N*-substituted nortropinones derived from the reaction of amine, 2,5-dimethoxytetrahydrofuran and acetonedicarbxylic acid. [9]

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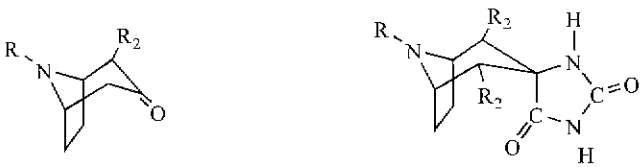
Materials and Methods

A representative example of synthesis **2a** is as the follow. The mixture of tropinone **2a** (1.39g, 1×10^{-2} mol), ethanol (20 mL), 5*N*-NaOH (2 mL) and benzaldehyde (1.6 g, 1.5×10^{-2} mol) was stirred under N_2 gas at room temperature for 30 minutes. After adding with water (10 mL), the product precipitated solid was removed by filteration. The filtered solid was recrystallized from *n*-Hexane and EtOAc. The first compound, which was isolated from *n*-Hexane and EtOAc, recrystallized from ehtanol once more to afford **2a** in a 57% yield. Identification of 2,4-diphenylmethenylnotropinone **2a** by ^{1}H NMR spectrum ($CDCl_3$, Me_4Si) showed 10 proton peaks corresponding to phenyl group at δ 7.25-7.44. The signal for 2 proton peaks of methenyl group clearly indicate at δ 7.83. The signals of the H-1 and H-5 clearly show at δ 4.39. And the signal of the methyl group attached nitrogen atom are seen at δ 2.31. Mass spectrum of **2a** showed molecular ion peaks at *m/z* 315 (12%). Structures of all other products were confirmed by the same manner as the **2a**. The biological studies of these compounds are in progress and will be reported in future.

Results and Discussion

2,4-Disubstituted nortropinones **2** were respectively synthesized by the reactions of *N*-substituted nortropinones **1**, ethanol, 5*N*-NaOH and benzaldehyde (R_1CHO) (Scheme 1). The reaction mixture was stirred at room temperature for reaction time as shown in table 1. After the reaction mixture was added with water, the product precipitated solid was removed by filteration. The filtered solid was recrystallized from *n*-Hexane and EtOAc. The first compound, which was isolated from *n*-Hexane and EtOAc, recrystallized from ethanol once more. The yield, mp, IR and ^{1}H NMR of the products (**2a**~**2m**) are summarized in footnote (Table 1).



3 4

Scheme 1

But the synthesis of 2-substituted nortropinones **3** as the 1:1 adduct from *N*-substituted nortropinones **1** was not successful. However we tried the various reaction to obtain 2-substituted nortropinones **3**. All the reactions by using sodium hydride (or sodium methoxide, or butyl lithium) and dimethyl carbonate (or diethyl carbonate) to 2-substituted nortropinones **3** did not occur.

The synthesis of corresponding *N*-substituted nortropane spirohydantoin **4** by using 2,4-substituted nortropinones **2**, ethanol, potassium cyanide and ammonium carbonate is in progress.

Spectral data of 2,4-disubstituted Nortropinone derivatives are as follows ;

2,4-Diphenylmethenylnortropinone 2a : Yield 57 %. mp 150-151 ℃. IR(ν, KBr, cm^{-1}) : 3050, 2950, 1650(C=O), 1610, 1580, 1450, 1200. ^{1}H NMR ($CDCl_3$) : δ 7.83(s, 2H), 7.44-7.25(m, 10H), 4.39(s, 2H), 2.31(s, 3H), 2.64-2.57(m, 2H), 2.04-2.00(g, 2H) Mass, *m/z*(rel. intensity, %) : 315(12), 237(100), 259(29), 182(12), 115(20), 77(10).

2,4-*p*-Dimethoxyphenyl-methenylnortropinone 2b : Yield 32 %. mp 162-163 ℃. IR(ν, KBr, cm^{-1}) : 2939, 2837, 1666(C=O), 1593, 1506, 1456, 1417, 1190. ^{1}H NMR ($CDCl_3$) : δ 7.37(d, 4H), 6.95(d, 4H), 4.41(s, 2H), 3.85(s, 6H), 2.63-2.58(m, 2H), 2.50(s, 3H), 2.02-1.99(q, 2H). Mass, *m/z* (rel. intensity, %) : 375(11), 247(100), 332(56), 288(8), 145(19), 115(12), 63(4),

2,4-Difurfuryl methenylnortropinone 2c : Yield 51 %. mp 134-135 ℃. IR(ν, KBr, cm^{-1}) : 3105, 2965, 1680(C=O), 1620, 1540, 1175. ^{1}H NMR($CDCl_3$) : δ 7.58-7.57(s, 2H), 7.45(s, 2H), 6.66(d, 2H), 6.53-6.50(m, 2H), 4.83(d, 2H), 2.55-2.51(m, 2H), 2.43(s, 3H), 1.80-1.77(q, 2H). Mass, *m/z*(rel. intensity, %) : 295(12), 267(100), 238(43), 210(30), 175(10), 116(7), 77(9).

2,4-Di-*N*-methylpyrrolylmethenylnortropinone 2d : Yield 23%. mp 173～173.5 ℃. IR(ν, KBr, cm^{-1}) : 3140, 2940, 1670(C=O), 1620, 1590, 1490, 1430, 1175. ^{1}H NMR ($CDCl_3$) : δ 7.77(s, 2H), 6.83(d, 2H), 6.46(d, 2H), 6,.27-6.24(m, 2H), 4.49-4.45(dd, 2H), 3.73(s, $3CH_3$, 6H), 2.58-2.52(m, 2H), 2.41(s, 3H), 1.86-1.82(q, 2H). Mass, *m/z* (rel. intensity, %) : 321(12), 293(100), 214(8), 188(8), 118(10), 77(5).

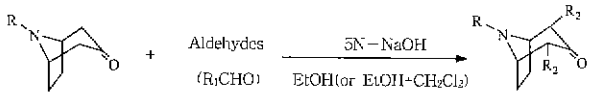
8-Carbethoxy-2,4-diphenylmethenylnortropinone 2e : Yield 50 %, mp 158～159 ℃. IR(ν, KBr, cm^{-1}) : 3830, 3000, 1695(C=O), 1615, 1500, 1480, 1450, 1175. ^{1}H NMR($CDCl_3$) : δ 7.75(s, 2H), 7.45-7.39(m, 10H), 5.44(d, 2H), 4.01-3.97(q, 2H), 2.55-2.51(m, 2H), 2.07-2.03(q, 2H), 1.07-1.00(t, 3H). Mass, *m/z*(rel. intensity, %) : 373(51), 345(86), 317(56), 272(100), 243(22), 115(69), 77(16).

8-Carbethoxy-2,4-*p*-dimethoxyphenylmethenyl notropinone 2f : Yield 30%. mp 158～158.5 ℃, IR(ν, KBr, cm^{-1}) : 3140, 2940, 1670, 1620, 1590, 1490, 1430, 1175. ^{1}H NMR($CDCl_3$) : δ 7.79(s, 2H), 7.44-7.40(dd, 4H), 6.98-6.93(dd, 4H), 5.47(d, 2H), 4.00-3.96(q, 2H), 3.85(s, 6H), 2.56-2.52(m, 2H), 2.07-2.03(q, 2H), 1.07-1.04(t, 3H). Mass, *m/z*(rel. intensity, %) : 435(20), 401(40), 383(100), 355(17), 278(11), 215(1.8), 115(43), 75(19).

8-Carbethoxy-2,4-difurfurylmethenylnortropinone 2g : Yield 50%. mp 206～207 ℃, IR(ν, KBr, cm^{-1}) : 3140, 3000, 1700(C=O), 1595, 1480, 1415, 1175. ^{1}H NMR($CDCl_3$) : δ 7.60(s, 2H), 7.37(s, 2H), 6.71(d, 2H), 6.54-6.51(m, 2H), 5.92-5.88(m, 2H), 4.11-4.04(q, 2H), 2.50-2.46(m, 2H), 1.90-1.87(q, 2H), 1.15-1.08(t, 3H). Mass, *m/z*(rel. intensity, %) : 353(40), 325(63), 297(30), 252(10), 224(19), 167(11), 105(15), 77(19).

8-Carbethoxy-2,4-Di-*N*-methylpyrrolylmethenylnortropinone 2h : Yield 20 %. mp 206～206.5℃. IR(ν, KBr, cm^{-1}) : 3020, 2960, 2900, 1690(C=O), 1595, 1450, 1175. ^{1}H NMR($CDCl_3$) : δ 7.63(s, 2H), 6.84(d, 2H), 6.55(d, 2H),

Table 1. Physical Data of 2,4-disubstituted Nortropinone Derivatives



1 2

1	Aldehydes R_1CHO	R_2	2	Reaction time(h)	Yield (%)
R: $-CH_3$	CHO		2a	0.5	57
	H_3CO-CHO	$-OCH_3$	2b	0.5	32
	furfuryl-CHO	furfuryl	2c	0.5	51
	N-CH_3-pyrrolyl-CHO	N-CH_3-pyrrolyl	2d	12	23
R: $C_2H_5O-\overset{O}{\overset{\|}{C}}-$	CHO		2e	0.5	50
	H_3CO-CHO	$-OCH_3$	2f	0.5	30
	furfuryl-CHO	furfuryl	2g	0.5	50
	N-CH_3-pyrrolyl-CHO	N-CH_3-pyrrolyl	2h	0.5	20
R: phenyl	CHO		2i	3	50
	furfuryl-CHO	furfuryl	2j	12	57
R: CH_3-phenyl	CHO		2k	3.5	43
R: OCH_3-phenyl	CHO		2l	0.5	55
	furfuryl-CHO	furfuryl	2m	0.5	54

6.28-6.25(m, 2H), 5.53(d, 2H), 4.06-4.02(q, 2H), 3.73(s, 6H), 2.53-2.49(m, 2H), 1.94-1.91(q, 2H), 1.15-1.08(t, 3H). Mass, m/z(rel. intensity, %) : 379(40), 351(100), 278(68), 246(11), 118(20), 77(5).

8-Phenyl-2,4-diphenylmethylnortropinone 2i : Yield 50 %. mp 222~223℃. IR (ν, KBr, cm^{-1}) : 3070, 2990, 1680(C=O), 1610, 1510, 1460. ^{1}H NMR ($CDCl_3$) : δ 7.78(s, 2H), 7.49-7.39(m, 10H), 6.94(t, 2H), 6.61(s, 1H), 6.16-6.12(dd, 2H), 5.24(d, 2H), 2.75-2.71(m, 2H), 2.28-2.25(q, 2H). Mass, *m/z* (rel. intensity, %) : 377(40), 349(100), 321(15), 224(10), 115(16), 77(21).

8-Phenyl-2,4-difurfurylmethenylnortropinone 2j : Yield 5.7 %. mp 208~209℃. IR (ν, KBr, cm^{-1}) : 3140, 2990, 1680(C=O), 1615, 1550, 1490. ^{1}H NMR($CDCl_3$) : δ 7.66(2, 2H) 7.43(s, 2H), 7.04(t, 4H), 6.71-6.55(m, 5H), 5.81(d, 2H), 2.68-2.60(m, 2H), 2.05-1.95(q, 2H). Mass, *m/z*(rel. intensity, %) : 375(45), 329(10), 300(27), 272(28), 237(18), 115(10), 77(21).

8-(p-Methylphenyl)-2,4-diphenylmethenylnortropinone 2k : Yield 43%. mp 229~230 ℃. IR (ν, KBr, cm^{-1}): 2959, 2837, 1672(C=O), 1605, 1493, 1446, 1160. ^{1}H NMR ($CDCl_3$) : δ 7.79(s, 2H), 7.49-7.38(m, 10H), 6.91-6.86(dd, 2H), 6.04-6.00(dd, 2H), 5.17(d, 2H), 2.75-2.71(m, 2H), 2.29-2.26(q, 2H), 1.58(s, 3H). Mass, *m/z*(rel. intensity, %) : 411(40), 383(100), 355(17), 215(1.8), 115(43), 75(19).

8-(*p*-Methoxyphenyl)-2,4-diphenylmethenylnortropinone 2l : Yield 55%. mp 228~229 ℃. IR(ν, KBr, cm^{-1}) : 3070, 3000, 1690(C=O), 1610, 1520, 1475. ^{1}H NMR($CDCl_3$) : δ 7.78(s, 2H), 7.50-7.40(m, 10H), 6.55-6.50(dd, 2H), 6.12-6.08(dd, 2H), 5.17(d, 2H), 3.63(s, 3H), 2.73(m, 2H), 2.27-2.23(q, 2H). Mass, *m/z*(rel, intensity, %) : 4.7(74), 379(100), 351(20), 274(10), 215(7), 115(14), 77(17).

8-(*p*-Methoxyphenyl)-2,4-difurfurylmethenylnortropinone 2m . Yield 54 %. mp 175~176 ℃. IR(ν, KBr, cm^{-1}) : 3250, 3120, 1680(C=O), 1600, 1540, 1440. ^{1}H NMR ($CDCl_3$) : δ 7.66(s, 2H), 7.26(s, 1H), 6.71-6.55(m, 10H), 5.76(d, 2H), 3.65(s, 3H), 2.68-2.61(m, 2H), 2.00-1.96(t, 2H). Mass, *m/z*(rel. intensity, %) : 387(70), 359('00), 330(33), 267(13), 134(10), 105(17), 77(21).

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