SYNTHESIS OF NOVEL POTENT NON-NARCOTIC LESS SIDE-EFFECT ANALGESICS : 2'-ACYLTHIO- AND 2'-ALKYLTHIO-6,7-BENZOMORPHANS[1]

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Abstract ——— 2'-Acylthio- and 2'-alkylthio-6,7-benzomorphans were synthesized from 2'-hydroxy-6,7-benzomorphans in 4 steps. Newman-Kwart rearrangement of 2'-N,N-dimethylthiocarbamoyloxy derivatives proceeded in almost quantitative yields to give rearranged 2'-N,N-dimethylcarbamoylthio derivatives. Reductive cleavage and successive acylation afforded title compounds. These novel sulfur-containing benzomorphans showed strong analgesic activities with less side effects.

The phenolic hydroxyl groups in morphine[2] and other opiates[3] and tyrosine hydroxyl group in synthetic opioid peptides[4] are very important to show the biological activities of these compounds and their abilities to bind the opioid receptor. In benzomorphan skeleton, modifications of the phenolic hydroxyl group such as alkylation or acylation gave no good result, but only reduced biological activities.[5] On the other hand, other functional groups such as nitro, amino, and halogens were introduced to the 2'-position of the benzomorphans in place of phenolic hydroxyl group, but these substituents did not exert good effect on analgesic activities either.[6]

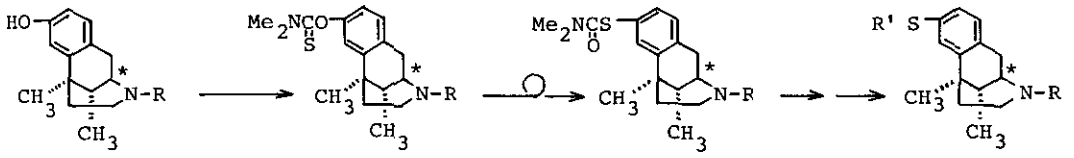
In order to elucidate the meanings of the phenolic hydroxyl group and to evaluate the effects of conversion of the hydroxyl group to mercapto group, we planned to synthsize 2'-mercaptobenzomorphans as target molecules.

We report here the synthesis of the novel sulfur-containing benzomorphans which showed strong analgesic activities and less side effects.

We planned two synthetic approaches : one is a way starting from 2'-nitrobenzomorphan and the other is a route using Newman-Kwart rearrangement. The Newman-

Kwart rearrangement is the useful reaction for the conversion from phenols to the corresponding thiophenols.[7,8] In the former method, nitration of 2'-deoxybenzomorphan gave a mixture of 2'-nitro and 3'-nitro isomer.[6] Another disadvantage of this route was that benzomorphans with N-aromatic substituents would suffer from nitration. Therefore we examined the latter synthetic route.

Benzomorphans with various N-substituents (1a-f) reacted with N,N-dimethylthiocarbamoyl chloride in the presence of NaH in DMF to give the 2'-N,N-dimethylthiocarbamoyloxybenzomorphans (2a-f) in high yields as shown in Table 1. Since Newman-



1a R = CH_3
1b R = $CH_2CH_2C_6H_5$
1c R = CH_2CH_2-(2-thienyl)
1d R = $CH_2CH{=}C(CH_3)_2$
1e R = $CH_2C_6H_5$
1f R = $CH_2C_3H_5$-c

2a-f 3a-e 4a-e

Scheme

Table 1. 2'-N,N-Dimethylthiocarbamoyloxy- and 2'-N,N-dimethylcarbamoylthio-5,9-dimethyl-6,7-benzomorphans

Comp.	2a-f Yield (%)	2a-f ^{1}H-NMR of 2'-Me_2N (δ-$CDCl_3$)	2a-f mp (°C)	2a-f $[\alpha]_D^{20}$ (in EtOH)	Reaction Conditions Temp (°C)	Reaction Conditions Time (min)	3a-e Yield (%)	3a-e ^{1}H-NMR* (δ-$CDCl_3$)	3a-e mp (°C)	3a-e $[\alpha]_D^{20}$ (in EtOH)
(±)a	85	3.33,3.46	124-126		300	5	92	3.04	202-203[2]	
S(+)a	64	3.33,3.46	126	+ 53.3°	300	5	73	3.04	184[2]	+ 30.2°
R(-)a	83	3.33,3.46	127	- 54.4°	300	5	85	3.07	185[2]	- 30.3°
b	100	3.28,3.46	203-205[1]		320	6	96	3.03	193-195[1]	
c	81	3.33,3.46	229-232(dec)[1]		310	5	96	3.05	175-178[1]	
(±)d	84	3.33,3.46	187-189[2]		325	0.5	11	3.08	95- 98[2]	
S(+)d	77	3.33,3.46	106.5	+102.7°	325	0.5	8	3.06	124[2]	+ 66.3°
R(-)d	75	3.33,3.46	106	-102.2°	325	0.5	8	3.06	124[2]	- 66.0°
e	72	3.30,3.43	185-188[3]		315	4	74	3.06	165-168[2]	
f	96	3.29,3.42	232-234(dec)[1]							

*Chemical shifts of 2'-Me_2N groups are shown. 1) as HCl salt 2) as oxalate 3) as HBr salt

Kwart rearrangement is a key step in the reaction sequence, the rearrangement of N-methyl-benzomorphan (2a) was precisely monitored with ^{1}H-NMR as a typical example. Two singlets of the dimethylamino group of 2a (3H x 2, 3.33, 3.46 ppm in $CDCl_3$) were decreased and a singlet of the rearranged dimethylcarbamoylthio group (6H, 3.04 ppm) was increased as the reaction proceeded. The rearrangement of 2a occurred above 250°C and optimum conditions were 300°C for 5 min. Likewise the optimum conditions for the optical active isomers of 2a and 2f and for other N-substituted derivatives (2b-f) were investigated and the results are shown in Table 1. The thermal rearrangement except N-prenyl (2d) and N-cyclopropylmethyl (2f) derivatives proceeded in almost quantitative yields to give rearranged compounds, but the N-cyclopropylmethyl derivative (2f) was decomposed. N-Prenyl derivative (2d) was also sensitive to heat, but in this case it afforded rearranged product (3d) with recovery of starting material under the conditions of short time and relatively high temperature (320°C, 0.5 min). The product (±)-, S(+)- and R(-)-3d were isolated in ca. 10% yield by silica gel column chromatography (ether:hexane:Et_3N = 1:10:1 as eluent).

For the unstability of SH group chemically and metabolically, protection of SH group was accomplished by the reductuin of 3 with $LiAlH_4$ and successive acylation or alkylation with appropriate acyl halides or alkylating agents, such as benzoyl cloride (4a-1, 4b-e), acetyl chloride (4a-2), or methyl iodide (4a-3). The results

Table 2. 2'-Acylthio- and 2'-alkylthio-6,7-benzomorphans

	R'	Yield (%)	mp (°C)	$[\alpha]_D^{20}$ in EtOH
(±) 4a-1	C_6H_5CO	86	153-154 (fumarate monohydrate)	
S(+) 4a-1	C_6H_5CO	86	132-133 (fumarate hemihydrate)	+ 34.0°
R(-) 4a-1	C_6H_5CO	84	132-133 (fumarate hemihydrate)	- 34.6°
4a-2	CH_3CO	98.6	oil ($bp_{0.5}$ 130-135°C)	
4a-3	CH_3	91	206 (fumarate)	
4b	C_6H_5CO	78	220-223 (HCl salt)	
4c	C_6H_5CO	84	207-209 (HCl salt)	
(±) 4d	C_6H_5CO	98	175-177 (fumarate)	
S(+) 4d	C_6H_5CO	45	101-103 (fumarate)	+ 76.7°
R(-) 4d	C_6H_5CO	56	100-102 (fumarate)	- 77.3°
4e	C_6H_5CO	72	191-193 (HCl salt)	

were shown in Table 2. These reaction proceeded cleanly to give acylthio- or alkylthiobenzomorphans in good yields. The structures of 4a-4e were confirmed by ^{1}H-NMR, IR, mass spectra and elemental analytical data.

These novel sulfur-containing benzomorphans showed strong analgesic activities compared to morphine with less side effects. Moreover 4a-1 did not develop dependence capacity in guinea-pig jumping test.[1] The pharmacological data will be published elsewhere.

Further application to sulfur-containing strong analgesics using Newman-Kwart rearrangement is now in progress.

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