Communications to the Editor

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SYNTHESIS OF A NEW POTENT ANTI-ULCER AND GASTRIC SECRETORY INHIBITING AGENT, (-)-cis-2,3-DIHIDRO-3-(4-METHYLPIPERAZINYLMETHYL)-2-PHENYL-1,5-BENZOTHIAZEPIN-4(5H)-ONE HYDROCHLORIDE(BTM-1086), AND RELATED COMPOUNDS

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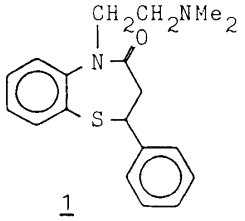
(-)-cis-2,3-Dihydro-3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5H)-one hydrochloride(BTM-1086) and its analogues, which possessed potent anti-ulcer and gastric secretory inhibiting activities, were synthesized and the structures of these compounds were established on the basis of spectral and chemical evidences.

KEYWORDS——2,3-dihydro-1,5-benzothiazepin-4(5H)-one; anti-ulcer agent; gastric secretory inhibiting agent; BTM-1086; BTM-1042

Tiazesim(1),[1] an antidepressant agent, and diltiazem(2),[2] a coronary vasodilator, are well known as biologically active compounds having 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one skeleton, and 2 is widely used clinically.

We now report synthesis of (-)-cis-2,3-dihydro-3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5H)-one[(-)-12a, hydrochloride: BTM-1086][3,4] and its analogues with potent anti-ulcer and gastric secretory inhibiting activities.



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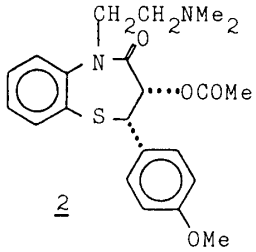

2

Treatment of benzylidenemalonates (3)[5] with 2-aminobenzenethiol afforded addition products(4)[4a: 91% yield, mp 70-71°C, δ($CDCl_3$): 0.93(t, J=7.2 Hz, $CH_2\underline{CH_3}$), 1.36(t, J=7.2 Hz, $CH_2\underline{CH_3}$), 3.88(q, J=7.2 Hz, $\underline{CH_2}CH_3$), 4.02(d, J=11.8 Hz, SCH), 4.15(br, NH_2), 4.28(q, J=7.2 Hz, $\underline{CH_2}CH_3$), 4.06(d, J=11.8 Hz, SCHCH), 6.35-6.66(2H, m, Ar H), 6.84-7.26(m, Ar H), 4e: oil]. The esters(4) were heated in the presence of triethylamine hydrochloride to give trans-amide-esters(6)[6a: 44% yield, δ($CDCl_3$): 1.07(t, J=7.0 Hz, $CH_2\underline{CH_3}$), 4.02(q, J=7.0 Hz, $\underline{CH_2}CH_3$), 4.06(d, J=11.2 Hz, C_3-H), 5.13(d, J=11.2 Hz, C_2-H), 7.03-7.72(m, Ar H), 9.13(br s, NH)]. The amide-esters(6) were also obtained by heating of the mixture of 3, 2-aminobenzenethiol, and triethylamine hydrochloride(6a: 32% yield).

The cyclizations of the esters(4) and the reactions of the malonates(3) and 2-aminobenzenethiol yielded by-products, 2-arylbenzothiazoles(5)[8](5a: 29 and 32% yield), with the desired compounds(6).

The esters(6) were reduced to alcohols(7)[7a: 91% yield, δ($CDCl_3$): 2.07(s, OH), 2.73-3.83(m, C_3-H and C_3-CH_2), 4.76(d, J=12.0 Hz, C_2-H), 6.90-7.73(m, Ar H), 8.23(br, NH)] with $LiAlH_4$ in tetrahydrofuran. The alcohols(7) were treated with thionyl chloride, methanesulfonyl chloride, or p-toluenesulfonyl chloride to afford chlorides(8)[8a: 94% yield, δ($CDCl_3$): 3.10(dd, J=10.0 and 1.6 Hz, C_3-C<u>H</u>H), 3.40(td, J=11.3 and 1.6 Hz, C_3-H), 4.03(t, J=10.0 Hz, C_3-CH<u>H</u>), 4.37(d, J=11.3 Hz, C_2-H), 7.00-7.80(m, Ar H), 8.30(br s, NH)], mesylates(9)[9a: 93% yield, δ($CDCl_3$): 2.87(s, Me), 3.37(td, J=12.0 and 2.5 Hz, C_3-H), 3.73(dd, J=9.3 and 2.5 Hz, C_3-C<u>H</u>H), 4.26(d, J=12.0 Hz, C_2-H), 4.56(t, J=9.3 Hz, C_3-CH<u>H</u>), 6.91-7.70(m, Ar H),

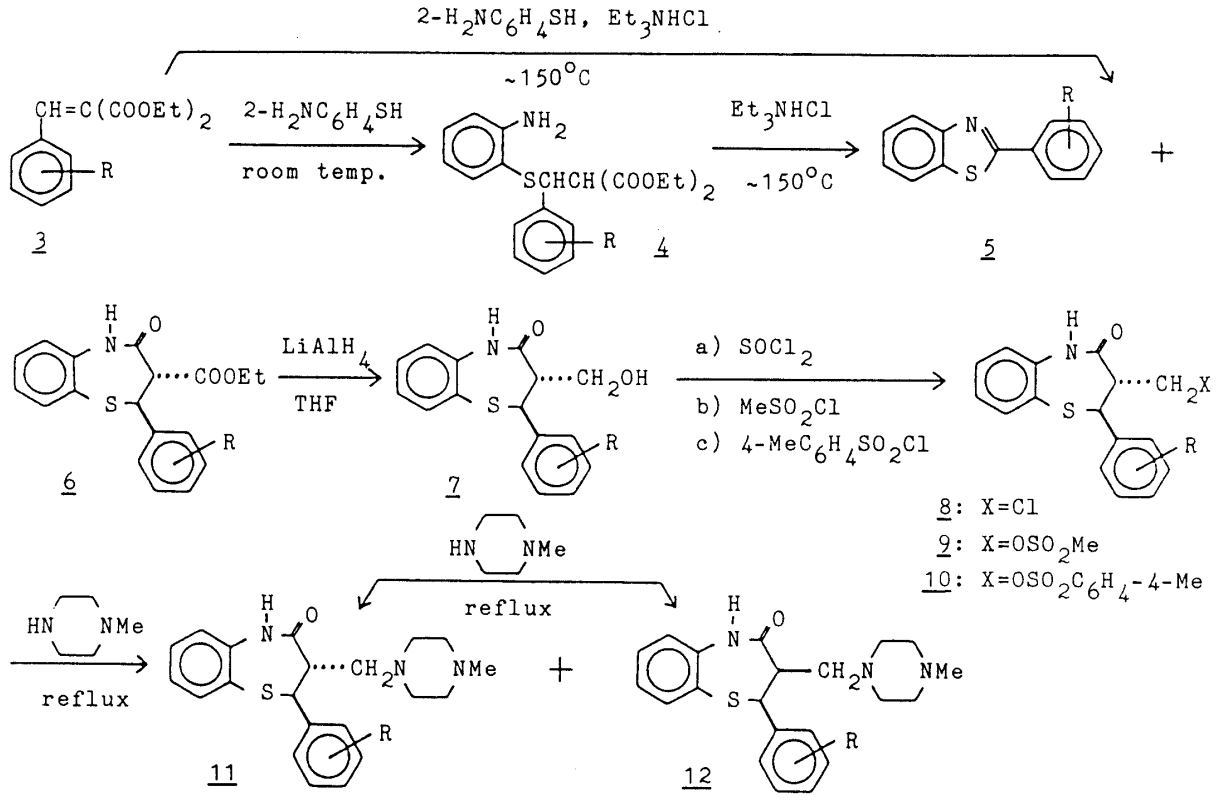

Chart 1

Table. Melting Points(°C) of 2,3-Dihydro-1,5-benzothiazepin-4(5H)-ones(6-12)

	R	6	7	8	9	10	11	12
a	H	198-200	246-248	230-233	213-215	213-215	257-260	203-205
b	4-Me	183-185	227-229		205-207		-[b]	194-196
c	4-Cl	204-206	237-239	238-241[a]			-[b]	245-248[a]
d	4-OMe	190-192	215-217	231-235[a]			-[b]	191-193
e	3-Me	175-177	213-216		213-214		207-210	114-117
f	3-Cl	195-197	233-236[a]			192-195	219-222	197-200

a) decomposition. b) not isolated.

8.19(br s, NH)] or tosylates(10)(10a: 88% yield), respectively.

Heating of the compounds(8-10) in N-methylpiperazine gave trans-2-aryl-2,3-dihydro-3-(4-methylpiperazinylmethyl)-1,5-benzothiazepin-4(5H)-ones(11)[11a: 35% yield from 9, δ($CDCl_3$): 1.83-2.50(m, C_3-CHH and $N(CH_2CH_2)_2N$), 2.17(s, Me), 3.00-3.53(m, C_3-H and C_3-CHH), 4.23(br d, J=11.0 Hz, C_2-H), 6.90-7.70(m, Ar H), 8.17 (br, NH)] and the cis-isomers(12)[9] [12a: 39% yield from 9, δ($CDCl_3$): 1.83-2.60(m, C_3-CH_2 and $N(CH_2CH_2)_2N$), 2.20(s, Me), 2.87-3.37(m, C_3-H), 5.07(d, J=6.4 Hz, C_2-H), 6.93-7.73(m, Ar H), 8.70(br, NH)].

The structures of 11 and 12 were established on the basis of NMR spectroscopy and the following reactions.

The pure 11a or 12a changed to the mixture of 11a and 12a by refluxing in N-methylpiperazine(11a/12a=ca. 9). Desulfurization of 11a or 12a with W-7 Raney-cobalt in ethanol afforded the anilide(13)[mp 99-101°C, δ($CDCl_3$): 2.00-3.57(m, $COCH(CH_2-)_2$ and $N(CH_2CH_2)_2N$), 2.28(s, Me), 6.87-7.80(m, Ar H), 10.72(br, NH)] and treatment of 11a or 12a with sulfuryl chloride in chloroform gave the 2,3-dehydro-compound(14)[mp 219-221°C, δ($CDCl_3$): 2.07(s, Me), 1.77-2.50(m, $N(CH_2CH_2)_2N$), 3.24 (s, C_3-CH_2), 6.93-7.70(m, Ar H), 9.46(br, NH), m/e: 365(M^+)].

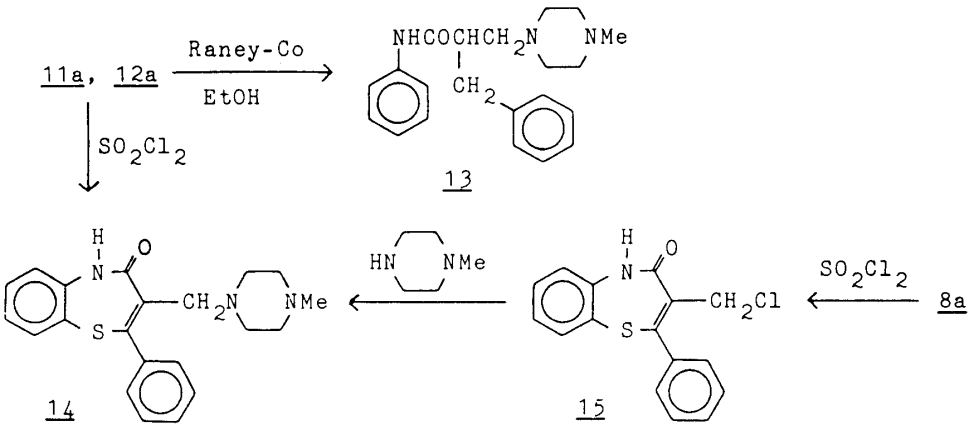

Chart 2

The compound(14) was alternatively synthesized from N-methylpiperazine and the chloride(15) which was prepared from 8a by treatment with sulfuryl chloride [15: mp 210-213°C, δ($CDCl_3$): 4.33(s, C_3-CH_2), 6.95-7.60(m, Ar H), 9.07(br, NH)].

In the NMR spectra the coupling constants between C_2-H and C_3-H of the compounds(11) were larger than those of the compounds(12). For example, the constants of 11a and 12a were 11.0 and 6.4 Hz, respectively. This spectral and chemical evidence shows that both 11 and 12 have the 2,3-dihydro-1,5-benzothiazepin-4(5H)-one skeleton and that the configurations are trans for 11 and cis for 12. These results are in good agreement with the results obtained in diltiazem(2)[2a] and related compounds.[10]

The cis-compounds(12) were optically resolved with tartaric acid in methanol [(-)-12a: mp 196-198°C, $[\alpha]_D^{20}$ -46.0°(c=2.4, $CHCl_3$), hydrochloride(BTM-1086): mp 256-260°C(d), $[\alpha]_D^{20}$ -63.0°(c=2.0, H_2O), (+)-12a: mp 196-198°C, $[\alpha]_D^{20}$ +46.0°(c=2.4,

$CHCl_3$)].

The (±) and (-)-cis-1,5-benzothiazepin-4(5H)-ones[12 and (-)-12] possessed potent anti-ulcer and gastric anti-secretory activities in biological tests.[3a,4b] For example, (-)-12a had potent inhibition effects on the acute ulcer models such as Shay's ulcers, cold restraint-stress ulcers and serotonin ulcers and on the chronic model such as acetic acid ulcers and also inhibited gastric secretions in pylorus-ligated rats, fistula rats and Shild's rats. The ED_{50} value of (-)-12a on cold restraint-stress ulcers was 0.1 mg/Kg orally in mice and its activity was 15 times that of atropine.[11] Acute toxicity of (-)-12a was weaker than that of (±) or (+)-12a.[3a,4a] The LD_{50} values of (-) and (±)-12a were 870 and 650 mg/Kg orally, and 160 and 65 mg/Kg intravenously, respectively, in mice.[11]

BTM-1086 is now under clinical trials.

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5) The benzilidenemalonates(3) were prepared according to the known method for diethyl benzilidenemalonate(3a).[6] A part of the compounds(3) was already described.[7]

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9) The cis-compounds(12) were obtained from the trans-compounds(8-10). We have found that the formation of 11 and 12 proceeded via intermediary ring-opening compounds, and will report in detail in the near future.

10) H. Kugita, H. Inoue, M. Ikezaki, M. Konda, and S. Takeo, Chem. Pharm. Bull., 18, 2284(1970); M. Miyazaki, T. Iwakuma, and T. Tanaka, ibid., 26, 2889(1978).

11) In these tests, the 1,5-benzothiazepin-4(5H)-ones[(-)-12a, (±)-12a] were used as the dihydrochlorides. The dihydrochloride of (-)-12a coded as BTM-1042.

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