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Synthesis and β-Adrenergic Blocking Action of a New Thiazolylthiopropanolamine Derivative

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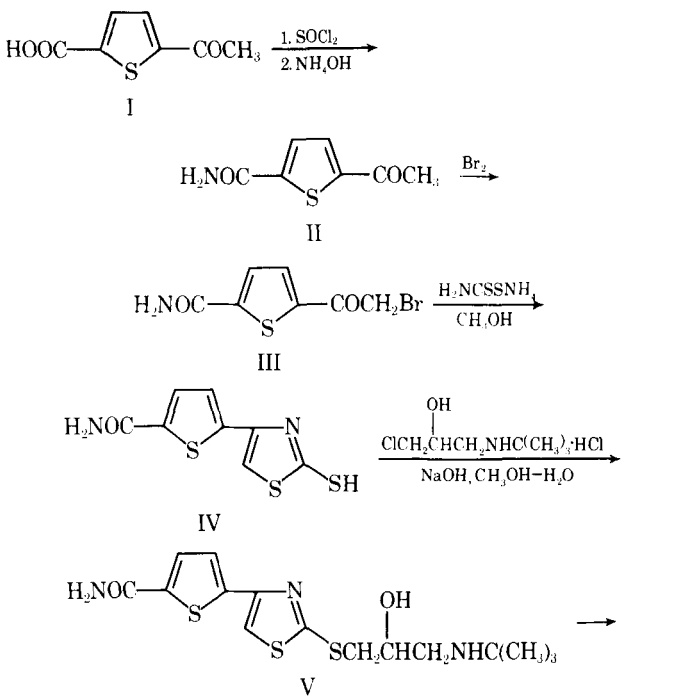
Abstract □ The synthesis of (±)-2-(3′-*tert*-butylamino-2′-hydroxypropylthio)-4-(5′-carbamoyl-2′-thienyl)thiazole hydrochloride is described. The new compound antagonized the cardiovascular effects, such as positive chronotropic, positive inotropic, or depressor arterial blood pressure responses, elicited by intravenous isoproterenol; it was 9–14 times as potent as propranolol in anesthetized open chest dogs. The oral administration of the compound reduced isoproterenol tachycardia in conscious dogs. It was about five times as potent as propranolol in this test, with maximal action after 1 hr, and its duration was significantly longer than that of propranolol.

Keyphrases □ Thiazolylthiopropanolamine derivative—synthesized, β-adrenergic blocking activity evaluated in dogs □ β-Adrenergic blocking activity—thiazolylthiopropanolamine derivative evaluated in dogs

Many amino alcohol derivatives have been described to have a β-blocking action, and some have been of interest for the treatment of angina pectoris and cardiac arrhythmias (1). Most compounds available for clinical use belong to the aryloxypropanolamine series, which is considered the second generation of β-blocking agents, in contrast with the arylethanolamine series, which includes original β-blocking agents such as dichloroisoproterenol and pronethalol (2).

During a search for drugs affecting the peripheral autonomic nervous system, various compounds with an *N*-substituted thiopropanolamine moiety attached to a heterocyclic nucleus were synthesized and tested for β-blocking action as well as the other pharmacological actions. A new compound, (±)-2-(3′-*tert*-butylamino-2′-hydroxypropylthio)-4- (5′-carbamoyl-2′-thienyl)thiazole hydrochloride[1] (VI), showed remarkable β-blocking action with low toxicity and was virtually devoid of other pharmacological actions.

The present report describes the chemical synthesis and β-blocking activity of this derivative compared with that of propranolol (3) in *in vivo* experiments.



Scheme I

EXPERIMENTAL[2]

Chemistry—Reaction of 5-carboxy-2-acetylthiophene (I, Scheme I) (4) with thionyl chloride in toluene and successive treatment with aqueous ammonia furnished the carbamoyl derivative (II), which was converted to its monobromide (III). Reaction of the bromide with ammonium dithiocarbamate resulted in isolation of 2-mercapto-4-(5′-carbamoyl-2′-thienyl)thiazole (IV). Condensation of IV with 1-chloro-3-*tert*-butylaminopropanol hydrochloride (5) by means of base in an equivalent mixture of methanol and water provided 2-(3′-*tert*-butylamino-2′-hydroxypropylthio)-4-(5′-carbamoyl-2′-thienyl)thiazole (V), from which its crystalline hydrochloride (VI) was derived.

5-Carbamoyl-2-acetylthiophene (II)—To a suspension of I, 22 g (0.129 mole) of thionyl chloride in 200 ml of toluene was added dropwise with vigorous stirring. The mixture was heated under a gentle reflux for 2 hr and evaporated *in vacuo* to dryness. The residue was dissolved in 150 ml of toluene again and treated with aqueous ammonia below 10°.

The white precipitate was collected by suction filtration, washed with water, and dried, yielding 20 g (92.8%), mp 226–228° (methanol); NMR:

[1] S-596.

[2] Melting points were obtained on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. IR spectra were determined in mineral oil mulls on a Hitachi EPI-G3 IR spectrometer. NMR spectra were taken in deuterated dimethyl sulfoxide on a Varian Associates T-60 instrument with tetramethylsilane as the internal standard.

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2.55 (s, 3H, acetyl) and 7.82 (*AB*q, J_{AB} = 4 Hz, δ_{AB} = 3 Hz, 2H, 3,4-H on the thiophene) ppm; IR: 3400, 3180 (NH), 1660 (C=O), and 1640 (amide) cm^{-1}.

Anal.—Calc. for $C_7H_7NO_2S$: C, 49.70; H, 4.14; N, 8.28; S, 18.94. Found: C, 49.51; H, 4.20; N, 8.30; S, 19.00.

5-Carbamoyl-2-bromoacetylthiophene (III)—Compound II, 21.9 g (0.131 mole), was dissolved in 350 ml of hot acetic acid; bromine, 21.9 g (0.136 mole), was added dropwise at 80°. After the addition was complete, the resulting solution was maintained at the same temperature for 1.5 hr, evaporated to half, and filtered.

The product was washed with water thoroughly and dried, yielding 26.2 g (80.6%), mp 198–199° dec. (acetic acid); NMR: 4.80 (s, 2H, bromoacetyl) and 7.85 (*AB*q, J_{AB} = 4 Hz, δ_{AB} = 6 Hz, 2H, 3,4-H on the thiophene) ppm; IR: 3400, 3170 (NH), and 1670 (amide and bromoacetyl) cm^{-1}.

Anal.—Calc. for $C_7H_6BrNO_2S$: C, 33.87; H, 2.42; N, 5.65; S, 12.90. Found: C, 33.68; H, 2.40; N, 5.75; S, 12.70.

2-Mercapto-4-(5'-carbamoyl-2'-thienyl)thiazole (IV)—To a solution of 15.6 g (0.138 mole) of ammonium dithiocarbamate in 145 ml of methanol was added 26.2 g (0.106 mole) of III in 260 ml of dimethylformamide, dropwise, under 5°. The resulting mixture was stirred at room temperature for 3 hr and heated under reflux for a further 2 hr. Water, 150 ml, was added and the mixture was cooled at 0° overnight.

The precipitate was collected by suction filtration, washed with water, and dried, yielding 19.6 g (76.7%), mp 263–265° dec. (dimethylformamide–water); NMR: 7.30 (s, 1H, 5-H on the thiazole) and 7.68 (*AB*q, J_{AB} = 4 Hz, δ_{AB} = 5 Hz, 2H, 3,4-H on the thiophene) ppm; IR: 3400 (NH) and 1630 (amide) cm^{-1}.

Anal.—Calc. for $C_8H_6NOS_3$: C, 39.67; H, 2.48; N, 11.57; S, 39.67. Found: C, 39.75; H, 2.50; N, 11.75; S, 39.38.

2-(3'-tert-Butylamino-2'-hydroxypropylthio)-4-(5'-carbamoyl-2'-thienyl)thiazole (V)—To a solution of 3.2 g (0.0132 mole) of IV in 20 ml of 0.3% aqueous sodium hydroxide was added 1.26 g (0.008 mole) of 1-chloro-3-*tert*-butylaminopropanol hydrochloride (5) in 20 ml of methanol while the temperature was maintained at 20°. The reaction solution was stirred at room temperature for 4 hr and then condensed to half *in vacuo*. The residual solution was mixed with 100 ml of water and extracted with chloroform.

The chloroform extract was washed with water, dried, and evaporated *in vacuo* to give a residue, 4.8 g. This residue was recrystallized from chloroform–light petroleum ether to yield 4.0 g (74.3%) of V as needles, mp 148–149°; IR: 3350, 3320, 3200 (OH, NH), and 1650 (amide) cm^{-1}.

Anal.—Calc. for $C_{15}H_{21}N_3O_2S_3$: C, 48.52; H, 5.66; N, 11.32; S, 25.88. Found: C, 48.31; H, 5.42; N, 11.15; S, 25.00.

Treatment of this material with concentrated hydrochloric acid (aqueous) in methanol and subsequent recrystallization from methanol–water (1:1) provided its hydrochloride (VI) in an 80% yield, mp 234–235.5° dec.; NMR: 1.35 (s, 9H, *tert*-butyl), 3.20 (m, 2H), 3.52 (m, 3H), 4.25 (m, 1H), 7.70 (*AB*q, J_{AB} = 8 Hz, δ_{AB} = 8 Hz, 2H, 3,4-H on the thiophene), and 8.00 (s, 1H, 5-H on the thiazole) ppm.

Anal.—Calc. for $C_{15}H_{21}N_3O_2S_3 \cdot HCl$: C, 44.12; H, 5.39; N, 10.29; S, 23.53. Found: C, 43.87; H, 5.37; N, 10.26; S, 23.24.

Biological Evaluation—For the estimation of β-blocking activities of VI and propranolol, *in vivo* studies were carried out in pentobarbital-anesthetized, bilaterally vagotomized, open chest dogs. Doses of 0.3 μg of isoproterenol/kg were given; responses on heart rate, cardiac contractile force, and arterial blood pressure were recorded. Compound VI or propranolol was intravenously administered at 15-min intervals in increasing doses. Isoproterenol was injected 5 min after a dose of the blocking agents, and the sequence was continued until nearly total suppression of the cardiovascular effects of isoproterenol was achieved.

The oral β-blocking activities of VI and propranolol were examined in conscious beagle dogs. The ECG and heart rate were recorded from needle electrodes inserted through the skin of limbs. Dogs fasted for 24 hr were dosed orally with either VI (0.1 or 0.5 mg/kg) or propranolol (0.5 or 2.5 mg/kg). Each dose of a blocking agent, with lactose and starch (1:1) as the vehicle, was administered in a gelatin capsule. Intravenous isoproterenol (0.3 or 0.5 μg/kg) challenges were repeated at 20- or 40-min intervals for 3 hr, and all experiments were terminated 24 hr after oral dosing.

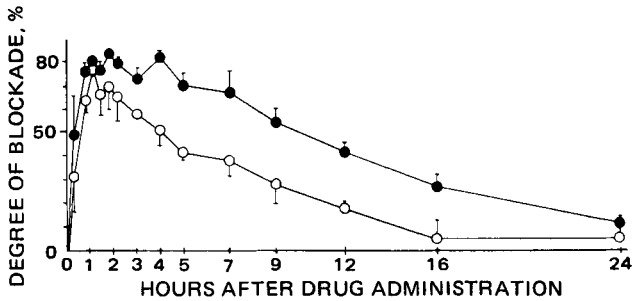

Figure 1—*Time–effect curves for β-adrenergic blocking activity of VI and propranolol, given orally, on the positive chronotropic responses to 0.3 μg of isoproterenol/kg iv in conscious beagle dogs. Each point represents the mean value ± SE from three experiments. Key: ●, VI, 0.5 mg/kg; and ○, propranolol, 2.5 mg/kg.*

RESULTS AND DISCUSSION

The β-blocking activities of VI and propranolol in the anesthetized dogs were evaluated following cumulative intravenous administration (0.3–10 and 10–300 μg/kg, respectively). Dose–response curves for VI for inhibition of the isoproterenol challenge were parallel to those for propranolol. Both drugs showed similar antagonistic effect on the chronotropic, inotropic, and depressor responses of isoproterenol, but the effect of VI was more potent than that of propranolol.

The following estimates of intravenous ED_{50} values were obtained for VI and propranolol: 3.1 and 40.5 μg/kg against the chronotropic response to 0.3 μg of isoproterenol/kg, 2.9 and 41.5 μg/kg against the inotropic response, and 2.5 and 24.0 μg/kg against the depressor response, respectively. Thus, VI appears to be 9–14 times as potent as propranolol. In conscious beagle dogs, VI or propranolol antagonized the tachycardia produced by repeated intravenous injection of isoproterenol. Typical results are shown in Fig. 1. Compound VI was about five times as potent as propranolol in this test, with maximal action after 1 hr. The duration of the β-blockade after VI was significantly longer than after propranolol.

Compound VI blocks the explored classical responses associated with β-adrenergic stimulation, *i.e.*, isoproterenol-induced cardiac stimulation and vascular relaxation. Thus, VI, like propranolol, is a β-adrenergic blocking agent with no special selectivity for a particular type of β-receptor (6). However, VI possesses no intrinsic sympathomimetic activity, as indicated by tachycardia in reserpinized rats, and does not show membrane-stabilizing properties such as local anesthetic and antiarrhythmic activities[3]. The LD_{50} values of VI in mice were 86 mg/kg iv, more than 360 mg/kg ip, and more than 5000 mg/kg po; the propranolol values were 23, 120, and 320–420 mg/kg, respectively. Thus, VI is one of the most specific β-adrenergic blocking agents with low toxicity and the least other pharmacological activities.

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