## Selective β-Adrenergic Myocardial Stimulant

Various 1-amino-2-propanols substituted at the 3-position with naphthoxy or phenoxy groups produce blockade of cardiac and smooth muscle β-sympathetic effects[1]. Some of these also produce β-stimulant effects[2]. Recently, selective β-agonistic blocking agents were found. Butoxamine only blocks β-sympathetic smooth muscle and metabolic effects[3]; practolol (ICI-50,17 2) produces a cardioselective blockade[4].

This communication describes the synthesis and some pharmacological properties of (±)-1-isopropylamino-3-(2-thiazoloxy)-2-propanol HCl (VIb, Figure 3), abbreviated ITP, which, unlike the aforementioned agents, is a selective myocardial β-stimulant.

*Methods.* 14 open chest pentobarbital anesthetized mongrel dogs of either sex were used. Femoral arterial blood pressure was measured from an indwelling catheter and transducer. Myocardial force was measured with a strain gauge[5] on the right ventricle and heart rate was recorded by a tachometer.

*Results and discussion.* As little as 0.1 mg/kg of ITP i.v. produced a marked increase in heart rate and force (Figure 1). Unlike isoproterenol, which is short acting,

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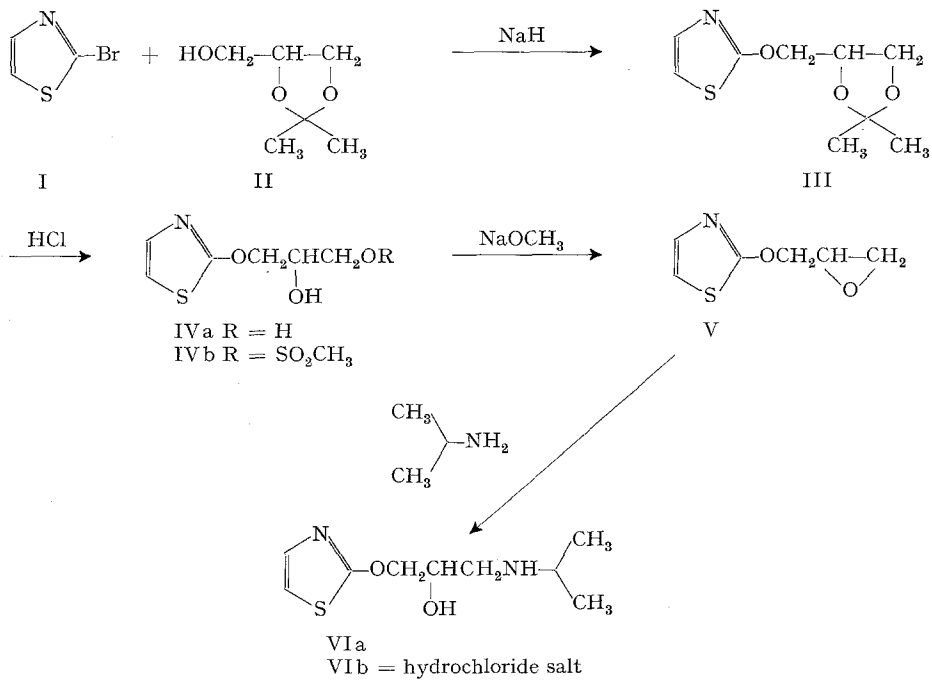
Figure 3



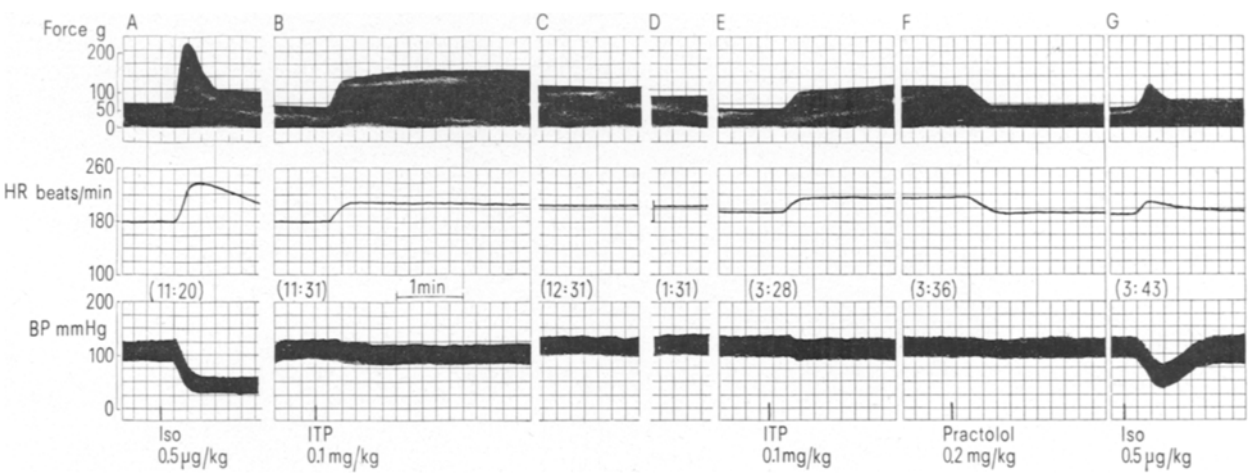




Fig. 1. Responses of the pentobarbital-anesthetized dog's blood pressure (BP), heart rate (HR) and force of myocardial contraction (Force) to i.v. isoproterenol (Iso), ITP and practolol. Calibration of blood pressure in mm Hg, force in grams tension and heart rate in beats/min. The speed of recording was 2.5 cm/min. Panels shown are exerpts from a single day's experiment. Actual time of compound injection is indicated between bottom two recordings.

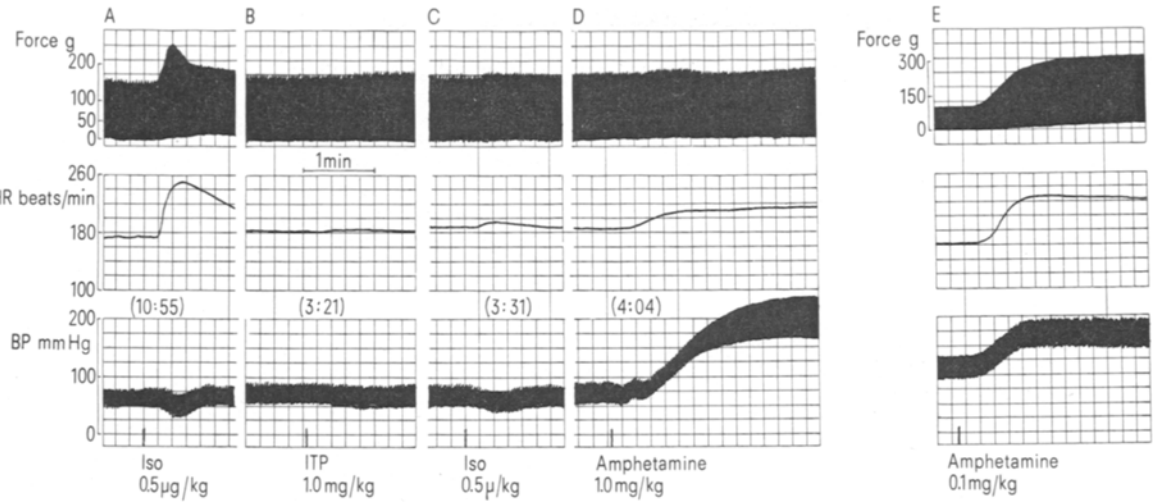



Fig. 2. Legend as in Figure 1. Panels A through D are excerpts from one day's experiment. Panel E was taken from a different study. Note that force calibrations are different in these two studies. A cumulative total of 0.31 mg/kg ITP was given i.v. between A and B.

ITP effects persisted for 2 to 3 h (Figure 1C and D). Depressor responses were absent or minimal at low myocardial stimulant dose levels (compare Figure 1A with B) but were evident at higher dose levels.

We find this absence of blood pressure alteration by ITP difficult to explain. The $\beta$-agonistic vascular action of ITP must be absent or minimal and thus, largely restricted to the heart. However, ITP increases in cardiac force, rate and output should cause a pressor response if peripheral resistance was unaltered. If ITP produced some peripheral vasodilatation which exactly counterbalanced cardiac output, administration of a cardioselective $\beta$-blocker, viz., practolol, should inhibit cardiac responses and unmask any obscured ITP vasodilator effect. Practolol (0.2 mg/kg, i.v.) superimposed upon an on-going ITP response due to 0.1 mg/kg induced a blockade of the ITP increase in heart rate and force but no vasodilatation was seen (Figure 1F), even though isoproterenol (0.5 µg/kg, i.v.) depressor responses persisted (Figure 1G).

ITP appeared to produce tachyphylaxis (compare Figure 1B with E). To examine this further, i.v. doses of ITP, viz., 10, 20, 40, 80, 160 and 1000 µg/kg, were given to 3 dogs, spaced at 30 min intervals. All cardiovascular responses diminished after the first or second dose. Figure 2B indicates the final 1 mg/kg dose of ITP. Administration of 1 mg/kg, i.v., of amphetamine caused an unusually small heart force and rate response while a marked pressor response persisted (Figure 2D). In Figure 2E, 0.1 mg/kg of amphetamine in an untreated animal caused a pronounced increase in heart rate and force but a less intense pressor response.

Such tachyphylaxis to ITP and cross tachyphylaxis with amphetamine may be explained in several ways. It is possible that ITP acts indirectly like amphetamine or tyramine by causing a release and/or by inhibiting a reuptake of sympathomimetic amines[6]. We find difficulty with this contention because a) ITP would have to cause a sustained release; b) the release would have to occur specifically in the myocardium and not peripherally.

Large doses of ITP inhibit all of the effects of isoproterenol (Figure 2, A and C), but little inhibition occurs with lower doses. Thus, ITP tachyphylaxis could also be explained on the basis of a self imposed $\beta$-blockade. To clarify the pharmacological actions of ITP, further studies are being carried out.

The synthesis of ITP is outlined in the formulae. Reaction of 2-bromothiazole (I)[7] with the sodium alkoxide of glycerol acetonide (II) in monoglyme at reflux furnished the ether (III)[8] [bp 95–100° (0.3 mm); $n_D^{25}$ 1·4966; $\lambda_{max}$ 235 nm (log $\varepsilon$ 3.73)]. Brief exposure of (III) to aqueous 0.1% HCl afforded the diol (IVa) [$n_D^{25}$ 1·5470; $\lambda_{max}$ 236 nm (log $\varepsilon$ 3.71)] which was converted into the mesylate (IVb) by treatment with 1·2 equiv. of methanesulfonyl chloride in pyridine (5 °C). After 30 min the resulting mixture was diluted with dry ether and treated directly with an excess of solid sodium methoxide to give the epoxide (V) [ca. 75–80° (0.05 mm); $n_D^{25}$ 1·5254; $\lambda_{max}$ 235 nm (log $\varepsilon$ 3.71)][9].

Reaction of (V) with an excess of isopropylamine in ethanol solution yielded the liquid (±)-1-isopropylamino-3-(2-thiazoloxy)-2-propanol (VIa) which was transformed into the crystalline hydrochloride salt (VIb) (ITP) upon exposure to dry HCl gas in ether [mp 162–163°; $\lambda_{max}$ 235 nm (log $\varepsilon$ 3.71)][10].

*Zusammenfassung.* ITP, dessen Synthese beschrieben wird, erwies sich am Hunde als ein starkes, kardiales $\beta$-Stimulans. Da auch nach myokardialer $\beta$-Blockade mit Practolol der Blutdruck durch ITP nicht wesentlich gesenkt wurde, kann es als herzspezifisch angesehen werden.

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[8] Satisfactory elemental analyses and/or mass spectra were obtained for all fully characterized compounds. IR- and NMR-spectra were also consistent with the assigned structures.

[9] We wish to thank Imperial Chemicals, Ltd., for a sample of practolol.

[10] This paper represents contribution No. 404 from the Syntex Institute of Organic Chemistry.