Maximal responses and pD_2-values of noradrenaline and histamine on the mesenteric artery of the rabbit.

	25 °C		42 °C	
	Control	Prindolol (100 n*M*)	Control	Prindolol (100 n*M*)
Noradrenaline				
Maximal responses (mg)	2096.4 ± 461.0 (9)	2040.1 ± 300.0 (9)	2939.9 ± 656.0 (10)	2857.6 ± 520.3 (10)
pD_2-values	6.54 ± 0.13 (9)	6.72 ± 0.08 (9)	6.42 ± 0.07 (10)	6.40 ± 0.08 (10)
Histamine				
Maximal responses (mg)	2950.0 ± 244.5 (9)	–	4565.3 ± 438.8[a] (7)	–
pD_2-values	5.29 ± 0.11 (9)	–	4.87 ± 0.11[a] (9)	–

Given are means ± SE, number of experiments in brackets. [a] $p < 0.02$ compared with 25 °C.

respectively. Noradrenaline (0.01–50 μM) and histamine (0.5–100 μM) elicited increasing contractile responses with cumulative administration of increasing doses and exerted maximal responses which were in all cases higher for histamine than for noradrenaline (Table). The elevation of temperature from 25° up to 42 °C did not significantly alter the maximal response for noradrenaline. Also the pD_2-value (negative logarithm of that molar concentration causing a half maximal effect) at 25° did not differ from that at 42 °C. On the other hand, the elevation of temperature enhanced significantly the maximal effect induced by histamine. At the same time, the pD_2-value for this amine at 42 °C decreased significantly. The β-adrenoceptor stimulant isoprenaline in concentrations up to 0.1 mM did not elicit any relaxing effect on strips from the mesenteric artery contracted by 10 μM histamine. In the presence of the β-adrenolytic drug prindolol (100 nM), the maximal contractile response to noradrenaline was not altered at all, either at 25° or at 42 °C (Table). If β-adrenoceptors were present in the mesenteric artery of the rabbit, it would be anticipated that their blockade would increase the contractile response to noradrenaline. Likewise the pD_2-value for noradrenaline after prindolol should be elevated by excluding the inhibitory effect of β-adrenoceptor stimulation. In fact, prindolol yielded no alteration of the pD_2-value for noradrenaline (Table). These observations imply that in the mesenteric artery of the rabbit β-adrenoceptors are lacking.

The results presented are consistent with observations on the rat aorta which describe the peak contractile responses to several drugs to be enhanced by elevation of temperature[4]. Histamine was found to have a higher ceiling effect than noradrenaline at both temperatures investigated. In addition, it was demonstrated that the pD_2-value of histamine decreased with increasing temperature, whereas that of noradrenaline remained unaffected. Although the effects of histamine on vascular smooth muscle are closely related to the adenyl cyclase system, whereas that of α-sympathomimetic drugs is not[5], it is still rather unsettled whether the receptor itself or the metabolic events following the stimulation of the receptor were affected by temperature. A comparison with the effects of catecholamines on β-adrenoceptors on this organ is impossible since the results presented demonstrate the absence of β-adrenoceptors on the mesenteric artery of the rabbit. Also the pulmonary artery of the guinea-pig does not contain β-adrenoceptors[6,7].

Summary. On the rabbit mesenteric artery, the elevation of temperature from 25° up to 42° diminished the affinity of histamine, whereas that of noradrenaline to the α-adrenoceptors remained unchanged. The presence of β-adrenoceptors could not be demonstrated.

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Bufuralol, a New β-Adrenoceptor Blocking Agent

The continuing search for drugs which will block β-adrenoceptors has led to the observation that compounds with an N-substituted ethanolamine or oxypropanolamine moiety attached to a heterocyclic or aryl nucleus can produce the desired pharmacological effect[1].

Consideration of the structural relationship between phenoxypropanolamines and oxygen-heterocyclic ethanolamines directed attention to a series of benzofuran-2-ethanolamines **1**. Structure-activity studies indicated that maximum β-adrenoceptor blocking potency was achieved with 7-alkyl or 7-alkenyl substituents, and with small branched alkyl substituents on the amino function. This led to the choice of 1-(7-ethylbenzofuran-2-yl)-2-*tert*-butylamino-1-hydroxyethane **2**, Ro 03-4787, bufuralol, for extended pharmacological, and eventually clinical, evaluation.

Bufuralol has been prepared by the following route. Treatment of 5-bromo-3-ethylsalicylaldehyde **3** in ethanolic sodium hydroxide solution with chloroacetone

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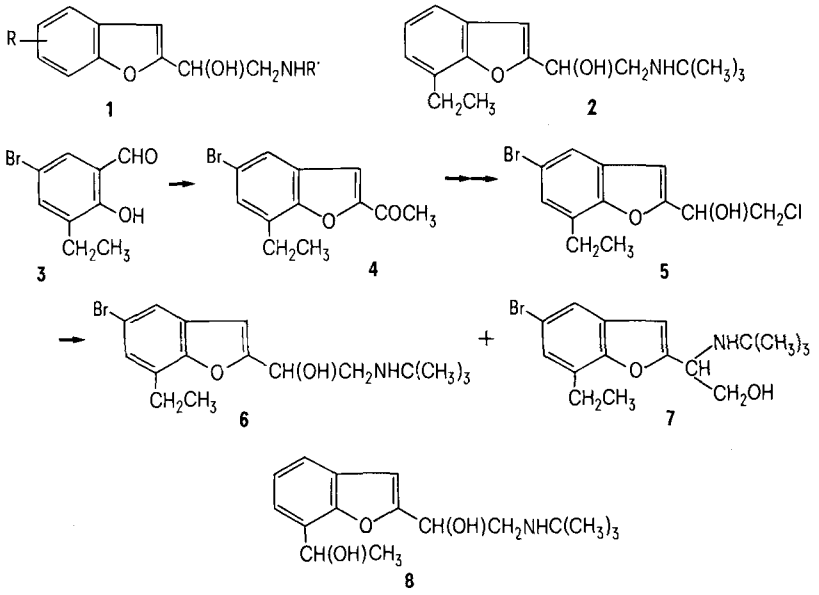
afforded methyl 5-bromo-7-ethylbenzofuranyl ketone **4**. Chlorination with sulphuryl chloride followed by reduction with sodium borohydride gave 1-(5-bromo-7-ethylbenzofuran-2-yl)-2-chloro-1-hydroxyethane **5**. Reaction with an excess of *tert*-butylamine led to the formation of the amino-alcohol **6**, separated from a small quantity of the isomeric primary ethanolamine **7** by fractional crystallization. Debromination was effected by catalytic hydrogenation over palladium/charcoal and the racemic alcohol **2** was isolated as the crystalline hydrochloride, antiarrhythmic activity, but is devoid of α-adrenoceptor blocking activity. Bufuralol antagonizes the catecholamine-induced release of free fatty acids from isolated fat cells and in the intact animal. It also blocks the activation of glycogen phosphorylase by catecholamines in rat diaphragm in vitro. and single doses of the drug cause raised glycogen levels in a number of tissues as a consequence of this action.

In man the biological half-life of bufuralol is 3 to 5 h. The principal metabolite after oral or i.v. administration



m.p. 149–150°, for which satisfactory microanalytical and spectroscopic data were obtained.

Bufuralol has been resolved into its optical isomers by fractional crystallization from ethanol of the diastereoisomeric salts formed with (+)- and (−)-di-*p*-toluoyl tartaric acid. β-Adrenoceptor blocking activity resides only in the laevorotatory form, [hydrochloride, m.p. 122–123°; $[\alpha]_{365}^{20} - 136.0°$ (c = 1, ethanol)], but local anaesthetic and antiarrhythmic properties are observed in both enantiomers.

Pharmacological studies in several species of experimental animals show that bufuralol exhibits non-selective β-adrenoceptor blocking properties similar to those of propranolol[2] and of comparable potency. These effects are exerted on the β-adrenoceptor stimulant actions of injected amines and of sympathetic nerve stimulation. However bufuralol, unlike propranolol, possesses some instrinsic sympathomimetic activity as indicated by tachycardia in reserpinized rats. Bufuralol shows membrane-stabilizing properties, such as local anaesthetic and is a monohydroxylated compound **8** which also possesses potent β-adrenoceptor blocking activity; this metabolite is present in both urine and plasma. Bufuralol is an active β-adrenoceptor blocking agent and antihypertensive in man.

Summary. The synthesis and biological properties of bufuralol, 1-(7-ethylbenzofuran-2-yl)-2-*tert*-butylamino-1-hydroxy-ethane, a new, non-selective β-adrenoceptor blocking agent, are described.

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The Influence of Pigmentation of Rats and Guinea-Pigs on the Ototoxicity of Kanamycin and Neomycin

Numerous studies have shown a variety of substances, particularly the aminoglycoside antibiotics, to be toxic to the inner ear. The rate and extent of accumulation of these compounds in inner ear fluids (endolymph and perilymph) have been studied in guinea-pigs[1,2] and evidence has been provided that this is due to their affinity for melanin pigment which is present, in the cochlea, mainly in the stria vascularis – one of the sites where endolymph is thought to be produced[3]. In vitro studies showed that kanamycin had a very high affinity for melanin and by

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