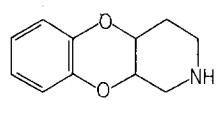
A New Cardioselective β-Adrenoceptor Blocking Agent

During the last few years we have sought β-adrenoceptor blocking agents with cardioselective properties which would be of value clinically in the management of angina pectoris and cardiac arrhythmias whilst having a low tendency to increase bronchospasm and contributing to the control of arrhythmia. We first examined the possibility of conferring selectivity on conventional β-blocking agents by incorporating the usual hydroxyisopropyl-amino-propoxy side-chain into heterocyclic systems such as hexahydropyrido-benzodioxans **1**,[1] benzoxazepines **2**[2] or benzoxazocines **3**[3]. Extension of this work led us to prepare a series of oximes of general structure **4** in which vascular or cardiac specificity could be enhanced by appropriate substituents. We now wish to report that a ketone derived from this series, RS-1-(2-acetyl-4-n-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride **5** (M&B 17803A), possesses marked cardioselective β-adrenoceptor blocking properties.



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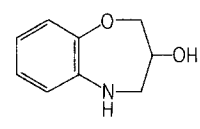

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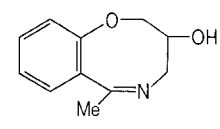

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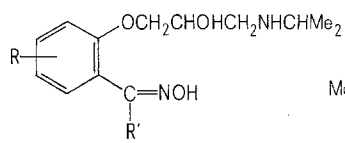

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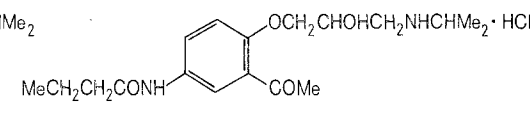
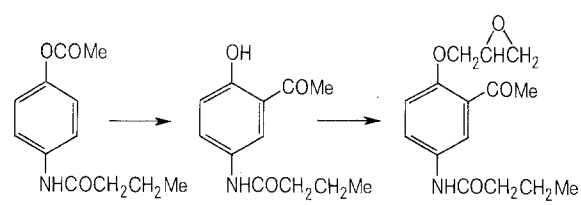


5 M&B 17803A



6 **7** **8**

→ **5**

The compound has been prepared by the following route. Fries rearrangement of 4-*n*-butyramidophenyl acetate **6** to 2-acetyl-4-*n*-butyramidophenol **7** followed by treatment with epichlorhydrin afforded the epoxide **8**. Treatment with isopropylamine gave RS-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane, m.p. 129–130°. The hydrochloride, M&B 17803A, has m.p. 143–144°; analysis for $C_{18}H_{28}N_2O_4$·HCL· Calculated: C, 58.0; H, 7.8; N, 7.5: Found: C, 57.9; H, 7.9; N, 7.2%, γ_{max}^{EtOH} 236 nm (log = 4.39), 332 nm (log = 3.40).

Pharmacological studies in experimental animals[4,5] indicate that M&B 17803 A is a cardioselective β-adrenoceptor blocking agent with potency comparable to that of practolol. It differs from the latter drug and resembles propranolol in possessing significant local anaesthetic properties and in increasing the refractory period of isolated rabbit atria. M&B 17803A is an active β-adrenoceptor blocking agent in man[6,7].

Full reports of the chemistry and pharmacology of this compound and its analogues will be presented later.

Zusammenfassung. Es wird die Synthese des cardiospezifisch β-adrenozeptorblockierenden (RS-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-oxy-3-isopropylaminopropan hydrochlorids beschrieben.

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