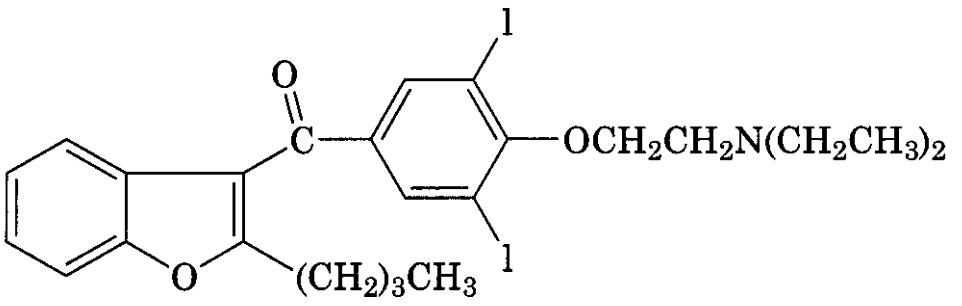
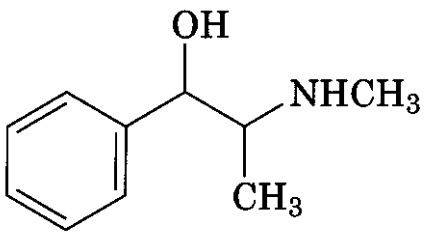


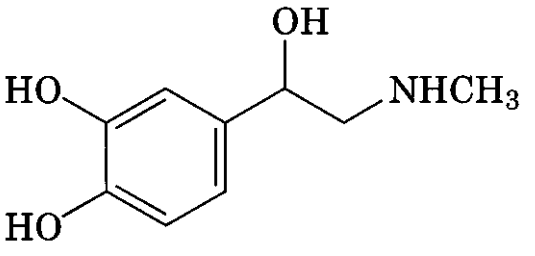
(145) amiodarone

fever for thousands of years. The extract is prepared from several species of ***Ephedra,*** a small leafless shrub found in China. Following experiments at the Peking Union Medical College and then at the University of Pennsylvania and the Mayo Clinic in the United States, the active ingredient, ephedrine (**146**), was introduced into Western medicine in 1926 as an orally active bronchodilator for the treatment of acute asthma (190,191).

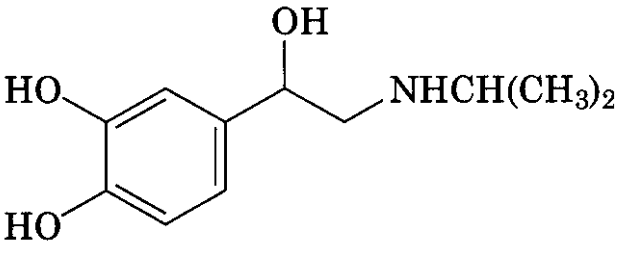


(146)

Ephedrine is related to another natural product that has been used to treat asthma, that is, the adrenal hormone adrenaline (147) (epinephrine). Adrenaline is a potent agonist of both α- and β-adrenoceptors and thus produces arterial hypertension as an undesirable side effect. In 1951 a synthetic alternative, isoprenaline (**148**), was introduced and for almost 20 years it was considered the drug of choice for treating bronchospasm associated with acute asthmatic attack (191). Isoprenaline is a specific β-adrenoceptor agonist and, although it has no vasoconstrictor activity, the compound does have marked cardiac stimulant properties and a short duration of action. Ahlquist's concept (192) of two types of adrenoceptor was developed further by Lands et al. (193), who established the existence of β_1- and β_2-adrenoceptor subtypes. Clear structure-activity relationships emerged with the preparation of compounds related to adrenaline and ephedrine; the basic requirement for β-adrenoceptor agonist activity was an aromatic ring substituted by an ethanolamine side-chain. The branched methyl substituent on the side-chain was associated with prolonged duration of action (i.e., ephedrine), whereas aromatic hydroxylation (in isoprenaline) prevented penetration across the blood–brain barrier and thus prevented stimulation of the CNS (191). However, 1,2-dihydroxy substituents were found to promote enzymic degradation, and replacement of the 3-hydroxy group by a hydroxymethyl substituent was required to extend the duration of action. In 1969 salbutamol (149) was launched by Glaxo as a longer-lasting, selective &-adrenoceptor agonist for the treatment of bronchial asthma (194) and, recently, a lipophilic ether analog, salmeterol (**150**), was introduced with an even longer duration of action that has potential advantage in the prevention of nocturnal asthma.



(147)



(148)

Despite the many chemical alterations that have been carried out on the phenylethanolamine "template," the key chemical features associated with modern β-agonists can be seen