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THE OPTICAL RESOLUTION OF (±)-GALANTHAMINE

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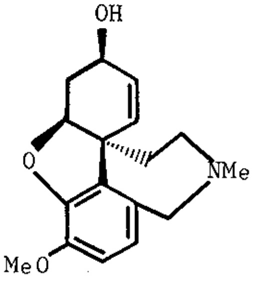
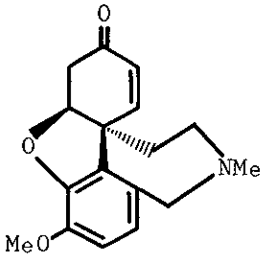
(±)-Galanthamine has been resolved using optically active di-p-toluoyltartaric acid.

The Amaryllidaceae alkaloid, galanthamine (1)[1,2] has long been of considerable interest because of the pharmacological activity that it exhibits. Both the racemic (±)- and naturally occurring (-)-forms show analgesic activity comparable to that of morphine.[3] (-)-Galanthamine is said to possess valuable applications in Soviet medicine.[4] The alkaloid has therefore been the subject of numerous synthetic investigations.[3-7] We were interested in achieving the optical resolution of (±)-galanthamine in order to be able to test the pharmacological activity of the (+)-form. It is well known that quite often optical isomers possess different activity.

Barton and Kirby[4] have previously reported that they were unable to resolve either (±)-galanthamine (1) or (±)-narwedine (2) by using standard methods of resolution. Optical resolution of (±)-narwedine was achieved however in a novel manner by crystallisation of (±)-narwedine in the presence of (-)-galanthamine.[4]



(1)



(2)

We report here the successful resolution of (±)-galanthamine using the optically active forms of di-p-toluoyltartaric acid in methanol solution. (2R : 3R)-2'-Nitrotartranilic acid[8] was also tried but gave negative results. Optical resolution of (±)-galanthamine (1), m.p. 123 - 124°, obtained according to our method by phenolic oxidation,[5] was carried out as follows.

(±)-Galanthamine (50 mg) in methanol (0.2 ml) was treated with a solution of di-p-toluoyl-(+)-tartaric acid (68 mg) in methanol (0.4 ml). The solution was then concentrated and allowed to crystallise to give (+)-galanthamine di-p-toluoyl-(+)-tartrate (45 mg), m.p. 193 - 194.5° (from methanol). This salt was converted into the free base by treatment with dilute ammonia in chloroform, which readily crystallised from ether to give (+)-galanthamine (14 mg), m.p. 133 - 135°, $[\alpha]_D^{18}$ + 126.1° (c = 0.083, EtOH), showing the same i.r. (KBr disk) spectrum with that of natural galanthamine.

The mother liquor which was obtained from the crystallisation was basified to give the free base (26 mg). This was treated with di-p-toluoyl-(-)-tartaric acid (35 mg), and the resulting salt (m.p. 185 - 186°) was decomposed with dilute ammonia as above to afford (-)-galanthamine (6 mg), m.p. 133 - 134°, $[\alpha]_D^{16.5}$ - 132° (c = 0.083, EtOH), which was identical with natural galanthamine in i.r. (KBr disk) spectral comparisons and mixed melting point test.

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