Synthesis of 2-Substituted Benzthiazoles as Tetramisole Analogs

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A number of 2-substituted benzthiazoles (3-11) have been synthesized as analogs of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole (tetramisole). All the compounds were tested against two intestinal nematodes in rats and hamsters but none showed any noteworthy activity.

(Keywords: 6-(2-Benzthiazolyl)imidazo[2,1-b]thiazoles; Tetramisole analogs)

Introduction

Among the several modern anthelmintics, 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole (tetramisole)² has been studied in greater detail because of its broad spectrum anthelmintic activity³. A large number of structural congeners of tetramisole have been synthesized⁴⁻¹⁰ in search of its more potent analogs. However, attempts to synthesize 2,3,5,6-tetrahydroimidazo[2,1-b]thiazoles carrying versatile benzthiazole pharmacophore is lacking. The present communication describes the synthesis of a number of 2-substituted benzthiazoles (3-11) as tetramisole analogs; their preliminary anthelmintic testing results are also reported.

Results and Discussion

The key intermediate, 2-bromoacetyl benzthiazole (2), was prepared by bromination of 2-acetylbenzthiazole (1).¹¹ Treatment of 2 with 2-aminothiazole resulted in the formation of 6-(2-benzthiazolyl)-imi-
dazo[2,1—b]thiazole (3). A similar reaction of 2 with 2-aminothiazoline yielded the required 2-[(2-imino-3-thiazolinyl)acetyl]benzthiazole hydrobromide (4). Acetylation of 4 using acetic anhydride did not afford the required N-acetyl derivative 5, instead the diacetyl derivative 1-acetoxyl-1-(2-benzthiazolyl)-2-(2-acetylimino-3-thiazolidinyl)ethylene (6) was obtained. Attempts to liberate the free base of 4 using triethylamine induced the facile intramolecular cyclisation to yield 6-(2-benzthiazolyl)-6-hydroxy-2,3,5,6-tetrahydroimidazo[2,1—b]thiazole (7) which was smoothly dehydrated by sulphuric acid to 6-(2-benzthiazolyl)-2,3-dihydroimidazo[2,1—b]thiazole (8). Treatment of compounds, obtained by replacing the benzthiazole by phenyl or furanyl residues, with triethylamine gave the corresponding free bases and no cyclic carbinols corresponding to 7 could be isolated. These free bases were easily cyclised on heating to the respective 6-phenyl/furanyl-2,3-dihydroimidazo[2,1—b]thiazoles.

Reduction of 4 with sodium borohydride yielded the desired carbinol, 1-(2-benzthiazolyl)-1-hydroxy-2-(2-imino-3-thiazolidinyl)ethane (9). Attempts to cyclise 9 in presence of polyphosphoric acid (PPA) did not give the expected 6-(2-benzthiazolyl)-2,3,5,6-tetrahydroimidazo[2,1—b]thiazole (11), instead 9 underwent preferential dehydration to afford 1-(2-benzthiazolyl)-2-(2-imino-3-thiazolidinyl)ethylene (10). The product was found to be exclusively the E-isomer as evident from its NMR spectrum. However, 11 was conveniently prepared by treating 9 with thionyl chloride.

All the compounds were tested against Nippostrongylus brasiliensis in rats and Ancylostoma ceylanicum in hamsters at a dose of 250 mg/kg given for three days but none of the compounds showed any noteworthy activity.

**Experimental**

The structure of all the compounds, was checked by IR on Perkin-Elmer 157 and 177 spectrophotometers and the data are given in cm⁻¹. The NMR spectra were recorded on Varian A-60D (60 Hz) spectrometer using TMS as internal reference and the chemical shifts are expressed in δ values. Mass spectra were taken on a Jeol JMS D-300 instrument. The purity of all the compounds was checked on silica gel G plates and the spots were located by iodine vapours or KMnO₄ spray. Melting points were taken in sulphuric acid bath and are uncorrected.

6-(2-Benzthiazolyl)imidazo[2,1—b]thiazole (3)

A solution of 2 (2.56 g, 0.01 mol) and 2-aminothiazole (1.0 g, 0.01 mol) in dry DMF (20 ml) was refluxed for 6 h. The reaction mixture was cooled and the contents poured into water. The product separated was filtered and washed successively with chloroform and methanol; yield 1.6 g (60%), m.p. > 260 °C. MS: m/e 257 (M+).