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Synthesis of 2-Substituted Benzthiazoles as Tetramisole Analogs[1]

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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)

Synthese 2-substituierter Benzthiazole als Tetramisol-Analoge

Es wurde eine Reihe 2-substituierter Benzthiazole (**3**—**11**) als Analoge des 6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1—b]thiazols (Tetramisol) synthetisiert. Alle dargestellten Verbindungen wurden auf ihre anthelmintische Wirkung überprüft, wobei allerdings keine nennenswerte Aktivität festzustellen war.

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 activity[3]. A large number of structural congeners of tetramisole have been synthesized[4–10] 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-

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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-acetyloxy-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[12], 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[12].

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-benthiazolyl)-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 $KMnO_4$ spray. Melting points were taken in sulphuric acid bath and are uncorrected.

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

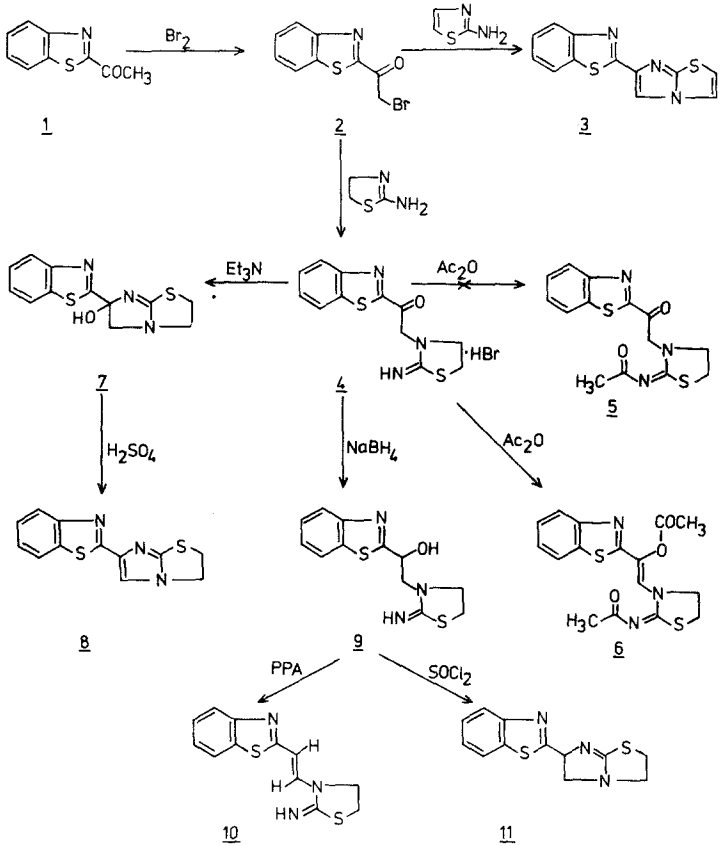
A solution of **2** (2.56 g, 0.01 mol) and 2-aminothiazole (1.0 g, 0.01 mol) in dry *DMF* (20 ml) was refluxed for 6 h. The reaction mixture was cooled and the contents poured into water. The product separated was filtered and washed successively with cloroform and methanol; yield 1.6 g (60%), m.p. >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

MS: *m/e* 257 (M^+).

2-[(2-Imino-3-thiazolidinyl)acetyl]benzothiazole hydrobromide (**4**)

A solution of 2-aminothiazoline (1.0 g, 0.01 mol) in dry benzene (10 ml) was added dropwise to a stirred solution of 2-bromoacetylbenzthiazole (2.56 g, 0.01 mol) in dry benzene (25 ml). After the addition was over, the reaction mixture was further stirred for 4 h and then refluxed for $^1/_2$ h. After cooling the reaction mixture, the product was filtered and washed thoroughly with benzene and ether; yield 2.6 g (72%), m. p. > 260 °C.

IR (KBr): 3 210 (NH), 1 700 (CO), 1 642 (C=N).



1-Acetyloxy-1-(2-benzthiazolyl)-2-(2-acetylimino-3-thiazolidinyl)ethylene (**6**)

A mixture of **4** (3.58 g, 0.01 mol), acetic anhydride (5 ml) and pyridine (20 ml) was stirred at room temperature for 12 h. Solvent was removed from the reaction mixture and the residue washed with water thoroughly. The solid, thus obtained, was crystallised from alcohol, yield 1.8 g (50%), m. p. 178 °C.

IR (KBr): 1765 ($OCOCH_3$), 1710 ($N—COCH_3$), 1645 (C=N), 1625 (C=C).

NMR ($CDCl_3$): 8.10 (s, 1H, N—CH=C), 7.9-7.6 (m, 2H, H-4 and H-7 of benzthiazole), 7.4-7.05 (m, 2H, H-5 and H-6 of benzthiazole), 3.95 (t, 2H, SCH_2), 3.1 (t, 2H, $N—CH_2$), 2.25 (s, 3H, $OCOCH_3$), 2.2 (s, 3H, $NCOCH_3$).

MS: *m/e* 361 (M^+).

$C_{16}H_{15}N_3O_3S_2$. Calc. C 53.19, H 4.15, N 11.63.
Found. C 53.09, H 4.10, N 11.52.

6-(2-Benzthiazolyl)-6-hydroxy-2,3,5,6-tetrahydroimidazo[2,1—b]thiazole (**7**)

A suspension of **4** (3.58 g, 0.01 mol) and triethylamine (2.9 ml, 0.02 mol) in chloroform (30 ml) was stirred at room temperature for 8 h. The separated solid was filtered and washed with chloroform. The product weighed 1.8 g. The filtrate was washed with water (2 × 5 ml), the organic phase dried (Na_2SO_4) and concentrated to get additional amount of **7** which weighted 0.3 g. Total yield 2.1 g (80%), m.p. 170 °C.

IR (KBr): 3600-3300 (OH).

MS: *m/e* 277 (M^+).

$C_{12}H_{11}N_3OS_2$. Calcd. C 51.98, H 3.97, N 16.60.
Found. C 51.85, H 4.34, N 16.42.

6-(2-Benzthiazolyl)-2,3-dihydroimidazo[2,1—b]thiazole (**8**)

A solution of **7** (2.77 g, 0.01 mol) and conc. H_2SO_4 (10 ml) was kept at room temperature for 4 h and then the reaction mixture was poured onto crushed ice in a beaker. The reaction mixture was basified with ammonia to *pH* 8 and the separated solid filtered, washed successively with acetone and methanol; yield 1.8 g (70%), m.p. > 280 °C.

IR (KBr): 1600 (aromatic, C=C), 1580 (C=N).

MS: *m/e* 259 (M^+).

1-(2-Benzthiazolyl)-1-hydroxy-2-(2-imino-3-thiazolidinyl)ethane (**9**)

Sodium borohydride (5.0 g, 0.05 mol) was added in portions to a stirred mixture of **4** (5.37 g, 0.015 mol) and methanol (150 ml) at 0 °C. After the addition was complete, the reaction mixture was stirred for 2 h at room temperature. The solvent was removed from the reaction mixture *in vacuo* and the residue treated with water (50 ml). The product was filtered and washed with ether; yield 3.7 g (79%), m.p. 126 °C.

IR (KBr): 3500-3300 (OH and NH), 1585 (C=N).

NMR ($CDCl_3$): 7.95-7.65 (m, 2H, H-4 and H-7 of benzthiazole), 7.52-7.18 (m, 2H, H-5 and H-6 of benzthiazole), 5.32-5.12 (dd, 1H, HOC—**H**), 4.1-2.85 (m, 6H, $CH_2NCH_2CH_2S$).

MS: *m/e* 279 (M^+).

1-(2-Benzthiazolyl)-2-(2-imino-3-thiazolidinyl)ethylene (**10**)

A mixture of **9** (1.4 g, 0.005 mol) and polyphosphoric acid (5 g) was heated at 120-130 °C for 18 h. The reaction mixture was poured into water and basified with aqueous ammonia to *pH* 8. The residue, thus separated, was filtered and crystallised from chloroform, yield 0.3 g (23%), m.p. 188 °C.

IR (KBr): 3300 (NH), 1630 (C=C).

NMR ($CDCl_3$ + *DMSO-d*$_6$): 8.06 (d, 1H, **H**C=CH—N, J = 15 Hz), 7.78-7.52 (m, 2H, H-4 and H-7 of benzthiazole), 7.36-7.02 (m, 2H, H-5 and H-6

of benzthiazole), 5.93 (d, 1 H, CH=C**H**—N, J = 14.5 Hz), 4.0-3.66 (m, 2 H, S**C**$\mathbf{H}_2$CH$_2$), 3.40-3.05 (m, 2 H, SCH$_2$C$\mathbf{H}_2$N).

$C_{12}H_{11}N_3S_2$. Calcd. C 50.64, H 4.64, N 17.72.
Found. C 50.41, H 4.42, N 17.60.

6-(2-Benzthiazolyl)-2,3,5,6-tetrahydroimidazo[2,1—b]thiazole (**11**)

A solution of thionylchloride (0.6 g, 0.005 mol) in dry chloroform (5 ml) was added dropwise to a stirred solution of **9** (1.12 g, 0.004 mol) in dry chloroform (20 ml) at 0 °C. After the addition was over, the reaction mixture was stirred for 24 h at room temperature and then refluxed for 2 h. The solvent was removed from the reaction mixture *in vacuo*. The residue was washed with ether and treated with 2*N*-Na_2CO_3 (10 ml). The separated solid was filtered and washed successively with ether and methanol. It weighed 0.42 g. The aqueous phase was extracted with ethyl acetate (5 × 25 ml). The combined extracts were dried (Na_2SO_4), solvent removed *in vacuo* and the residue chromatographed over a silica gel column using chloroform as eluant. The compound obtained after column chromatography weighed 0.13 g. Total yield 0.55 g (5%), m. p. 298 °C (d).

IR (KBr): 1600 (aromatic C=C), 1580 (C=N).

MS: m/e 261 (M^+), base peak 259.

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