A New Route to 6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole, A Broad Spectrum Anthelmintic

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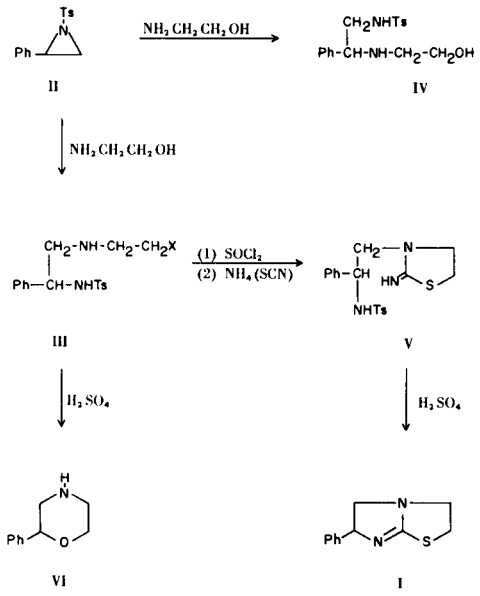
During the search for a more economical route to the broad spectrum anthelmintic, 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (I) (2), the use of styrene as a possible starting material was investigated. Previous syntheses have involved the use of phenacyl bromide and 2-aminothiazoline (3) and more recently, styrene oxide and ethyleneimine (4), as starting reagents. The formation of 1-arylsulphonylaziridines in high yield from olefins has been described by two of us (5). Utilizing this reaction, 2-phenyl-1-(*p*-toluenesulphonyl)aziridine (II) can be generated *in situ* by reacting styrene with *N,N*-dichloro-*p*-toluenesulphonamide in toluene solution, followed by treatment with ammonium hydroxide to remove the labile chlorine and then with sodium hydroxide solution to effect cyclization. The potential of this activated aziridine (II) as a building block for the synthesis of I forms the subject of this paper.

Reaction of 2-phenyl-1-(*p*-toluenesulphonyl)aziridine with ethanolamine gave a mixture of the isomeric amines (III, X = OH) and IV. The ratio of the products obtained was found to vary considerably with the solvent used. Aprotic solvents, in particular those containing the ether linkage, gave rise to predominantly the normal addition product (III, X = OH), whereas protic solvents such as 2-propanol favoured the abnormal addition product (IV). Optimum reaction conditions were obtained using dioxane as solvent, when 58% of (III, X = OH) was produced. Similar solvent effects have been reported by Parker & Rockett (6) for the reaction of styrene oxide with benzylamine. Excess ethanolamine to two equivalents, enhanced the rate of reaction but hardly effected the yield of the normal addition product. However, a vast excess of ethanolamine gave a very poor yield of III (X = OH).

The normal addition product was readily converted into the 2-iminothiazolidine (V) *via* the chloride (III, X = Cl), by treatment first with thionyl chloride and then with ammonium thiocyanate. An 85% overall yield of V was obtained. The 2-iminothiazolidine could also be produced by reacting the aziridine (II) with 2-aminothiazoline. The yield of the normal addition isomer (V) was favoured as in the case of the ethanolamine reaction by the employment of aprotic solvents, but the variation between different aprotic solvents was marginal, the preferred solvent, xylene, giving a 41% yield of V. Ring closure of the 2-iminothiazolidine was readily effected, utilising concentrated sulphuric acid at room temperature, to give the required 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole in 84% yield. Polyphosphoric acid also brought about this cyclization, but gave inferior results. Similar C-N fissions of sulphonamides rather than the normal N-S fissions in strong acid have been observed when it is possible to generate either a tertiary or a secondary aryl carbonium ion by such a fission (7). The ethanolamine (III, X = OH) also readily underwent an analogous cyclization in concentrated sulphuric acid to give 2-phenylmorpholine (VI) with expulsion of *p*-toluenesulphonamide.



EXPERIMENTAL (8)

Generation of 2-Phenyl-1-(*p*-toluenesulphonyl)aziridine (II) in Toluene Solution.

A solution of styrene (3.0 g.) in toluene (10 ml.) was added to a well stirred solution of *N,N*-dichloro-*p*-toluenesulphonamide (7.2 g.) in toluene (30 ml.) over a period of 15 minutes under nitrogen. The temperature of the reaction mixture was kept below 45° during the addition. The mixture was refluxed for 10 minutes and then cooled to 10° in an ice bath. Ammonia solution (0.88 sp. gr.) (3 ml.) was added gradually, while keeping the temperature below 15°. The cooling system was removed and the mixture was stirred for 30 minutes while attaining room temperature. A 10% sodium hydroxide solution (14 ml.) was added and the two phase system was stirred at room temperature for 2 hours. The organic phase was separated and dried. Thin layer chromatography (silica/benzene) indicated the cyclization to be complete and the solution of the aziridine could be used as required. Addition of light petroleum (b.p. 60-80°) (50 ml.) followed by cooling to

10° precipitated 2-phenyl-1-(*p*-toluenesulphonyl)aziridine (II) (5.2 g.) m.p. 88-89° (5).

Reaction of 2-Phenyl-1-(*p*-toluenesulphonyl)aziridine (II) with Ethanolamine.

The aziridine (2.73 g.) in dioxane (40 ml.) was refluxed with ethanolamine (1.2 g.). The solvent was removed *in vacuo* and 2-propanol (20 ml.) and toluene (20 ml.) were added effecting solution. Concentrated hydrochloric acid (1.5 ml.) was added and the mixture was stirred for 1 hour at 5° to give *N*-(1-phenyl-2-β-hydroxyethylaminoethyl)-*p*-toluenesulphonamide hydrochloride (III·HCl), (2.2 g.) as colourless prisms, m.p. 234-235° (from aqueous ethanol).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_3S$: C, 55.1; H, 6.2; Cl, 9.6; N, 7.6; S, 8.6. Found: C, 54.9; H, 6.3; Cl, 9.7; N, 7.5; S, 8.4:

The free base (III) had a m.p. 123-124° (ethyl acetate); NMR τ (60 Mc./sec.)(deuteriochloroform/deuterium oxide) 2.45 (2H, d), 2.85 (7H, m), 5.64 (1H, t, CH), 6.42 (2H, t, $-CH_2O-$), 7.30 (4H, m, $2CH_2$-N), and 7.67 (3H, s, Me).

The filtrate was made alkaline with 0.88 sp. gr. ammonia solution, diluted with four parts of water, and the organic phase was separated. Evaporation and trituration with a little cold ether gave *N*-(2-Phenyl-2-β-hydroxethylaminoethyl)-*p*-toluenesulphonamide, (IV) (0.9 g.) as colourless prisms (benzene), m.p. 98-100°; NMR τ (60 Mc./sec.)(deuteriochloroform/deuterium oxide) 2.25 (2H, d), 2.74 (7H, m), 6.33 (3H, m, CH and CH_2-O), 6.94 (2H, m, CH_2) 7.45 (2H, t, CH_2), and 7.62 (3H, s, Me). The two isomers (III) and (IV) could readily be differentiated by thin layer chromatography on silica using ethyl acetate as solvent; (III) R_f = 0.1, (IV) R_f = 0.3.

Anal. Calcd. for $C_{17}H_{22}N_2O_3S$: C, 61.1; H, 6.6; N, 8.4; S, 9.6. Found: C, 61.2; H, 6.5; H, 6.5; N, 8.3; S, 9.6.

N-(1-Phenyl-2-(2-iminothiazolidin-3-yl)ethyl)-*p*-toluenesulphonamide Hydrochloride (V·HCl).

N-(1-Phenyl-2-β-hydroxyethylaminoethyl)-*p*-toluenesulphonamide hydrochloride (2.0 g.), thionyl chloride (2 ml.) in ethylene dichloride (4 ml.) were refluxed for 30 minutes. The mixture was cooled in an ice bath and an 0.88 sp. gr. ammonia/water, 1:1 mixture (6 ml.) was added gradually during 10 minutes. Ammonium thiocyanate (0.62 g.) and 2-propanol (5 ml.) were added and the mixture was stirred and refluxed for 2 hours. Cooling and filtration, followed by a wash with a small amount of ice-cold water gave *N*-(1-phenyl-2-(2-iminothiazolidin-3-yl)ethyl)-*p*-toluenesulphonamide (V) hydrochloride (1.85 g.) as colourless prisms (aqueous ethanol, m.p. 234°; NMR τ (60 Mc./ sec.)(trifluoroacetic acid) 2.35 (2H, d), 2.74 (7H, m), 5.25 (1H, m, CH), 5.92 (4H, m, $2CH_2$-N), 6.53 (2H, t, $-CH_2S$), 7.60 (3H, s, Me).

Anal. Calcd. for $C_{18}H_{22}ClN_3O_2S_2$: C, 52.5; H, 5.4; Cl, 8.6; N, 10.2; S, 15.6. Found: C, 52.5; H, 5.8; Cl, 8.4; N, 9.7. S, 15.3.

Reaction of 2-Phenyl-1-(*p*-toluenesulphonyl)aziridine (II) with 2-Aminothiazoline.

The aziridine (2.7 g.) and 2-aminothiazoline (1.1 g.) in xylene (50 ml.) were refluxed for 3 hours. The solvent was removed and the residue was taken up in 2-propanol (25 ml.). *p*-Toluenesulphonic acid (1.6 g.) in xylene (40 ml.) and 2-propanol (12 ml.) was added and the mixture was stirred 30 minutes. Filtration gave *N*-(1-phenyl-2-(2-iminothiazolidin-3-yl)ethyl)-*p*-toluenesulphonamide (V) *p*-toluenesulphonic acid salt. (2.25 g.) as colourless needles (ethanol), m.p. 237°.

Anal. Calcd. for $C_{25}H_{29}N_3O_5S_3$: C, 54.8; H, 5.3; N, 7.7; S, 17.6. Found: C, 54.6; H, 5.6; N, 7.4; S, 17.8.

6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole Hydrochloride (I).

(1) Cyclization of (V) with Concentrated Sulphuric Acid.

N-(1-Phenyl-2-(2-iminothiazolidin-3-yl)ethyl)-*p*-toluenesulphonamide (V) hydrochloride (10.0 g.), which had been through a 60 mesh sieve, was added portionwise with stirring to concentrated sulphuric acid (20 ml.), the reaction mixture being kept at 5° during the addition. The cooling system was removed and the mixture was stirred for 50 minutes when room temperature was attained. It was then poured onto ice (250 g.) and the *p*-toluenesulphonamide (3.5 g.) was filtered off. The filtrate was cooled to 10° and treated with 0.88 sp. gr. ammonia solution until the *p*H was 9. The base was extracted with ethyl acetate, the extract was dried and concentrated to small volume and converted by addition of a solution of hydrogen chloride in ether to 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (I) hydrochloride (4.8 g.), m.p. 263° (ethanol).

Anal. Calcd. for $C_{11}H_{13}ClN_2S$: C, 55.0; H, 5.4; N, 11.7; S, 13.3. Found: C, 54.6; H, 5.4; N, 11.6; S, 13.3.

Cyclization of V using Polyphosphoric Acid.

The thiazolidine (10 g.) and polyphosphoric acid (50 ml.) were heated with stirring on a steam bath for 3 hours. Work up as in the case of the concentrated sulphuric acid cyclization gave 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (I) hydrochloride (2.8 g.) as colourless needles, m.p. 262-263° (ethanol).

2-Phenylmorpholine (VI).

N-(1-Phenyl-2-β-hydroxyethylaminoethyl)-*p*-toluenesulphonamide hydrochloride (5 g.) was added gradually to well stirred concentrated sulphuric acid (20 ml.), the temperature being kept below 5°. After the addition, the ice-bath was removed and the mixture was stirred 30 minutes at room temperature. The solution was then poured onto ice (40 g.) and the *p*-toluenesulphonamide was removed by filtration. The filtrate was cooled to 10° and treated with 0.88 sp. gr. ammonia solution until *p*H 9 was obtained. Extraction with ethyl acetate gave 2-phenylmorpholine (VI) (0.78 g.) as a yellow oil, hydrogen oxalate, colourless prisms, m.p. 171-173° (ethanol); NMR τ (100 Mc./sec.) (deuterium oxide) 2.56 (5H, s), 5.15 (1H, m, CH). 5.76 (2H, m, CH_2-O), 6.72 (4ii, m, $2CH_2N$).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.9; H, 5.9; N, 5.5. Found: C, 57.0; H, 6.0; N, 5.5.

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(8) The melting points are uncorrected. The N.M.R. spectra were determined on Varian A-60 and HA-100 instruments.

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