THE SYNTHESES OF COMPOUNDS RELATED TO 2-THIENYLMETHYL 2-(2-IMIDAZOLINYL) SULPHIDE

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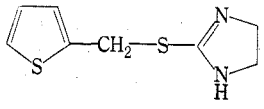
Summary

The syntheses of the anthelmintic 2-thienylmethyl 2-(2-imidazolinyl) sulphide and a series of related compounds are described.

Introduction

The compound 2-thienylmethyl 2-(2-imidazolinyl) sulphide (I) has been reported[1] to be highly effective as an anthelmintic against a wide variety of nematodes which infect farm animals. Lynch and Nelson[2] showed that the hydrochloride of (I) was more effective than other anthelmintics in clearing infections with *Nematospiroides dubius* from mice.



(I)

Compound (I) and a series of related compounds were synthesized in an attempt to relate chemical structure to anthelmintic activity. The compounds were prepared by treating the appropriate chloromethyl derivatives with the thiols or their sodium salts. The former reaction gave the hydrochloride derivative.

A number of the compounds described below, as well as (I), proved lethal to liver fluke (*Fasciola hepatica*) when tested *in vitro* by the kymographic technique of Chance and Mansour.[3]

Experimental

Analyses are by Dr. K. W. Zimmermann, CSIRO and University of Melbourne Microanalytical Laboratory.

(*a*) *2-Thienylmethyl 2-(2-Imidazolinyl) Sulphide Hydrochloride.*—2-Imidazolinylthione (20 g) was dissolved in refluxing methanol (87 ml), and 2-chloromethylthiophene (26·2 g) was added in small portions during 45 min. The reaction mixture was refluxed for 1 hr on a hot plate, then allowed to cool to room temperature. Diethyl ether (87 ml) was added. The precipitated product was filtered off to give a cream powder (37·2 g, 65%), m.p. 182°. Fractional recrystallization from methanol (33 ml) and diethyl ether (33 ml) gave white crystals, m.p. 183°. The material was reported[1] as having m.p. 183°. On occasions the crude product had m.p. 159–162°, but this material was readily purified by fractional recrystallization (Found: C, 41·2; H, 4·9; N, 11·9%. Calc. for $C_8H_{11}N_2S_2Cl$: C, 40·9; H, 4·7; N, 11·9%).

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[1] Pfizer & Co. Inc., U.S. Pat. 2,956,923.

[2] Lynch, J. E., and Nelson, B., *J. Parasitol.* 1959, **45**, 659.

[3] Chance, M. R., and Mansour, T. E., *Brit. J. Pharmacol.*, 1949, **4**, 7.

(*b*) *Phenylmethyl 2-(2-Imidazolinyl) Sulphide Hydrochloride.*—The 2-imidazolinylthione (5 g) and benzyl chloride (9·1 g) were treated as in (*a*) to give white crystals (10·8 g, 96%), m.p. 171°. Recrystallization from methanol and diethyl ether did not alter the melting point (Found: C, 52·5; H, 5·7; N, 12·3%. Calc. for $C_{10}H_{13}N_2ClS$: C, 52·4; H, 5·7; N, 12·1%).

(*c*) *4-Thiazolylmethyl 2-(2-Imidazolinyl) Sulphide Hydrochloride.*—The 2-imidazolinylthione (5 g) and 4-chloromethylthiazole (6·6 g) were treated as in (*a*) to give a white powder. Recrystallization from methanol gave white cubes (9·6 g, 82%), m.p. 210·5° (Found: C, 35·6; H, 4·2; N, 17·3; S, 27·1%. Calc. for $C_7H_{10}N_3S_2Cl$: C, 35·7; H, 4·3; N, 17·8; S, 27·2%).

(*d*) *4-Thiazolylmethyl 2-Benzimidazolyl Sulphide Hydrochloride.*—The 2-mercaptobenzimidazole (5 g) and 4-chloromethylthiazole (5·8 g) were treated as in (*a*). The precipitate obtained was recrystallized from ethanol to give colourless plates (6·8 g, 68%), m.p. 195° (Found: C, 46·6; H, 3·6; N, 14·8; S, 22·3%. Calc. for $C_{11}H_{10}N_3S_2Cl$: C, 46·6; H, 3·6; N, 14·8; S, 22·6%).

(*e*) *Phenylmethyl 2-Benzimidazolyl Sulphide Hydrochloride.*—The reaction was carried out as in (*a*) using 2-mercaptobenzimidazole (5 g) and benzyl chloride (4·3 g) to give white needles (8·5 g, 92%), m.p. 234°. Recrystallization from methanol and diethyl ether did not alter the melting point (Found: C, 60·7; H, 4·7; N, 10·1%. Calc. for $C_{14}H_{13}N_2SCl$: C, 60·9; H, 5·0; N, 10·1%).

(*f*) *2-Thienylmethyl 2-Imidazolyl Sulphide.*—The sodium salt of 2-mercaptoimidazole was prepared by dissolving 2-mercaptoimidazole (3 g) in anhydrous ethanol (30 ml) which contained dissolved sodium hydroxide (2 g). To the mixture was added 2-chloromethylthiophene (8 g) in portions. The mixture was refluxed on a water-bath for 2 hr. The ethanol was removed under vacuum to give an oil, which on recrystallization from ethanol–water gave white needles (6·4 g, 65%), m.p. 123°. A further recrystallization gave m.p. 126° (Found: C, 49·1; H, 4·4; N, 14·3; S, 32·7%. Calc. for $C_8H_8N_2S_2$: C, 48·9; H, 4·1; N, 14·3; S, 32·7%).

(*g*) *2-Thienylmethyl 2-Benzimidazolyl Sulphide.*—The reaction was carried out as described in (*f*), with 2-mercaptobenzimidazole (6 g) in anhydrous ethanol (30 ml) containing dissolved sodium hydroxide (1·6 g). The dropwise addition of the 2-chloromethylthiophene (5·4 g) resulted in an exothermic reaction with the deposition of a white powder. The precipitate was recrystallized from ethanol–water to give white needles (6·6 g, 62%), m.p. 206° (Found: C, 58·3; H, 4·2; N, 11·0; S, 25·9%. Calc. for $C_{12}H_{10}N_2S_2$: C, 58·5; H, 4·1; N, 11·4; S, 26·2%).

(*h*) *2-Thienylmethyl 3-(1,2,4-Triazolyl) Sulphide.*—The reaction was carried out as in (*f*) using 1,2,4-triazole-3(5)-thiol (5 g) in anhydrous ethanol (30 ml) containing dissolved sodium hydroxide (2 g). The 2-chloromethylthiophene (8 g) was added dropwise to the refluxing mixture, and heating was continued for 2 hr. Removal of the ethanol under vacuum gave an oil, which was recrystallized from ethanol–water to give white plates (5·6 g, 42%), m.p. 108° (Found: C, 42·1; H, 3·5; N, 21·3; S, 32·6%. Calc. for $C_7H_7N_3S_2$: C, 42·6; H, 3·6; N, 21·3; S, 32·5%).

(*i*) *2-Thienylmethyl Pentachlorophenyl Sulphide.*—Pentachlorothiophenol (5 g) was dissolved in anhydrous ethanol (30 ml) containing dissolved sodium hydroxide (0·71 g). The mixture was treated with 2-chloromethylthiophene (3·8 g) as in (*f*). Immediate precipitation of product took place. Heating was continued for 2 hr. The mixture was concentrated in volume, cooled, and the product collected. Recrystallization from ethanol gave fawn-coloured needles (5·5 g, 75%), m.p. 107° (Found: C, 35·0; H, 1·8; Cl, 46·6; S, 16·8%. Calc. for $C_{11}H_5Cl_5S_2$: C, 34·9; H, 1·3; Cl, 46·8; S, 16·9%).

(*j*) *4-Thiazolylmethyl 3-(1,2,4-Triazolyl) Sulphide.*—The sodium salt of 1,2,4-triazole-3(5)-thiol (6 g) was dissolved in refluxing anhydrous ethanol (30 ml), and 4-chloromethylthiazole hydrochloride (10 g), dissolved in anhydrous ethanol, was added. The mixture was refluxed on a water-bath for 4 hr, made slightly alkaline, and the ethanol removed under vacuum. The compound was recrystallized from ethyl acetate (charcoal) to give short white needles (6·2 g, 62%), m.p. 123° (Found: C, 36·6; H, 3·1; N, 27·9; S, 32·5%. Calc. for $C_6H_6N_4S_2$: C, 36·3; H, 3·1; N, 28·3; S, 32·2%).

(*k*) *2-Benzimidazolylmethyl 2-Imidazolyl Sulphide.*—A mixture of 2-mercaptoimidazole (5 g) and sodium hydroxide (2 g) were dissolved in anhydrous ethanol (30 ml). While the mixture was refluxed on a water-bath, 2-chloromethylbenzimidazole (10·9 g), dissolved in anhydrous

ethanol, was added. After refluxing 4 hr, the ethanol volume was reduced, and the solution allowed to stand overnight. A white powder was deposited (9·3 g, 81%). The m.p. was 226° after recrystallization from ethanol (Found: C, 57·3; H, 4·5; S, 13·9%. Calc. for $C_{11}H_{10}N_4S$: C, 57·4; H, 4·4; S, 13·9%).

(*l*) *2-Benzimidazolylmethyl Pentachlorophenyl Sulphide.*—Pentachlorothiophenol (5 g) was dissolved in refluxing anhydrous ethanol which contained dissolved sodium hydroxide (0·71 g). To the mixture was added 2-chloromethylbenzimidazole (3·8 g) dissolved in anhydrous ethanol. The mixture was refluxed for 4 hr, cooled, and the precipitated material collected. Recrystallization from ethanol gave fawn needles (5·5 g, 75%), m.p. 250° (Found: C, 40·7; H, 1·7; S, 7·9%. Calc. for $C_{14}H_7Cl_5N_2S$: C, 40·8; H, 1·7; S, 7·8%).

(*m*) *Phenylmethyl 2-Benzimidazolyl Sulphide.*—The reaction was carried out as in (*f*), using 2-mercaptobenzimidazole (5 g) in anhydrous ethanol containing sodium hydroxide (1·3 g). Benzyl chloride (5·5 g) was added to the refluxing mixture, which was heated for 2 hr after all the benzyl chloride was added. The reaction mixture was poured into water, the solid collected and dried to give a fawn powder (7·8 g), m.p. 180°. Recrystallization from ethyl acetate gave long white needles (7·2 g, 90%), m.p. 186° (Found: C, 70·3; H, 5·0; N, 11·5; S, 13·5%. Calc. for $C_{14}H_{12}N_2S$: C, 70·0; H, 5·0; N, 11·7; S, 13·4%).

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