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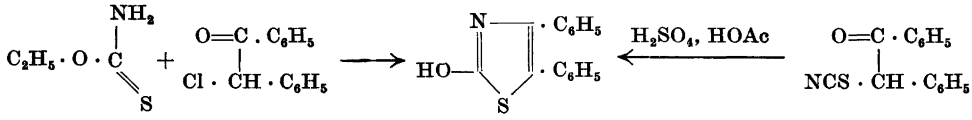
Aminoalkyl Ethers of 2-Hydroxythiazoles

RICHARD DAHLBOM

Centrallaboratoriet, AB Astra, Södertälje, Sweden

It is known that dialkylaminoalkyl ethers of suitably substituted phenols may exert antihistaminic activity [1,2]. As an extension of work in this laboratory on aminoalkyl compounds containing a thiazole nucleus [3,4] a number of β-dialkylaminoethyl ethers of some 2-hydroxythiazoles were prepared.

The new compounds were smoothly obtained by the reaction of the appropriate dialkylaminoethyl chloride with the sodium salt of a 2-hydroxythiazole. Two of the 2-hydroxythiazoles used as starting materials, 2-hydroxy-4-methylthiazole and 2-hydroxy-4-phenylthiazole, are known in the literature. A new member of this class, 2-hydroxy-4,5-diphenylthiazole, was synthesised in analogous manners, *i.e.* by the reaction of xanthogenamide with desyl chloride or by rearrangement of desyl thiocyanate.



The new aminoalkyl ethers possessed a very weak antihistaminic and antispasmodic action. The diphenyl derivatives showed good local anesthetic activity but were strong irritants.

EXPERIMENTAL

2-Hydroxythiazoles

2-Hydroxy-4-methylthiazole was prepared by rearrangement of thiocyanoacetone according to Hantzsch [5].

2-Hydroxy-4-phenylthiazole was prepared from xanthogenamide and phenacyl bromide [6] or by rearrangement of phenacyl thiocyanate [7]. Both methods yielded a product melting at 210–211° (from chloroform), which is somewhat higher than the m.p. reported in the literature (204°).

2-Hydroxy-4,5-diphenylthiazole. Method A. Xanthogenamide (10.5 g, 0.1 mole) and desyl chloride (23 g, 0.1 mole) were thoroughly mixed and heated on the waterbath for 30 minutes. The mixture melted at first and, after a few minutes began to crystallise. After cooling, the reaction product was triturated with cold ethanol (100 ml) and collected. The crude product (18.2 g, 72 %) melted at 255—256°. Recrystallisation from ethanol did not raise the m.p. (Found: C 71.3; H 4.48; N 5.56; S 12.4. Calc. for $C_{15}H_{11}NOS$ (253.3): C 71.2; H 4.38; N 5.53; S 12.7 %).

Method B. A mixture of desyl thiocyanate[8] (1.5 g), glacial acetic acid (8 ml) and conc. sulphuric acid (0.15 ml) was refluxed for 2 hours. After cooling, the reaction product crystallised from the acid mixture. Water (50 ml) was added to the mixture and the crystals (1.3 g, 87 %) were collected. M.p. 255—256° after recrystallisation from ethanol, undepressed on admixture with the compound prepared by method A above.

2-Chloro-4,5-diphenylthiazole. The hydroxy group in the preceding thiazole was easily replaced by chlorine. The hydroxy compound (2.5 g) was refluxed with phosphorus oxychloride (15 ml) for four hours. After cooling, the mixture was cautiously poured into ice water. The oil which was precipitated crystallised rapidly. The crude product (2.65 g, 97 %) was recrystallised from 50 % acetone; m.p. 73—74°. (Found: C 66.3; H 3.99; Cl 13.2. Calc. for $C_{15}H_{10}ClNS$ (271.8): C 66.3; H 3.71; Cl 13.0 %.)

2-Aminoethoxythiazoles

The compounds described below were all prepared in essentially the same way. As an example, the preparation of 2-(β-diethylaminoethoxy)-4-methylthiazole is given.

2-(β-Diethylaminoethoxy)-4-methylthiazole. 2-Hydroxy-4-methylthiazole (1.5 g, 0.013 mole) was added to a solution of sodium (0.3 g, 0.013 mole) in a mixture of ethanol (10 ml) and toluene (40 ml). The ethanol was removed by distillation until the temperature reached 110°. A solution of β-diethylaminoethyl chloride in toluene, prepared from β-diethylaminoethyl chloride hydrochloride (3.45 g, 0.02 mole) according to the directions given by Cheney, Smith and Binkley[2] for the dimethyl analogue, was added with stirring, and the mixture was refluxed for 4 hours. After cooling, the reaction mixture was filtered and the filtrate extracted with *N* hydrochloric acid. The extract was made alkaline with sodium carbonate solution and the oily base was extracted with ether. By addition of ethanolic picric acid to the extract the *picrate* of the base was isolated (2.55 g, 44 %); m.p. 173—175° (from methanol). (Found: N 16.0. Calc. for $C_{10}H_{18}N_2OS \cdot C_6H_3N_3O_7$ (443.4): N 15.8 %.)

The picrate (2.0 g) was suspended in a mixture of water (65 ml), 5 *N* sodium hydroxide (25 ml) and chloroform (25 ml) and stirred on the water bath for one hour. The chloroform layer was separated and dried and the solvent was evaporated. The residue was distilled *in vacuo* giving a colourless oil (0.8 g) boiling at 150° (bath temperature) at 0.1 mm. (Found: C 56.3; H 8.61; N 13.2. Calc. for $C_{10}H_{18}N_2OS$ (214.3): C 56.0; H 8.46; N 13.1 %.)

2-(β-Piperidinoethoxy)-4-methylthiazole oxalate. This compound was prepared similarly in 58 % yield from 2-hydroxy-4-methylthiazole and β-piperidinoethyl chloride. The oily base was isolated as the oxalate; m.p. 224—225° (decomp., from acetone). (Found: C 49.9; H 6.17; N 8.76. Calc. for $C_{11}H_{18}N_2OS \cdot H_2C_2O_4$ (316.4): C 49.3; H 6.37; N 8.86 %.)

2-(β-Dimethylaminoethoxy)-4-phenylthiazole oxalate. Prepared in 67 % yield from β-dimethylaminoethyl chloride and 2-hydroxy-4-phenylthiazole. M.p. 187—188° (de-

comp.) after recrystallisation from acetone. (Found: C 53.2; H 5.15; N 8.11. Calc. for $C_{13}H_{16}N_2OS \cdot H_2C_2O_4$ (338.4): C 53.3; H 5.36; N 8.28 %.)

2-(β-Diethylaminoethoxy)-4-phenylthiazole oxalate. Prepared in 86 % yield; m.p. 135—136° (decomp., from acetone). (Found: C 55.9; H 6.03; N 7.81. Calc. for $C_{15}H_{20}N_2OS \cdot H_2C_2O_4$ (366.4): C 55.7; H 6.05; N 7.65 %.)

2-(β-Piperidinoethoxy)-4-phenylthiazole oxalate. Prepared in 61 % yield; m.p. 185—187° (decomp., from acetone). (Found: C 57.0; H 5.75; N 7.46. Calc. for $C_{16}H_{20}N_2OS \cdot H_2C_2O_4$ (378.4): C 57.1; H 5.85; N 7.41 %.)

2-(β-Dimethylaminoethoxy)-4,5-diphenylthiazole. Prepared in 60 % yield from β-dimethylaminoethyl chloride and 2-hydroxy-4,5-diphenylthiazole. The solid base was recrystallised from light petroleum; m.p. 104—105°. (Found: C 70.4; H 6.44; N 8.84. Calc. for $C_{19}H_{20}N_2OS$ (324.4): C 70.4; H 6.22; N 8.64 %.)

2-(β-Diethylaminoethoxy)-4,5-diphenylthiazole. Prepared in 50 % yield; m.p. 88—89° (from light petroleum). (Found: C 72.0; H 7.04; N 7.97. Calc. for $C_{21}H_{24}N_2OS$ (352.5): C 71.6; H 6.86; N 7.95 %.)

2-(β-Piperidinoethoxy)-4,5-diphenylthiazole hydrochloride. Prepared in 52 % yield; m.p. 239—241° (from acetone). (Found: C 65.5; H 6.26; N 6.90. Calc. for $C_{22}H_{24}N_2OS \cdot HCl$ (401.0): C 65.9; H 6.28; N 6.99 %.)

SUMMARY

A number of β-dialkylaminoethyl ethers of 2-hydroxythiazoles have been prepared and tested for pharmacological activity.

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