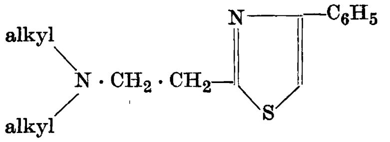
ACTA CHEMICA SCANDINAVICA 7 (1953) 885–888

Dialkylaminoalkylthiazoles

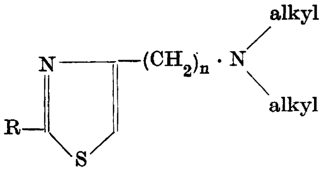
RICHARD DAHLBOM

Centrallaboratoriet, AB Astra, Södertälje, Sweden

Attempts to prepare dialkylaminoalkylthiazoles of type I met with unexpected difficulties owing to the peculiar reaction of β-dialkylamino-substituted propio- and butyronitriles with hydrogen sulphide [1]. It was therefore decided to interchange the substituents in the thiazole nucleus and prepare a series of thiazoles of the general structure II.



I.



$R = CH_3-$, C_6H_5- or $C_6H_5 \cdot CH_2-$

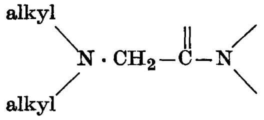
$n = 1$ or 2

II.

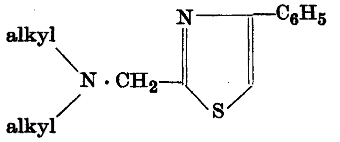
Compounds of type II were easily obtained by the reaction of 4-chloromethylthiazoles with secondary amines ($n = 1$) or by the reaction of thioamides with 1-bromo-4-dialkylamino-2-butanones ($n = 2$).

The new compounds were tested pharmacologically. None of them possessed antihistaminic or spasmolytic properties. When the substituent R was phenyl or benzyl the compounds were strong local anesthetics superior, in some cases, to Xylocaine, when tested on rabbit *cornea*. They were, however, irritating to the rabbit eye and had a longer time of onset than Xylocaine.

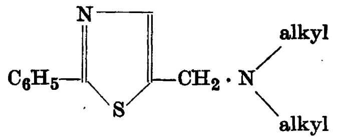
The local anesthetic effect of these thiazoles was somewhat unexpected, as the related aminoalkyl derivatives of 2-benzylthiazole [2] had no such properties. In order to investigate if the anesthetic effect was due to the group



which is also present in Xylocaine [3] (and *iso*gramine [4]) some isomeric 2-dialkylaminomethyl-4-phenylthiazoles (III) and 5-dialkylaminomethyl-2-phenylthiazoles (IV) were synthesized.

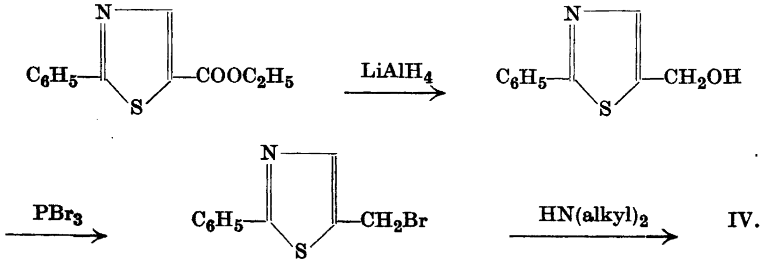


III.



IV.

The compounds of type III were prepared by the reaction of 2-bromomethyl-4-phenylthiazole with secondary amines. The compounds of type IV were obtained by the following reaction sequence:



The compounds of both types possessed considerable anesthetic activity, but like their isomers of type II they were eye irritants and had a longer time of onset than Xylocaine. No noticeable antihistaminic or antispasmodic effects were found.

EXPERIMENTAL

4-Dialkylaminomethylthiazoles

4-Diethylaminomethyl-2-methylthiazole. A solution of 4-chloromethyl-2-methylthiazole [5] (4.5 g, 0.03 mole) and diethylamine (5.9 g, 0.08 mole) in nitrobenzene (25 ml) was heated on the water bath for one hour. The mixture was cooled, washed with water and extracted with 2 *N* hydrochloric acid. On addition of an aqueous solution of picric acid to the extract the reaction product separated as the *picrate* (2.9 g, 24 %); m.p. 98—99° on recrystallisation from methanol. (Found: N 17.5. $C_9H_{16}N_2S \cdot C_6H_3N_3O_7$ (413.4) requires N 16.9 %.)

The free base was obtained as an oil, from the picrate, in the usual way. B.p. 150° (bath temperature) at 0.01 mm. (Found: C 58.1; H 8.60; N 14.9. $C_9H_{16}N_2S$ (184.3) requires C 58.6; H 8.75; N 15.2 %.)

4-Dimethylaminomethyl-2-phenylthiazole dihydrochloride. 4-Chloromethyl-2-phenylthiazole [6] (2.1 g) and dimethylamine (4 ml) were heated in ethanol (25 ml), in a sealed bottle, at 70° overnight. The reaction mixture was cooled, poured into water and the resulting oil was extracted with ether. The ethereal solution was dried and the dihydrochloride of the thiazole base was precipitated by the addition of ethereal hydrogen chloride. The crude salt (2.0 g, 69 %) was recrystallised from methanol; m.p. 199—200°. (Found: C 50.2; H 5.42; N 10.1. $C_{12}H_{14}N_2S \cdot 2\ HCl$ (291.2) requires C 49.5; H 5.54; N 9.62 %.)

4-Diethylaminomethyl-2-phenylthiazole. 4-Chloromethyl-2-phenylthiazole (9.0 g) and diethylamine (11.2 g) were heated in nitrobenzene (40 ml) on the water bath for 3 hours. The mixture was cooled, washed with water and extracted with 2 *N* hydrochloric acid. The extract was made alkaline, and the resulting oil was extracted with ether. The ethereal solution was dried, the solvent was evaporated and the residue distilled *in vacuo* giving an almost colourless oil (7.6 g, 68 %), b.p. 170—180/0.05 mm. (Found: C 68.1; H 7.36. $C_{14}H_{18}N_2S$ (246.4) requires C 68.2; H 7.36 %.)

The thiazole base was further characterized by the preparation of the *picrate* m.p. 103—104° (from methanol), (Found: C 50.3; H 4.24; N 14.9. $C_{14}H_{18}N_2S \cdot C_6H_3N_3O_7$ (475.5) requires C 50.5; H 4.45; N 14.7 %), and the oxalate m.p. 129—131° (from acetone), (Found: C 57.5; H 6.20. $C_{14}H_{18}N_2S \cdot H_2C_2O_4$ (336.4) requires C 57.1; H 5.99 %).

4-Pyrrolidinomethyl-2-phenylthiazole. This compound was prepared in the usual way by refluxing 4-chloromethyl-2-phenylthiazole and pyrrolidine in ethanol for 10 hours. The reaction product was isolated in 23 % yield as the *picrate*, m.p. 134—136° (from ethanol). (Found: N 14.9. $C_{14}H_{16}N_2S \cdot C_6H_3N_3O_7$ (473.5) requires N 14.8 %.)

The free base obtained from the picrate distilled at 250° (bath temperature) at 0.01 mm. (Found: C 68.9; H 6.67; N 11.3. $C_{14}H_{16}N_2S$ (244.4) requires C 68.8; H 6.60; N 11.5 %.)

4-(β-Dialkylaminoethyl)-thiazoles

These compounds were all prepared in the same way. Equivalent amounts of the appropriate thioamide (thioacetamide, thiobenzamide or phenylthioacetamide) and a 1-bromo-4-dialkylamino-2-butanone hydrobromide (dialkylamino = dimethylamino-, diethylamino-, and piperidino-) were dissolved in ethanol and refluxed on the water bath for one hour. The solution was filtered and cooled, giving the crystalline dihydrobromide (in one case the monohydrobromide) of the 4-(β-dialkylaminoethyl)-thiazole in almost pure form. The salt was recrystallised from ethanol. The 1-bromo-4-dialkylamino-2-butanone hydrobromides required as starting materials were prepared by the method of Djerassi, Mizzoni and Scholz [7].

4-(β-Dimethylaminoethyl)-2-phenylthiazole dihydrobromide. M.p. 240—242° (dec.); yield 49 %. (Found: C 39.9; H 4.81; Br 39.4. $C_{13}H_{16}N_2S \cdot 2\ HBr$ (394.2) requires C 39.6; H 4.60; Br 40.5 %).

4-(β-Dimethylaminoethyl)-2-benzylthiazole dihydrobromide. M.p. 228—230°; yield 64 %. (Found: C 41.0; H 4.88; Br 37.8. $C_{14}H_{18}N_2S \cdot 2\ HBr$ (408.2) requires C 41.2; H 4.94; Br 39.2 %).

4-(β-Diethylaminoethyl)-2-methylthiazole dihydrobromide. M.p. 222—224°; yield 72 %. (Found: C 33.0; H 5.27; Br 43.9. $C_{10}H_{18}N_2S \cdot 2\ HBr$ (360.2) requires C 33.3; H 5.60; Br 44.4 %).

4-(β-Diethylaminoethyl)-2-phenylthiazole dihydrobromide. This compound was rather soluble in cold ethanol. It was therefore precipitated from the reaction mixture with ether, and recrystallised from methanol. M.p. 195—197°; yield 57 %. (Found: C 42.5; H 5.20; Br 38.0. $C_{15}H_{20}N_2S \cdot 2\ HBr$ (422.2) requires C 42.7; H 5.25; Br 37.9 %).

4-(β-Diethylaminoethyl)-2-benzylthiazole dihydrobromide. Precipitated with ether and recrystallised from methanol. M.p. 192—193°; yield 63 %. (Found: C 44.0; H 5.36; Br 36.6. $C_{16}H_{22}N_2S \cdot 2\ HBr$ (436.3) requires C 44.0; H 5.54; Br 36.6 %.)

4-(β-Piperidinoethyl)-2-methylthiazole dihydrobromide. M.p. 229—230°; yield 44 %. (Found: C 35.3; H 5.60; Br 42.0. $C_{11}H_{18}N_2S \cdot 2\ HBr$ (372.2) requires C 35.5; H 5.42; Br 42.9 %).

4-(β-Piperidinoethyl)-2-phenylthiazole monohydrobromide. M.p. 230—232° (dec.); yield 42 %. (Found: C 53.9; H. 5.97; Br 23.8. $C_{16}H_{20}N_2S \cdot HBr$ (353.3) requires C 54.4; H 5.99; Br 22.6 %).

4-(β-Piperidinoethyl)-2-benzylthiazole dihydrobromide. M.p. 275—277°; yield 47 %. (Found: C 44.6; H 5.36; Br 34.2. $C_{17}H_{22}N_2S \cdot 2\ HBr$ (448.3) requires C 45.5; H 5.40; Br 35.7 %).

2-Dialkylaminomethylthiazoles

2-Bromomethyl-4-phenylthiazole. The method of Olin and Johnson [8] could not be repeated, and the compound was therefore prepared in the following way. A mixture of 2-hydroxymethyl-4-phenylthiazole (4.3 g), phosphorus tribromide (10.0 g) and chloroform (30 ml) was refluxed for one hour. The reaction mixture was cooled, washed with cold sodium bicarbonate solution, and the chloroform was separated and dried over calcium chloride. The solvent was evaporated and the residue distilled *in vacuo* giving a colourless oil (3.3 g, 58 %), b.p. 140—145/0.05 mm (Olin and Johnson [8] record b.p. 195°/15 mm). The distillate soon solidified to white crystals; m.p. 45—46° on recrystallisation from light petroleum. (Found: C 47.3; H 3.30; Br 31.2. Calc. for $C_{10}H_8BrNS$ (254.2): C 47.3; H 3.17; Br 31.5 %).

2-Dimethylaminomethyl-4-phenylthiazole oxalate. 2-Bromomethyl-4-phenylthiazole (5.1 g) reacted readily at room temperature with a solution of dimethylamine (3.5 ml) in benzene (40 ml). The mixture was filtered, washed with water and extracted with 2 *N* hydrochloric acid. The extract was made alkaline with sodium carbonate solution and the oily base was extracted with ether. By addition of ethereal oxalic acid to the extract, the oxalate of the base was isolated (4.55 g, 74 %); m.p. 179—180° (dec.) on recrystallisation from acetone. (Found: C 54.6; H 5.20; N 9.35. $C_{12}H_{14}N_2S \cdot H_2C_2O_4$ (308.4) requires C 54.5; H 5.23; N 9.09 %).

2-Diethylaminomethyl-4-phenylthiazole oxalate. This compound was prepared in the same way in 60 % yield by the above method. M.p. 146—147° (from acetone). (Found: C 57.6; H 6.10; N 8.36. $C_{14}H_{18}N_2S \cdot H_2C_2O_4$ (336.4) requires C 57.1; H 5.99; N 8.33 %).

2-Piperidinomethyl-4-phenylthiazole. The solid base was obtained in 89 % yield. M.p. 67—68° on recrystallisation from 50 % ethanol. (Found: C 69.3; H 6.80; N 10.5. $C_{15}H_{18}N_2S$ (258.4) requires C 69.7; H 7.02; N 10.8 %).

5-Dialkylaminomethylthiazoles

5-Hydroxymethyl-2-phenylthiazole. A solution of ethyl 2-phenylthiazole-5-carboxylate [9] (6.0 g) in ether (50 ml) was added, with mechanical stirring, to a suspension of lithium aluminium hydride (1.0 g) in ether (30 ml), at such a rate that gentle reflux was obtained. The mixture was stirred under reflux for a further half hour. Excess hydride was destroyed with ethyl acetate (5 ml), and the mixture was made strongly alkaline with 5 *N* sodium hydroxide. The ether layer was separated, the aqueous solution extracted thoroughly with ether, and the combined ether solutions were dried over calcium chloride. The solvent was evaporated and the residue distilled *in vacuo* giving a colourless oil (4.2 g, 85 %). The distillate soon solidified to white crystals; m.p. 76—77° on recrystallisation from light petroleum-ethanol (6 : 1). (Found C 62.4; H 4.70; S 16.5. $C_{10}H_9NOS$ (191.2) requires C 62.8; H 4.74; S 16.8 %.)

5-Bromomethyl-2-phenylthiazole. The above hydroxy compound (1.4 g) was refluxed with phosphorus tribromide (4.3 g) in chloroform for one hour. After cooling, the mixture was washed with sodium bicarbonate solution, the chloroform was separated, and dried over calcium chloride. The solvent was evaporated and the solid residue (1.6 g, 86 %) crystallised from methanol; m.p. 72—73°. (Found: C 48.0; H 3.09; Br 31.9. $C_{10}H_8BrNS$ (254.2) requires C 47.3; H 3.17; Br 31.5 %.)

5-Dimethylaminomethyl-2-phenylthiazole hydrochloride. The above bromo compound reacted readily at room temperature with dimethyl amine in toluene solution. The reaction product was isolated as the hydrochloride. Yield 81 %; m.p. 236—237°, from ethanol. (Found: C 56.6; H 5.81; Cl 14.3. $C_{12}H_{14}N_2S \cdot HCl$ (254.8) requires C 56.6; H 5.93; Cl 13.9 %.)

5-Diethylaminomethyl-2-phenylthiazole hydrochloride. The reactants were refluxed in benzene for one hour. Yield 60 %; m.p. 173—175°, from ethanol. (Found: C 59.7; H 6.41; N 9.57. $C_{14}H_{18}N_2S \cdot HCl$ (282.8) requires C 59.4; H 6.77; N 9.91 %.)

SUMMARY

A series of new dialkylaminoalkyl derivatives of substituted thiazoles has been prepared for pharmacological study.

REFERENCES

1. Dahlbom, R. *Acta Chem. Scand.* **5** (1951) 690.
2. Dahlbom, R. *Acta Chem. Scand.* **4** (1950) 744.
3. Löfgren, N. *Arkiv Kemi, Mineral. Geol.* **A 22** (1946) No 18.
4. Erdtman, H., and Löfgren, N. *Svensk Kem. Tidskr.* **49** (1937) 163.
5. Hooper, F. E., and Johnson, T. B. *J. Am. Chem. Soc.* **56** (1934) 470.
6. Hooper, F. E., and Johnson, T. B. *J. Am. Chem. Soc.* **56** (1934) 484.
7. Djerassi, C., Mizzoni, R. H., and Scholz, C. R. *J. Org. Chem.* **15** (1950) 700.
8. Olin, J. F., and Johnson, T. B. *J. Am. Chem. Soc.* **53** (1931) 1470.
9. Erlenmeyer, H., Buchmann, P., and Schenkel, H. *Helv. Chim. Acta* **27** (1944) 1432.

Received March 9, 1953.