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# 3-CARBOXYMETHYLBENZOTHIAZOLINES

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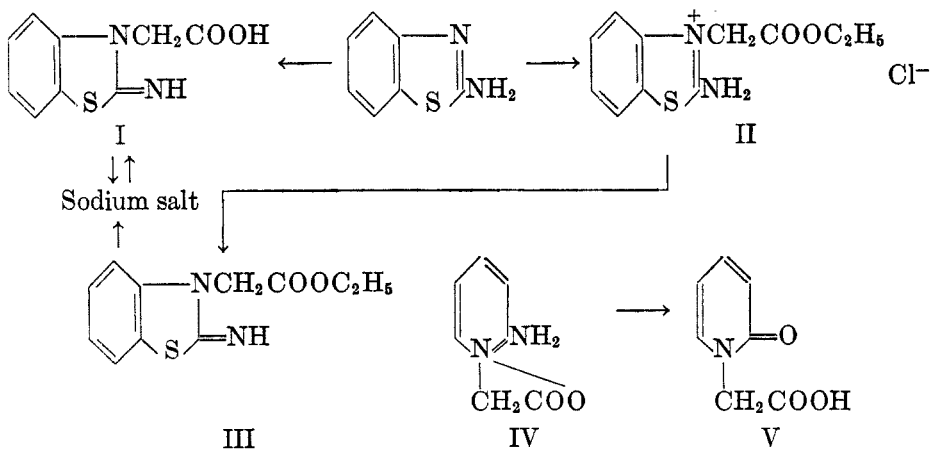
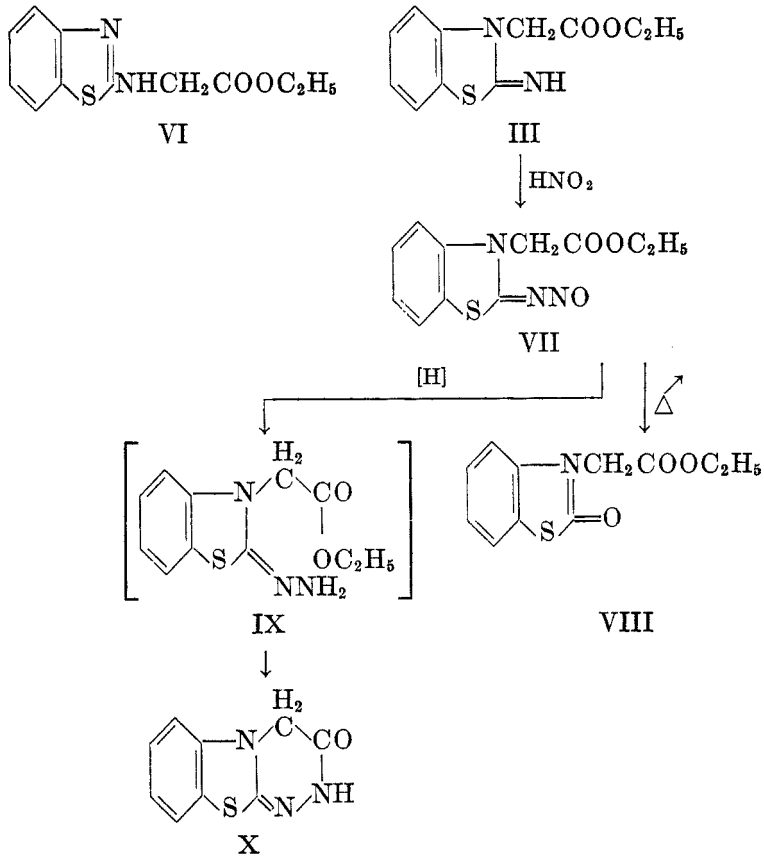
In an earlier paper (1) the failure of 2-acetoacetaminobenzothiazole to cyclize was mentioned, and this behavior was contrasted with the heterolog in the pyridine series. Attention was subsequently turned to the simpler system that resulted from the addition of chloroacetic acid to 2-aminobenzothiazole, which was expected to be comparable to the 2-aminopyridine heterolog. This present paper contains observations on the reactions of 2-aminobenzothiazole with chloroacetic acid, its sodium salt, and its ethyl ester.

In aqueous or acetic acid solution, equivalent amounts of 2-aminobenzothiazole and chloroacetic acid form a salt, from which the base can be recovered by making a solution of the salt alkaline and extracting with ether. Sodium chloroacetate in aqueous solution, however, adds to the heterocyclic nitrogen atom, to give, after acidification, 3-carboxymethyl-2-iminobenzothiazoline (I).

Ethyl chloroacetate gives an addition product (II) from which the free ester (III) is obtained by the action of sodium carbonate or dilute sodium hydroxide. When this ester is treated with hot sodium hydroxide solution, it is saponified and the sodium salt of (I) separates. In contrast to the behavior of 2-aminopyridylglycine (IV), which (a) crystallizes from dilute alkali unchanged, (b) evolves ammonia, on boiling with sodium hydroxide, to give N-carboxymethyl-2-pyridone (V), and (c) gives (V), on treatment with nitrous acid; 3-carboethoxymethyl-2-iminobenzothiazoline gives (a) the sodium salt of the acid on crystallization from dilute alkali, (b) does not evolve ammonia on boiling with caustic, and (c) gives a nitrosoamine on treatment with nitrous acid. On the basis of these facts, 3-carboxymethyl-2-iminobenzothiazoline is assigned an open-chain structure, whereas pyridylglycine has been assigned a betaine structure (2).

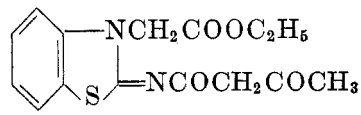


The ester formed from ethyl chloroacetate might have one of two structures, (III) or (VI). The evidence that favors (III) and excludes (VI) lies in its behavior with nitrous acid. With this reagent, a nitrosoamine (VII) is formed; when the latter is heated, nitrogen is evolved and the thiazolone (VIII) results. This behavior is characteristic of iminobenzothiazolines (3).




Reduction of the nitrosoamine, which would be expected to give the hydrazone (IX), gives a substance, the analysis of which shows that a molecule of alcohol has been lost; the tricyclic structure (X) is provisionally suggested for this product.

The imino-ester (III) gives an imide (XI) when treated with ethyl acetoacetate; attempts to cyclize this substance to a 7-membered ring were unsuccessful, the only reaction observed being hydrolysis of the ester to the free acid.




XI

In the earlier paper (1), the failure of 2-acetoacetaminobenzothiazole to cyclize,

under conditions which resulted in ring closure with other heterocyclic acetoacetamides, was attributed to the inherent difficulty in forming the ring system composed of two fused 5-membered rings, attached, linearly, to a benzene nucleus. Subsequently, it has been claimed (4) that such a ring system is formed when 2-methylbenzobenzothiazole is treated with ethylene bromide. Now, in view of the well-known fact that alkylene halides in general give *bis*-quaternary salts with heterocyclic bases (5–10), it appears more likely that the substance mentioned in the patent (4) is, in reality, a "double-ender" salt.

As a test case, a substance described in example 1 of the patent was prepared from 2-methylbenzothiazole and trimethylene bromide.[1] This would form a 6-membered ring, and, thus, be the most favorable case to test. While the analytical figures for per cent of bromine do not distinguish between the two possibilities, the values for carbon differ by three per cent. The value, 45.0%, found for carbon agrees reasonably well with that calculated for the *bis*-salt (45.6%), and not with that calculated for a tricyclic ring system (48.8%). Consequently, it seems highly probable that all substances so obtained are *bis*-quaternary salts and not a 6,5,5-tricyclic system.

## EXPERIMENTAL

*2-Aminobenzothiazole chloroacetate*[2] crystallized when a hot (90°), clear solution of 3.7 g. of 2-aminobenzothiazole, 2.4 g. of chloroacetic acid, and 40 ml. of water was cooled. The yield was 5.5 g. (92%). The salt retains solvent of crystallization tenaciously; it melts at 119–120°, with previous sintering after recrystallization from water and drying in a current of warm air. Acetic acid is also a suitable solvent for the reaction.

*Anal.* Calc'd for $C_9H_9ClN_2O_2S$: C, 44.2; H, 3.7; N, 11.4.
Found: C, 44.2; H, 3.4; N, 11.5.

The free base is liberated upon treatment with potassium carbonate or sodium acetate.

*3-Carboxymethyl-2-iminobenzothiazoline* (I). A solution of 15 g. of 2-aminobenzothiazole in 50 ml. of alcohol was added to the sodium chloroacetate prepared by mixing 9.4 g. of chloroacetic acid, 5.3 g. of sodium carbonate, and 10 ml. of water. The clear solution was heated on the steam-bath for 24 hours, the alcohol removed *in vacuo*, and 80 ml. of water added. The crude product was filtered, taken up in 3% ammonium hydroxide, treated with Norit, filtered, and acidified. On chilling, the acid crystallized. The analytical sample was recrystallized from acetic acid; it melted at 258°.

*Anal.* Calc'd for $C_9H_8N_2O_2S$: N, 13.5. Found: N, 13.2.

The sodium salt of this acid separated in shimmering plates, on chilling a hot solution made up from 2 g. of the acid, 30 ml. of water, and 5.6 g. of a 40% sodium hydroxide solution.

*Anal.* Calc'd for $C_9H_7N_2NaO_2S$: S, 13.9. Found: S, 14.1.

*2-Amino-3-carboethoxymethylbenzothiazolium chloride* (II) separates from a mixture of 15 g. of 2-aminobenzothiazole, 10.6 g. of ethyl chloroacetate, and 30 ml. of alcohol, after 15 hours' refluxing. The yield was 20 g. (74%). After recrystallization from ethanol, the melting point was 240–242°.

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[1] This was selected instead of the benzobenzothiazole because the percentage compositions of the two products that could result from this heterocycle are too close to enable one to distinguish the two possibilities.

[2] We are pleased to acknowledge the assistance of Dr. J. H. Clark, Mr. C. O Edens, and Miss E. R. Webster, who are responsible for the work in which acetic acid was used as a solvent, for the regeneration of the base, and for the preparation of analytical samples.

*Anal.* Calc'd for $C_{11}H_{13}ClN_2O_2S$: C, 48.5; H, 4.8; N, 10.3.
Found: C, 48.6; H, 4.5; N, 10.2.

The free base (III) is obtained by adding a hot sodium carbonate solution to a hot aqueous solution of the chloride; the yield was 10 g. (85%); the melting point was 122–123° after recrystallization from ethanol.

*Anal.* Calc'd for $C_{11}H_{12}N_2O_2S$: N, 11.9. Found: N, 12.0.

*3-Carboethoxymethyl-2-nitrosiminobenzothiazoline* (VII). To a solution of 7.2 g. of the base (III) in 40 ml. of acetic acid at room temperature was gradually added 3 g. of sodium nitrite in 16 ml. of water. The yellow solid that separated in a yield of 7.5 g. was crystallized from ethyl acetate; it melts at 148–149°, with decomposition.

*Anal.* Calc'd for $C_{11}H_{11}N_3O_3S$: N, 15.8; S, 12.1.
Found: N, 15.8; S, 11.8.

*3-Carboethoxybenzothiazolone* (VIII) was obtained by refluxing a solution of 4 g. of the nitroso derivative (VII) in 20 ml. of xylene for 1.5 hours; there was considerable foaming as the nitrogen was evolved. Most of the solvent was distilled, whereupon the thiazolone crystallized. It separated from ligroin (b.p. 90–120°) in long white needles; m.p. 96°.

*Anal.* Calc'd for $C_{11}H_{11}NO_3S$: S, 13.50. Found: S, 13.53.

*2-Acetoacetimino-3-carboethoxymethylbenzothiazoline* (XI) was prepared by the usual procedure (11) from a mixture of 7 g. of ethyl acetoacetate, 11.8 g. of the imino-ester (III), and 40 ml. of xylene; the solid that separated, when the solution was chilled, was recrystallized from benzene. The yield of product, m.p. 128°, was 12.3 g. (77%).

*Anal.* Calc'd for $C_{15}H_{16}N_2O_4S$: C, 56.2; H, 5.0.
Found: C, 56.1; H, 5.0.

The sodium salt of the acid resulted when 6 g. of the ester was refluxed for 2 hours with sodium ethoxide (made from 50 ml. of absolute methanol and 0.3 g. of sodium). The free acid was obtained by acidifying an aqueous solution of the salt; it melts at 168° after recrystallization from water.

*Anal.* Calc'd for $C_{13}H_{12}N_2O_4S$: C, 53.4; H, 4.1.
Found: C, 53.7; H, 3.9.

*3-Keto-3,4-dihydro-2H,1,2,4a-triaza-9-thiafluorene* (X). To a well-stirred mixture of 10 g. of the nitroso compound, 50 ml. of acetic acid, and 50 ml. of water, 20 g. of zinc dust was added in portions, the temperature being kept below 15°. After 1 hour, 10 ml. more of acetic acid was added, and the temperature allowed to rise to 21°, whereupon the suspension was decolorized. After the excess zinc was filtered, the filtrate was made alkaline with ammonium hydroxide, and the base was filtered; the yield was 8.4 g. After recrystallization from alcohol, the melting point was 260°.

*Anal.* Calc'd for $C_{11}H_{13}N_3O_2S$: N, 20.5. Found: N, 20.4.

*Trimethylene-bis-2-methylbenzothiazolium bromide* was prepared as directed (4); it melted at 254–256°, with decomposition.

*Anal.* Calc'd for a *bis*-salt, $C_{19}H_{20}Br_2N_2S_2$: C, 45.6; H, 4.0.
Calc'd for 3-ring substance, $C_{11}H_{12}BrNS$: C, 48.8; H, 4.5.
Found: C, 45.0; H, 3.9.

SUMMARY

2-Aminobenzothiazole forms a simple salt with chloroacetic acid, but sodium and ethyl chloroacetates give addition products from which 3-carboxymethylbenzothiazolines and 3-carboethoxymethylbenzothiazolines are easily obtainable. The behavior of these substances is contrasted with that of aminopyridylglycine. Other related compounds are described.

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## REFERENCES

(1) ALLEN, VANALLAN, AND WILSON, *J. Am. Chem. Soc.*, **66**, 1807 (1944).
(2) KIRPAL AND WOJNAR, *Ber.*, **71**, 1264 (1938).
(3) BESTHORN, *Ber.*, **43**, 1519 (1910).
(4) SCHWARZ, VANRYSWYCKLAAN, AND DESMIT, Brit. Patent 587,434 (1947) [*Chem. Abstr.* **42**, 619 (1948)].
(5) DAVIDSON, *Ann.*, **121**, 254 (1862).
(6) BAER AND PRESCOTT, *J. Am. Chem. Soc.*, **18**, 988 (1896).
(7) ALLEN AND VANALLAN, U. S. Patent 2,268,533 (1941) [*Chem. Abstr.*, **36**, 2732 (1942)].
(8) CARROLL AND ALLEN, U. S. Patent 2,288,226 (1942) [*Chem. Abstr.*, **37**, 45 (1943)].
(9) ALLEN AND WILSON, U. S. Patent 2,299,782 (1942) [*Chem. Abstr.*, **37**, 1724 (1943)].
(10) WILSON, U. S. Patent 2,425,774 (1947) [*Chem. Abstr.*, **42**, 50 (1948)].
(11) KIBLER AND WEISSBERGER, *Org. Syntheses*, **25**, 7 (1945).