ALKYLATION OF AMINOTHIAZOLES

X.* ALKYLATION OF 2-AMINO-4-ETHYLTHIAZOLE

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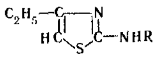
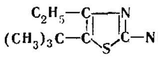
2-Alkylamino-4-ethylthiazoles were obtained by the alkylation of 2-amino-4-ethylthiazole with secondary alcohols, while 2-amino-4-ethyl-5-tert-butylthiazole was obtained by the reaction of the thiazole with tert-butyl alcohol.

2-Aminothiazoles are alkylated by secondary alcohols to form 2-alkylaminothiazoles [2-4], but alkylation proceeds at the 5 position of the thiazole ring in the case of tert-butyl alcohol [5]. In order to further study the alkylation of aminothiazoles with secondary and tertiary alcohols in sulfuric acid solutions, we have studied the alkylation of 2-amino-4-ethylthiazole. We obtained yields of up to 76% of 2-alkylamino-4-ethylthiazoles (I) from isopropyl alcohol, sec-butyl alcohol, and cyclohexanol. tert-Butyl alcohol gives 2-amino-ethyl-5-tert-butylthiazole (II).



I



II

The structure of the alkylation products (I) was proved by their synthesis from 1-chloro-2-butanone and the appropriate 1-alkylthiourea [6]; the presence of a free amino group in II was proved by replacement of the amino group by halogen via the Sandmeyer reaction by a method similar to that in [7].

EXPERIMENTAL

2-Amino-4-ethylthiazole was prepared from 1-chloro-2-butanone and thiourea and had bp 108-110° (3-4 mm) [bp 140° (23 mm) [5]].

Alkylation of 2-Amino-4-ethylthiazole. 2-Amino-4-ethylthiazole [6.4 g (0.05 mole)] was dissolved with cooling in 70 ml of 80% sulfuric acid in such a way that the temperature did not exceed 30°, and the mixture was stirred until all of the solid had dissolved. The solution was heated to 80° (in the case of isopropyl or sec-butyl alcohols) or to 60° (in the case of cyclohexanol), and 0.05 mole of the anhydrous alcohol was added from a dropping funnel with vigorous stirring. The mixture was stirred at the specified temperature for 4-6 h, cooled, and poured into 150 g of ice. The mixture was cooled while it was neutralized with concentrated ammonium hydroxide. The amine, which separated as an oil, was extracted with benzene, and the benzene layer was dried with solid KOH and vacuum distilled.

In the case of tert-butyl alcohol, the alkylation was carried out at 20-25°.

2-Isopropylamino-4-ethylthiazole. This compound was obtained in 76% yield as a colorless viscous oil with bp 109-111° (3 mm). On cooling it crystallized to give opaque little needles with mp 104-105° (from n-octane). Found %: N 16.4. $C_8H_{14}N_2S$. Calculated %: N 16.4. The product of the reaction of 1-chloro-2-butanone with 1-isopropylthiourea had mp 104°. A mixture of the two products melted without a melting point depression. The picrate was obtained as little yellow needles with mp 218° (from acetic acid). Found %: N 17.4. $C_8H_{14}N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 17.5.

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*See [1] for communication IX.

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2-sec-Butylamino-4-ethylthiazole. This compound was obtained in 72% yield as a yellowish oil with bp 117-118° (4 mm) and n_D^{20} 1.5535. Found %: N 15.4. $C_9H_{16}N_2S$. Calculated %: N 15.5. The picrate was obtained as filamentary yellow needles with mp 234° (dec., from acetic acid). Found %: N 17.1. $C_9H_{16}N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 16.9. The product of the reaction of 1-chloro-2-butanone with 1-sec-butylthiourea gave a picrate, a mixture of which with the picrate described above melted at 233-234°.

2-Cyclohexylamino-4-ethylthiazole. This was obtained as a viscous, yellowish oil with bp 140-145° (3 mm) that crystallized on cooling to give 60% of a product with mp 66-67° (from petroleum ether). Found %: N 13.6. $C_{11}H_{18}N_2S$. Calculated %: N 13.8. The product of the reaction of 1-chloro-2-butanone with 1-cyclohexylthiourea had mp 67°. A mixture of the two products melted without depression. The picrate was obtained as little yellow needles with mp 208-209° (from acetic acid). Found %: N 16.0. $C_{11}H_{18}N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 16.2.

2-Amino-4-ethyl-5-tert-butylthiazole. This compound was obtained in 76% yield by the standard method with an amine–alcohol ratio of 1 : 1.5. The colorless oil had bp 115-118° (3 mm). It crystallized on cooling to give a product with mp 92-93° (from n-heptane). Found %: N 15.5. $C_9H_{16}N_2S$. Calculated %: N 15.5. The picrate was obtained as yellow needles with mp 213° (dec., from alcohol). Found %: N 16.8. $C_9H_{16}N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 16.9.

2-Acetamido-4-ethyl-5-tert-butylthiazole. This was obtained as colorless leaflets with mp 194-195° (from dilute alcohol) by heating the base in acetic anhydride. Found %: N 11.8. $C_{11}H_{18}N_2OS$. Calculated %: N 11.6.

2-Salicylamido-4-ethyl-5-tert-butylthiazole. Equimolar amounts of the base and phenyl salicylate were heated at 160-170° for 6 h. The phenol was removed by steam distillation, and the residue was crystallized from dilute acetic acid to give colorless little needles with mp 186-187°. Found %: N 9.3. $C_{16}H_{20}N_2O_2S$. Calculated %: N 9.2.

2-Chloro-4-ethyl-5-tert-butylthiazole. Dry $NaNO_2$ (2.5 g) was added with stirring at –5° to a solution of 4.6 g (0.025 mole) of II in 50 ml of 5 N hydrochloric acid, and the mixture was stirred for 30 min. The resulting diazonium solution was added dropwise to 3.75 g of copper carbonate in 50 ml of 5 N hydrochloric acid. The solution was allowed to stand overnight and made alkaline with 40% NaOH. The chlorothiazole was removed by steam distillation, extracted with ether, dried, and vacuum distilled to give 3 g (60%) of a colorless oil with a slight camphor odor, bp 78-81° (4 mm), and n_D^{19} 1.5115. Found %: Cl 17.5; N 7.0. $C_9H_{14}ClNS$. Calculated %: Cl 17.4; N 6.9.

2-Bromo-4-ethyl-5-tert-butylthiazole. A solution of 4.6 g (0.025 mole) of II in 50 ml of 80% orthophosphoric acid was placed in a three-necked flask with a dropping funnel (lowered to the bottom), a stirrer, and a thermometer. A total of 4.5 ml of 65% HNO_3 was then added through the dropping funnel, and the mixture was cooled to –5° and held at this temperature for 1 h. At the same temperature, a solution of 2.7 g of $NaNO_2$ in 10 ml of water was added, and the mixture was allowed to stand at this temperature for 1 h. A solution of 5 g of $CuSO_4 \cdot 5H_2O$ in 20 ml of water was prepared separately, and a solution of a diazonium salt and a solution of 5 g of NaBr in 10 ml of water were added dropwise simultaneously to this solution. The mixture was allowed to stand overnight and was then neutralized with sodium carbonate. The oil was extracted with ether, dried with anhydrous Na_2SO_4, and vacuum distilled to give 3 g (50%) of a colorless oil with a slight camphor odor, bp 90-92° (4 mm), and n_D^{19} 1.5360. Found %: Br 32.1; N 5.6. $C_9H_{14}BrNS$. Calculated %: Br 32.2; N 5.6.

4-Ethyl-5-tert-butylthiazole. A solution of 2 g (0.01 mole) of 2-chloro-4-ethyl-5-tert-butylthiazole in 15 ml of glacial acetic acid was heated almost to the boiling point, and 1 g of zinc dust was added gradually. The mixture was refluxed for 1 h, made alkaline, and the thiazole was removed by steam distillation. Extraction with ether, drying with KOH, and distillation gave 1.3 g (77%) of a colorless oil with a camphor odor, bp 60-62° (8 mm), and n_D^{15} 1.5570. Found %: N 8.1. $C_9H_{15}NS$. Calculated %: N 8.3.

LITERATURE CITED

1. V. A. Krasovskii and S. I. Burmistrov, Khim. Geterotsikl. Soedin., No. 3, 168 (1971).
2. S. I. Burmistrov and V. A. Krasovskii, Zh. Obshch. Khim., 34, 685 (1964).
3. S. I. Burmistrov and V. A. Krasovskii, Zh. Obshch. Khim., 34, 3822 (1964).
4. V. A. Krasovskii and S. I. Burmistrov, Khim. Geterotsikl. Soedin., 303 (1965).

5. V. A. Krasovskii and S. I. Burmistrov, Khim. Geterotsikl. Soedin., 56 (1969).
6. I. Metzger and B. Koether, Ann. Univ. Saraviensis, 1, 23 (1952); Chem. Abstr., 47, 10,524 (1953).
7. P. Roussel and I. Metzger, Bull. Soc. Chim. France, 2075 (1962).