ALKYLATION OF AMINOTHIAZOLES

VII. Alkylation of 2-Aminothiazole and 2-Amino-4-methylthiazole with tert-Butyl Alcohol*

V. A. Krasovskii and S. I. Burmistrov

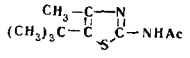
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 56–58, 1969

UDC 547.789.1:542.951

The alkylation of 2-aminothiazole and 2-amino-4-methylthiazole with tert-butyl alcohol in sulfuric acid has been repeated. In correction of preceding information, it has been found that alkylation takes place in position 5 of the thiazole ring and not at the amino group. The presence of a primary amino group in the alkylation products was shown by the production of arylsulfonyl derivatives soluble in alkalies and of 2-halothiazoles by the Sandmeyer replacement of the amino group by halogen. Alkylation with alkyl halides yielded the corresponding thiazolone imides.

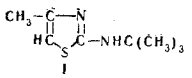
In a paper published previously [1], it was reported that 2-amino-4-methylthiazole is alkylated by tert-butyl alcohol, and that this gives a crystalline substi-

Table 1

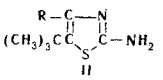


Ac	Mp, °C	N, % found	N, % calculated
$C_6H_5SO_2$	191.5—192.5	9.08	9.01
p-$CH_3C_6H_4SO_2$	166	9.00	8.91
p-$ClC_6H_4SO_2$	208—209	9.10	8.99
p-$NO_2C_6H_4CO$	187—188	13.04	13.15
m-$NO_2C_6H_4CO$	164—165	13.28	13.15
C_6H_5CO	103—103.5	11.60	11.56

tution product to which we ascribed the structure of 2-tert-butylamino-4-methylthiazole (I).

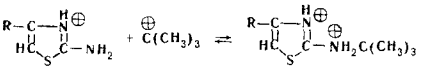


I



II

However, at that time we noted a markedly different behavior of the alkylation product with respect to diazonium salts (only a weak yellow coloration with p-nitrobenzenediazonium salts), which led us to doubt the correctness of formula I for the alkylation product. In actual fact, further investigations have shown that both 2-amino-4-methylthiazole and 2-aminothiazole unsubstituted in position 4 alkylate at a carbon atom of the thiazole ring to give 2-amino-4-R-5-tert-butylthiazoles (II) (R = H, CH_3). The presence of a primary, and not a secondary, amino group in the alkylation products was shown by the preparation of arenesulfonyl derivatives soluble in alkalies and also by the replacement of the amino group by halogen (chlorine, bromine) using the Sandmeyer reaction. Apparently, in this case alkylation at the exocyclic nitrogen atom does not take place because of the low stability of the doubly charged cation formed from the cation of the aminothiazole salt and the tertiary butyl cation, i.e., because of the shift to the left of the equilibrium,



In fact, the low stability of N-tert-butyl substituted derivatives has been observed for other weak bases, for example arylsulfonamides [2]; 2-aminopyridine also does not alkylate with tert-butyl alcohol [3].

In an attempt to obtain I by independent synthesis from 1-tert-butylthiourea and bromoacetone, intermolecular migration of the tert-butyl radical from the nitrogen atom to position 5 apparently took place.

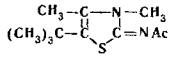
EXPERIMENTAL

The alkylation of the 2-amino-4-methylthiazole was carried out by the method described previously [1]. The yield of **2-amino-5-tert-butyl-4-methylthiazole** at a ratio of amine to alcohol of 1 : 15 was 90%. The **picrate** was obtained by precipitating an alcoholic solution of the base with an alcoholic solution of picric acid. Short yellow needles, mp 215–216° C (from ethanol). Found, %: N 17.46. Calculated for $C_8H_{14}N_2S \cdot C_6H_3N_3O_7$, %: N 17.53.

5-tert-Butyl-4-methyl-2-salicyloylaminothiazole. Equimolar amounts of the base and phenyl salicylate were heated at 160–170° C for 6 hr. The phenol was

*For part VI, see [6].

Table 2



Ac	Mp, °C	N, % found	N, % calculated
$C_6H_5SO_2$	184—185	8.50	8.63
p-$CH_3C_6H_4SO_2$	166—167	8.34	8.27
p-$ClC_6H_4SO_2$	153	8.05	7.80
p-$CH_3CONHC_6H_4SO_2$	196—197	11.04	11.01
C_6H_5CO	145—146	9.71	9.78
m-$NO_2C_6H_4CO$	207—208	12.50	12.60
p-$NO_2C_6H_4CO$	190	12.43	12.60

Table 3

Acyl Derivatives of 2-Amino-5-tert-butylthiazole

Ac	Mp, °C	N, %	
		found	calculated
o-HOC_6H_4CO	139–140	9.98	10.13
p-$CH_3C_6H_4SO_2$	176–177	9.05	9.02
$C_6H_5SO_2$	146–147	9.35	9.45

distilled off with steam and the residue was crystallized from acetic acid. Elongated white prisms, mp 223° C. Found, %: N 10.23. Calculated for $C_{15}H_{18}N_2O_2S$, %: N 10.36.

The arylsulfonyl and benzoyl derivatives were obtained by boiling solutions of the base, the sulfonyl chloride or benzoyl chloride, and sodium carbonate in acetone for 2 hr. They were purified by crystallization from ethanol (Table 1). The arylsulfonyl derivatives were soluble on gentle heating in 5–10% alkali solution.

2-Bromo-5-tert-butyl-4-methylthiazole. A three-necked flash with a dropping funnel reaching to the bottom, a stirrer, and a thermometer, was charged with 34 g (0.2 mole) of the base in 80 ml of 80% orthophosphoric acid. Then 36 ml of 65% HNO_3 cooled to −5° C was added through the dropping funnel and the mixture was kept for 1 hr, after which a solution of 17.2 g (0.25 mole) of sodium nitrite in 20 ml of water was added at the same temperature. The mixture was left for 1 hr. A solution of 40 g of $CuSO_4 \cdot 5H_2O$ in 120 ml of water was prepared separately in a one-liter flask, and to this solution were added simultaneously, dropwise, the diazonium solution and a solution of 40 g (0.4 mole) of NaBr in 50 ml of water. The resulting mixture was left overnight and was neutralized with sodium carbonate; the oil was extracted with ether and the extract was dried with anhydrous $CaCl_2$ and distilled in vacuum; bp 90–92° C (3 mm). Colorless oil crystallizing on cooling. Colorless needles with a camphor-like smell, mp 46–47° C (from n-hexane). Yield 20 g (43%). Found, %: N 5.88; S 13.68; Br 34.12. Calculated for $C_8H_{12}NBrS$, %: N 6.00; S 13.79; Br 34.27.

5-tert-Butyl-2-chloro-4-methylthiazole. A solution of 17 g (0.1 mole) of the base in 150 ml of 5N HCl was cooled to −5° C and, with vigorous stirring, 10 g of dry $NaNO_2$ was added and stirring was continued for 30 min. The resulting diazonium solution was added dropwise to 15 g of copper acetate in 100 ml of 5N HCl. The solution was left overnight and made alkaline with 40% NaOH, after which the chlorothiazole was distilled off with steam and extracted with ether, and the extracts were dried and distilled in vacuum. Colorless oil with a camphor-like smell, bp 78–80° C (5 mm), n_D^{20} 1.5330, d_{18}^{18} 1.0874. Yield 10.5 g (56%). Found, %: N 7.56; S 16.75; Cl 18.52. Calculated for $C_{18}H_{12}NClS$, %: N 7.56; S 16.90; Cl 18.68. The **picrate** of the chlorothiazole was obtained by the precipitation of alkaline solutions. Yellow needles, mp 145.5–146.5° C (from ethanol). Found, %: N 13.48. Calculated for $C_{18}H_{12}NSCl \cdot C_6H_3N_3O_7$, %: N 13.37.

5-tert-Butyl-4-methylthiazole. A solution of 11.7 g (0.05 mole) of 2-bromo-5-tert-butyl-4-methylthiazole in 30 ml of glacial acetic acid was heated almost to the boil, and 8 g of zinc dust was added gradually. The mixture was boiled for 1 hr and was made alkaline, and the thiazole was distilled off with steam. After extraction with ether, drying with KOH, and distillation in vacuum, 6.5 g (84%) of a colorless oil with a camphor like smell was obtained; bp 50–52° C (3 mm), n_D^{20} 1.5065, d_{18}^{18} 1.0065. Found, %: N 9.04; S 20.56. Calculated for $C_8H_{13}NS$, %: N 9.02; S 20.65. **Picrate**—yellow leaflets, mp 147–148° C (from methanol). Found, %: N 14.44. Calculated for $C_8H_{13}NS \cdot C_6H_3N_3O_7$, %: N 14.57.

5-tert-Butyl-3,4-dimethyl-2-thiazolone imide. A mixture of 17 g (0.1 mole) of 2-amino-5-tert-butyl-4-methylthiazole and 17 g (7.6 ml; 0.12 mole) of methyl iodide was boiled for 2 hr in 40 ml of n-propanol and cooled, and the white crystals were filtered off. Yield 17 g (50%); mp 212–213° C (from water). Found, %: N 9.04. Calculated for $C_9H_{16}N_2S \cdot HI$, %: N 9.03.

The free **base** was isolated by alkalinizing with 40% NaOH, extracting with benzene, and distilling in vacuum. Colorless oil, bp 120–122° C (3 mm), n_D^{20} 1.5530, d_{18}^{18} 1.0792. Found, %: N 15.02. Calculated for $C_9H_{16}N_2S$, %: N 15.20. **Picrate**—small yellow needles, mp 191–192° C (from ethanol). Found, %: N 17.09. Calculated for $C_9H_{16}N_2S \cdot C_6H_3N_3O_7$, %: N 16.94.

5-tert-Butyl-3,4-dimethyl-2-thiazolone acetylimide. This was obtained by boiling in acetic anhydride. Colorless needles, mp 116–117° C (from aqueous ethanol). Found, %: N 12.22. Calculated for $C_{11}H_{18}N_2OS$, %: N 12.37.

5-tert-Butyl-3,4-dimethyl-2-thiazolone salicyloylimide. Parallelipipeds with a greenish tinge, mp 203–204° C (from acetic acid). Found, %: N 9.09. Calculated for $C_{16}H_{20}N_2O_2S$, %: N 9.20.

Table 2 gives the arylsulfonyl and benzoyl derivatives of 5-tert-butyl-3,4-dimethyl-2-thiazolone imide.

2-Amino-5-tert-butylthiazole was obtained by alkylating 2-aminothiazole with tert-butyl alcohol [4]. At a ratio of amine to alcohol of 1 : 1.5, the yield of alkylation product was 85%. Table 3 gives some acyl derivatives of 2-amino-5-tert-butylthiazole.

2-Bromo-5-tert-butylthiazole. Obtained in a similar manner to the 4-methyl analog. Colorless oil, bp 77–78° C (5–6 mm), n_D^{20} 1.5365, d_{20}^{20} 1.3823. Yield 12 g (55%). Found, %: N 6.23. Calculated for $C_7H_{10}NSBr$, %: N 6.36.

5-tert-Butylthiazole. Obtained from the preceding compound in a similar manner to the 4-methyl analog. Colorless oil with a camphor-like smell, bp 53° C (5 mm), n_D^{20} 1.5000, d_{20}^{20} 1.0116. Yield 67%. Found, %:

N 9.96. Calculated for $C_7H_{11}NS$, %: N 9.91. According to the literature [5], the boiling point of 5-tert-butylthiazole is 117° C (100 mm), n_D^{25} 1.4988, d_4^{25} 1.0046. **Picrate**—yellow leaflets, mp 131–132° C (from methanol). Found, %: N 15.01. Calculated for $C_7H_{11}NS \cdot C_6H_3N_3O_7$, %: N 15.12. According to the literature [5], mp 132° C.

REFERENCES

1. S. I. Burmistrov and V. A. Krasovskii, ZhOKh, 34, 685, 1964.

2. S. I. Burmistrov and V. I. Markov, Ukr. khim. zhurn., 27, 663, 1961.

3. S. I. Burmistrov and V. A. Krasovskii, KhGS [Chemistry of Heterocyclic Compounds], 3, 174, 1967.

4. S. I. Burmistrov and V. A. Krasovskii, ZhOKh, 34, 3822, 1964.

5. M. Poite and J. Metzger, Bull. Soc. chim. France, 2078, 1962.

6. V. A. Krasovskii and S. I. Burmistrov, KhGS [Chemistry of Heterocyclic Compounds], 3, 154, 1967.

26 October 1966

Dnepropetrovsk Chemical and Technological Institute