ALKYLATION OF 2-AMINOTHIAZOLES

VI. Alkylation of 3,4-Dimethylthiazolone-2-Imide*

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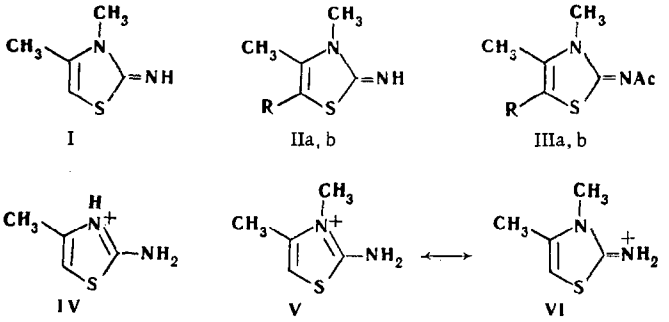
Alkylation of 3,4-dimethylthiazolon-2-imide with isopropanol or tert-butanol gives 3,4-dimethyl-5-alkylthiazolon-2-imides in up to 60% yield. Acyl derivatives are prepared.

Previous papers described the alkylation of 2-amino-4-methylthiazole [1] and 2-methylamino-4-methylthiazole [2] with secondary and tertiary alcohols in 80–85% H_2SO_4 at 20–90°. It is known that alkylation of 2-methylamino-4-methylthiazole leads to entry of the alkyl group at position 5 in the thiazole ring [2]. Developing the research, we undertook alkylation of 3,4-dimethylthiazolon-2-imide (I) with isopropanol and tert-butanol in 80–85% H_2SO_4, to find out the mode of alkylation of a compound isomeric with 2-methylamino-4-methylthiazole. It was found that under the stated conditions 3,4-dimethylthiazolon-2-imide alkylates to type II compounds. From the failure to couple with a p-nitrophenyldiazonium salt and formation of acyl derivatives III, it can be concluded that in alkylation the alkyl group enters at position 5 in the thiazole ring, and that the reaction products are 3,4-dimethyl-5-alkylthiazolon-2-imides (II).

The absence of alkylation at the nitrogen atom outside the ring, unlike what is found with 2-amino-4-methylthiazole, is of considerable theoretical interest. Actually the cation of the salt of 2-amino-4-methylthiazole IV differs from the cation of the salt of compound I only by absence of a methyl group at the ring nitrogen atom, and in electronic structure, it would appear, they should be similar. It would scarcely be possible to explain the mode of alkylation, by the presence of steric hindrance to entry of the alkyl group at the non-cyclic nitrogen atom. We are more inclined to explain the fact by the presence of two methyl groups at adjacent nitrogen and carbon atoms causing, in the cation of the salt of compound I, obstacles to formation of a cation with structure V, and consequently the positive charge is mainly concentrated on the nitrogen atom outside the ring (cation structure closer to VI than to V).



I IIa, b IIIa, b

IV V VI

a R = *i*-C_3H_7; b R = *t*-C_4H_9; Ac = acyl

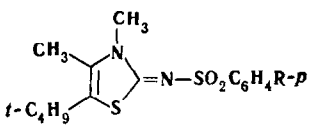
EXPERIMENTAL

3,4-Dimethylthiazolon-2-imide (I) was prepared from 2-amino-4-methylthiazole and methyl iodide [3]. It was characterized as 3,4-dimethylthiazolon-2(p-toluenesulfonyl)imide* (III, R = H, Ac-p-$MeC_6H_4SO_2$). Colorless crystals, mp 205–206°. Found: N 10.60%. Calculated for $C_{12}H_{14}N_2O_2S_2$. N 9.92%.

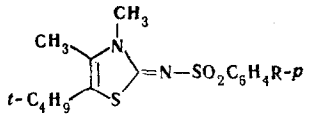
3,4-Dimethyl-5-isopropylthiazolon-2-imide (IIa). 6.4 g (0.05 mole) I was dissolved in 100 ml 85% H_2SO_4, heated to 80–90°, and 4.5 g (0.075 mole) dry isopropanol added dropwise. The mixture was held at 80° for 4 hr, cooled, poured onto ice, and neutralized with conc. NH_4OH. The mixed amines were extracted with benzene, the benzene extract dried over Na_2SO_4, the benzene distilled off at atmospheric pressure, and the residue vacuum-distilled. Yield 4.5 g (53%). Yellow oil, bp 113–115° (3 mm); n_D^{19} 1.5485; d_4^{20} 1.045.

*For Part V see [5].

*All the arylsulfanilamide derivatives were prepared by treating the corresponding bases with the arylsulfonyl chloride in acetone solution in the presence of Na_2CO_3, and were recrystallized from ethanol.



R	Formula	Mp, °C	N, % found	N, % calculated
Cl	$C_{14}H_{17}ClN_2O_2S_2$	139–140	8.34	8.12
H	$C_{14}H_{18}N_2O_2S_2$	117–118	9.36	9.02
CH_3	$C_{15}H_{20}N_2O_2S_2$	90–92	8.26	8.66
CH_3CONH	$C_{16}H_{21}N_3O_3S_2$	266–268	11.61	11.43



R	Formula	Mp, °C	N, % found	N, % calculated
Cl	$C_{15}H_{19}ClN_2O_2S_2$	147—147.5	8.01	7.79
H	$C_{15}H_{20}N_2O_2S_2$	174—175.5	9.16	8.63
CH_3	$C_{16}H_{22}N_2O_2S_2$	158.5—159.5	8.05	8.27
CH_3CONH	$C_{17}H_{23}N_3O_3S_2$	189—190	11.10	11.62

Found: N 16.33%, MR_D 51.8. Calculated for $C_8H_{14}N_2S$. N 16.45%; MR_D 50.9. The refraction of the C—S bond was assumed to be 4.61 [4]. The picrate was prepared by precipitating the base with an ethanol solution of picric acid. Yellow fibrous needles, mp 167.5° (ex AcOH). Found: N 17.25%. Calculated for $C_8H_{14}N_2S \cdot C_6H_3N_3O_7$. N 17.54%.

Arylsulfonylation of IIIa gave, similarly, 3,4-dimethylthiazolon-2-(p-toluenesulfonyl)imide (Table 1).

3,4-Dimethyl-5-isopropylthiazolon-2-(p-aminobenzenesulfonyl)-imide (IIIa) Ac-p-$NH_2C_6H_4SO_2$). Prepared by 4 hr refluxing of 3,4-dimethyl-5-isopropylthiazolon-2-(p-acetamidobenzenesulfonyl)imide with 15% HCl, followed by neutralization with NH_4OH. Brownish leaflets, mp 209–210°. Found: N 12.65%. Calculated for $C_{14}H_{19}N_3O_2S_2$. 12.91%.

3,4-Dimethyl-5-isopropylthiazolon-2-acetimide (IIIa, Ac-MeCHO). Prepared by boiling the base with acetic anhydride. Colorless leaflets, mp 117–118° (ex EtOH). Found: N 13.10%. Calculated for $C_{10}H_{16}N_2OS$. N 13.19%.

3,4-Dimethyl-5-isopropylthiazolon-2-benzoylimide (IIIa, Ac-C_6H_5CO). Prepared by boiling the base with benzoyl chloride and $NaHCO_3$ in acetone. Greenish needles, mp 129–130° (ex EtOH). Found: 10.05%. Calculated for $C_{15}H_{18}N_2OS$. N 10.21%.

3,4-Dimethyl-5-tert-butylthiazolon-2-imide (IIb). 6.4 g (0.05 mole) I was dissolved in 100 ml 85% H_2SO_4, and 5.5 g (0.075 mole) tert-BuOH added gradually. After 24 hr the products were poured onto ice, and worked up as described for the isopropyl homolog. Yield 5.5 g (60%). Straw colored oil, bp 130–132° (3–4 mm); n_D^{20} 1.5500; d_4^{20} 1.053. Found: N 15.31%. MR_D 55.76. Calculated for $C_9H_{16}N_2S$. N 15.25%. MR_D 55.54. Picrate, colorless fibrous needles, mp 190–191° (ex water). Found: N 16.70%. Calculated for $C_9H_{16}N_2S \cdot C_6H_3N_3O_7$: N 7.79%.

3,4-Dimethyl-5-tert-butylthiazolon-2-acetimide (IIIb, Ac-MeCO). Prepared by boiling the base with Ac_2O. Minute colorless needles, mp 120° (ex EtOH). Found: N 12.09%. Calculated for $C_{11}H_{18}N_2OS$. N 12.38%.

3,4-Dimethyl-5-tert-butylthiazolon-2-benzoylimide) (IIIb, Ac-C_6H_5CO). Minute colorless needles, mp 140.5–141.5° (ex EtOH). Found: N 9.72%. Calculated for $C_{16}H_{20}N_2OS$. N 9.72%.

3,4-Dimethyl-5-tert-butylthiazolon-2-(o-hydroxybenzoyl)imide (IIIb, Ac-o-HOC_6H_4CO). Prepared by heating the base with salol in an oil-bath (4 hr, 170°), after which the phenol was steam-distilled off, and the residue recrystallized from AcOH. Minute colorless crystals, triangles under a microscope, mp 196–197°. Pale-green fluorescence in UV light. Found: N 9.02%. Calculated for $C_{16}H_{20}N_2O_2S$. N 9.20%.

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SYNTHESIS OF CHLORINATED 1,3-DIOXANES

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A new synthesis of chlorine-substituted 1,3-dioxanes is effected from methylallyl chloride and isocrotyl chloride by condensing them with paraformaldehyde in the presence of KU-2 cation-exchange resin.

One of the present authors first showed that the Prins reaction could be effected in the presence of a cation-exchange resin [1]. It was of interest to investigate the reaction using other olefins, particularly the chlorine-substituted olefins, methylallyl chloride and isocrotyl chloride. The synthesis of chlorine-substituted 1,3-dioxanes from these olefins had been carried out using mineral acids as the catalyst.