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COURSE OF BROMINATION OF THIAZOLE AND 2-METHYLTHIAZOLE

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Bromination of thiazole by bromine in the presence of aluminum chloride in neutral solvent or without solvent takes place at the 2-position. Such an orientation contradicts the traditional addition–cleavage mechanism, and agrees with the ylid mechanism of electrophilic substitution. 2-Methylthiazole brominates at the 5-position, and the reaction is impeded in the presence of aluminum chloride; this is due to heterocycle deactivation by complexation with the Lewis acid at the nitrogen atom.

We recently showed [1] that 2-phenylthiazole is smoothly brominated at the 5-position of the thiazole ring by bromine in a neutral solvent (benzene or chloroform). 2-Phenylthiazole can be considered as an analog of biphenyl. As established by ^{13}C NMR spectra and quantum chemical calculations [2], already in the ground state there is a transfer of electron density from the benzene ring to the thiazole; this is apparently the reason, to a substantial extent, for the high reactivity of the thiazole ring in electrophilic substitution.

In the present work we have studied the bromination of unactivated unsubstituted thiazole and of 2-methylthiazole. It is known that thiazole can not be brominated by bromine in a neutral solvent: only the perbromide is formed [3]. We used conditions that had previously permitted pyridine to be brominated [4], viz., the action of bromine in the presence of a catalytic amount of $AlCl_3$ in carbon tetrachloride or without solvent. Here we obtained a small yield of a mixture in which the main product, and also the only monobromothiazole, was 2-

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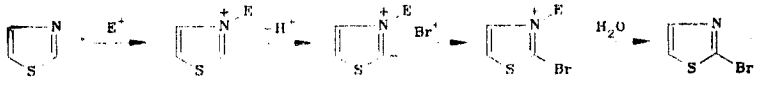
bromothiazole. Such a result was unexpected because for 1,3-azoles in electrophilic substitution by the addition–cleavage mechanism the relative reactivity of the positions changes in the sequence 5 > 4 ≫ 2. Furthermore, attack at $C_{(2)}$ is extremely unfavorable due to participation in positive charge delocalization by limiting σ-complex structures:

with a positively charged bivalent nitrogen [5, 6].

2-Bromothiazole formation can be explained if we assume that it occurs by the so-called ylid mechanism of electrophilic substitution; in recent years this has been studied quite widely for 1,3-azoles, in particular thiazole (see, e.g., [6-8]). This mechanism calls for the initial formation of an azolium cation that easily cleaves a proton from the 2-position to form an ylid, which in turn adds an electrophilic particle to become 2-substituted (in the quaternized form). The possibility is not excluded that ylid formation promotes not only quaternization but also complexation with aluminum chloride at nitrogen. In this connection we point out that complexation with $AlCl_3$ and protonation at nitrogen lead to similar changes in electron density distribution in the 2-methylthiazole molecule [2]. As regards the bromination of thiazole the process can be described by the following scheme:



E–Br, H, Al Cl_3

We note that in all the cases of direct thiazole bromination previously described, the only monobromide is 2-bromothiazole. It is difficult to decide about the mechanism of high-temperature bromination [3] at 250-400° in the vapor phase, but the bromination of N-bromosuccinimide in CCl_4, which gives ∿10% of 2-bromothiazole [9], probably follows the above scheme. One of the reasons for the low yield under the conditions of [9] is, in our opinion, the fact that at an equimolar ratio of reagents practically all the N-bromosuccinimide is consumed in ylid formation, and no source of Br^+ is left in the reaction mixture. As we have established, the yield can be approximately doubled by using a twofold molar amount of N-bromosuccinimide. It should be noted that in all cases thiazole bromination is accompanied by appreciable resinification.

In going from thiazole to 2-methylthiazole the possibility of substitution by the ylid mechanism is naturally eliminated. In that case it is important to note that according to the ^{13}C NMR spectra and quantum chemical calculations by the valence approximation of CNDO/2 [2] the charge distribution over the heterocycle atoms in 2-methylthiazole is close to that found for 2-phenylthiazole. In agreement with this finding are the data on bromination of 2-methylthiazole by bromine in a chlorinated solvent in the presence of HBr as alkali acceptor, where the yield of 5-bromo-2-methylthiazole reaches 48% [10]. Without an alkali acceptor, as we have shown, the yield is cut approximately in half. In the presence of an equimolar amount of $AlCl_3$ the bromination yield falls even more substantially (to ∿10%). Approximately the same yield as of 5-bromo-2-methylthiazole was also obtained in the bromination of N-bromosuccinimide, and in the reaction of bromine in acetic acid by the procedure of [11].

Thus 2-methylthiazole (as probably other 2-alkylthiazoles) can be brominated under mild conditions; but the presence of protonic or aprotic acids that form complexes at the nitrogen atom sharply decreases the reactivity of the thiazole ring toward an electrophilic reagent. In the case of unsubstituted thiazole even in the presence of a Lewis acid bromination takes place at the 2-position, probably by the ylid mechanism.

EXPERIMENTAL

Chromatographic analysis was carried out on a LKhM-80 chromatograph with flame ionization detector, nitrogen carrier gas at 20 ml/min, 130-170°, stainless steel columns: A) 2 × 2000 mm with 5% SE-30 on Chromatone N-AW-DMCS; B) 2 × 1500 mm with 15% Carbowax 20 M on Chromatone N-AW-DMCS.

The starting compounds and the reference bromothiazole samples were prepared by known methods from 2-aminothiazole: thiazole by the method of [12], 2-methylthiazole by [13], 2-bromothiazole by [14], 5-bromo-2-methylthiazole by [11], 2,5-dibromothiazole by [12].

5-Bromothiazole was prepared by boiling 2,5-dibromothiazole with zinc in acetic acid, in 35% yield, bp 65-68° (17 mm), n_D^{20} 1.5920, in agreement with [15].

Bromination of Thiazole in the Presence of $AlCl_3$. A. To 5 g (60 mmole) of thiazole was added 9.6 g (60 mmole) of bromine with vigorous stirring and cooling (0 to −10°C); a solid orange complex formed. After addition of 0.5 g (3.7 mmole) of anhydrous aluminum chloride the mixture was heated at 100-150°C for 2.5 h; it became liquid and darkened. The mass that solidified when cooled was treated with sodium hydroxide solution until alkaline and was steam-distilled. The distillate was made alkaline to pH 10 and was extracted with ether. According to GLC the extract contained ∿80% starting thiazole, ∿10% 2-bromothiazole, ∿5% 2,5-dibromothiazole, and three unidentified compounds totaling ∿5%. Thiazole, 0.93 g (18% recovery) was separated by distillation.

B). To a solution of 1 g (12 mmole) of thiazole in 7 ml of CCl_4 were added 0.1 g (0.7 mmole) of anhydrous $AlCl_3$, then a solution of 1.92 g (12 mmole) of bromine in 3 ml of CCl_4 dropwise. The mixture was heated for 2 h at 65-67°C; an orange-brown resin deposited on the wall of the flask. After cooling, the solution was separated and washed with water, dilute NaOH solution, and again water. The solvent was removed. According to GLC with 2,3-lutidine as internal standard, the residue contained 3.5 mg (0.08%) yield of 2-bromothiazole and 3.5 mg (0.12% yield) of 2,5-dibromothiazole. The resinous material was dissoved in conc. NaOH and steam-distilled and the distillate was extracted with ether. The extract contained, by GLC, 0.26 g of thiazole (26% recovery) and traces of 2-bromothiazole.

Bromination of Thiazole with N-Bromosuccinimide. A. A mixture of 3 g (35.4 mmole) of thiazole and 6.3 g (35.5 mmole) of N-bromosuccinimide in 10 ml of CCl_4 was heated 45 min at 65-67°C. After cooling the solution was decanted from the resin and washed with water, dilute NaOH solution, and again water. According to GLC with 2,3-lutidine as internal standard the solution contained 0.4 g of starting thiazole (13% recovery) and 0.6 g of 2-bromothiazole, 11% yield.

B). In an analogous experiment with twice the amount of N-bromosuccinimide the yield of 2-bromothiazole was 23% and the thiazole recovery was 6%.

Bromination of 2-Methylthiazole. A. To a mixture of 0.5 g (5 mmole) of 2-methylthiazole in 3 ml of CH_2Cl_2 was added a solution of 0.8 g (5 mmole) of bromine in 3 ml of CH_2Cl_2. The mixture was stirred for 1 h at 20°C, then for 2 h during boiling, then left for 24 h at room temperature. It was then washed with water, sodium carbonate solution, and again water. According to GLC the solution contained the starting 2-methylthiazole and 5-bromo2-methylthiazole in 5:95 ratio, as well as ∿1% of two unidentified substances. The residue after evaporation of CH_2Cl_2 was boiled for 12 h with 5 ml of methyl iodide. Excess CH_3I was evaporated and the residue was washed with acetone. The acetone-insoluble part was crystallized from water with carbon to give 0.36 g of 5-bromo-1,2-dimethylthiazolium iodide, mp 245° (see [11]), 22% yield.

B) When bromination was carried out under the conditions of the preceding experiment but in the presence of an equimolar amount of $AlCl_3$, a mixture was obtained (0.62 g) the volatile components of which contained the starting 2-methylthiazole, 5-bromo-2-methylthiazole, and unknown compounds in 4:90:6 ratio according to GLC. From this mixture there was obtained 0.14 g (8% yield) of 5-bromo-1,2-dimethylthiazolium idodide.

C) 2-Methylthiazole, 0.75 g (7.5 mmole), and 1.5 g (8.4 mmole) of N-bromosuccinimide in 8 ml of CCl_4 were boiled for 3 h. After cooling the precipitate was filtered off, and the solution was washed with dilute NaOH solution and water and evaporated. The residue (0.25 g) contained, according to GLC, 2-methylthiazole and 5-bromo-2-methylthiazole in 55:45 ratio. The residue was boiled for 12 h with 5 ml of CH_3I to give 0.3 g of 5-bromo-1,2-dimethylthiazolium iodide, 12% yield.

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SYNTHESIS OF MACROCYCLIC COMPOUNDS CONTAINING THIOPHENE AND THIAZOLE NUCLEI

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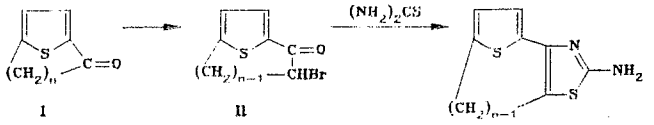
Macrocyclic ketones that contain a thiophene nucleus and have 14 or more carbon atoms in the ring can form systems with a condensed thiazole ring, in high yield.

The introduction of a macrocyclic segment into a physiologically active molecule can facilitate its directed transport through cell membranes to the appropriate receptors. Starting from this hypothesis we undertook the synthesis of pyrazolone systems condensed with a macrocycle [1]. The synthesis of macrocyclic compounds condensed with a thiazole ring has also been demonstrated [2]. The present work is devoted to a detailed description of such systems that are based on macrocyclic ketones.

The objective can be reached by various paths. If we arrange for quite simple syntheses of macrocyclic ketones of formula I that contain a thiophene ring [3], it is natural to seek a selective method for their halogenation α to the carbonyl group, and so convert them to thiazoles by the classical method [4]:



n=9, 10, 11

Macrocyclic ketones I (n = 9, 11) were obtained by intramolecular acylation of the acid chlorides of long-chain ω-thienylalkanoic acids, using the high dilution technique [3]. [11]-α-Cyclothienone-1 (I, n = 10) (for nomenclature of macrocyclic ketones containing a thiophene ring, see [3]) was obtained by ketonic cleavage of 2-carbethoxy-5-(9-iodononyl)acetylthiophene in methyl ethyl ketone in the presence of K_2CO_3 [5].

To develop the conditions for bromination of macrocyclic ketones at the α-carbon atom, 5-ethyl-2-propiothienone (IV) was synthesized as model compound (in view of the quite limited availability of ketones I). It was subjected to the action of various brominating agents:

*Deceased.

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