SYNTHESIS AND REACTIONS OF 4-(BENZOTHIAZOL-2-YL)-2,6-DIMETHYLPYRYLIUM PERCHLORATE

G. N. Dorofeenko, A. V. Koblik,
B. A. Tertov, and T. I. Polyakova

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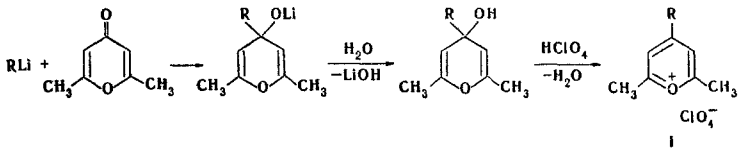
A new method has been developed for the synthesis of 4-(benzothiazol-2-yl)-2,6-dimethylpyrylium perchlorate from 2,6-dimethyl-γ-pyrone and 2-lithiobenzothiazole. The reaction of this salt with ammonia and with primary and secondary amines, hydrazine, phenylhydrazine, and hydroxylamine leads to the formation of difficultly accessible hetaryl-substituted benzothiazoles.

The preparation of hetaryl-substituted benzothiazoles, which find use in organic synthesis and are also employed as dyes [1] and antimicrobial agents [2], is frequently associated with great difficulties. Consequently, we have attempted to use for these purposes heterocyclic derivatives of pyrylium salts. As is well known, 2,4,6-trimethylpyrylium perchlorate is readily converted by reaction with nucleophilic reagents into compounds of the aromatic and heterocyclic series [3]. However, such reactions for other pyrylium salts and, in particular, for compounds with heterocyclic substituents, have been studied only on individual, partial, examples.

The existing methods of synthesizing pyrylium salts are unsuitable for the introduction of heterocyclic substituents into the pyrylium ring. In view of this, we have developed a new method for synthesizing 4-(2-hetaryl)-2,6-dimethylpyrylium perchlorates containing benzothiazole, pyridine, and thiophene residues [4]. The essence of the method consists in the reaction of 2,6-dimethyl-γ-pyrone with organolithium derivatives of heterocycles, which have not previously been employed in the synthesis of pyrylium salts. The reaction takes place through the intermediate formation of a metal derivative, which is hydrolyzed to a pyranol, this being converted by the action of dilute perchloric acid into the 4-(2-hetaryl)-2,6-dimethylpyrylium perchlorate; for example, (I). According to our observations, lithiobenzothiazole does not react with the product (I) under the reaction conditions, in contrast to aryllithiums and arylmagnesiums [5], which enables the pure salt (I) to be obtained in high yield.



I

R= benzothiazol-2-yl

To obtain difficultly accessible aromatic and heterocyclic benzothiazole derivatives, the perchlorate (I) was brought into reaction with a number of nucleophilic agents. As was expected, in nucleophilic addition reactions, the salt (I) behaves analogously to 2,4,6-trimethylpyrylium perchlorate [3], i.e., the presence of the heterocyclic substituent in position 4 has no appreciable influence on the reactivity of the pyrylium ring. The perchlorate (I) reacts smoothly with ammonia and primary amines, forming 4-(benzothiazol-2-yl)-2,6-dimethylpyridine (II) and 1-substituted 4-(benzothiazol-2-yl)-2,6-dimethylpyridinium salts (III, IV). Its reaction with diethylamine under mild conditions takes place with the opening of the

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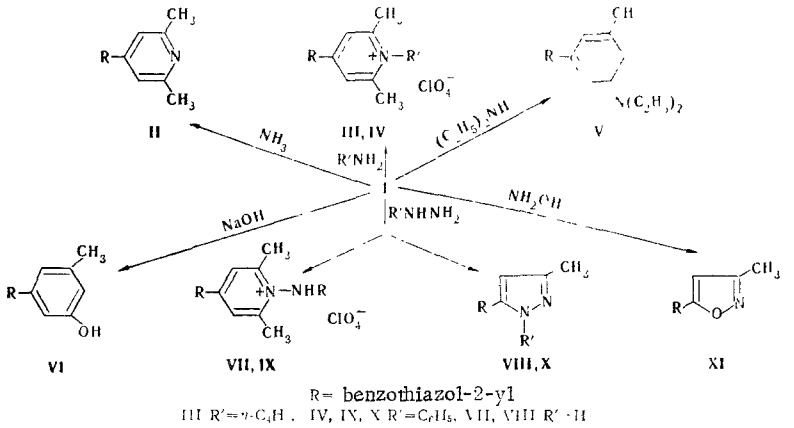
pyridine ring and subsequent recyclization to 2-[5-(diethylamino)-3-methylphenyl]benzothiazole (V). Boiling the perchlorate (I) with ethanolic alkali led to 2-(5-hydroxy-3-methylphenyl)benzothiazole (VI).



R= benzothiazol-2-yl

III R'=γ-C5H4N, IV, IX, X R'=C6H5, VII, VIII R'=H

2,4,6-Trimethylpyrylium perchlorate reacts with hydrazine,forming aminopyridinium salts and 3,5-substituted pyrazoles [6], while 2,4.6-triarylpyrylium perchlorates give the corresponding diazepines [7]. It is known that the reaction of pyrylium salts with phenylhydrazine gives 1-phenyl-substituted pyrazoles [7] or 1-phenylaminopyridinium salts [8], and their reaction with hydroxylamine gives isoxazoles [9]. We have found that with an equimolecular amount of hydrazine hydrate the perchlorate (I) forms 1-amino-4-(benzothiazol-2-yl)-2,6-dimethylpyridinium perchlorate (VII), and with an excess of hydrazine it forms a mixture of the salt (VII) and 2-(3-methylpyrazol-5-yl)benzothiazole (VIII). The reaction with phenylhydrazine takes place similarly, giving compounds (IX) and (X). The formation of the salts (VII) and (IX), and not the corresponding diazepines, is confirmed by the presence of the absorption bands of the stretching vibrations of an NH_2 group in the 3415-and 3330-cm^{-1} regions for (VIII) and one band of the absorption of an NH group in the 3350-cm^{-1} region for (IX). The disappearance of these absorption bands in the 4-(benzothiazol-2-yl)-1-benzylideneamino-2,6-dimethylpyridinium perchlorate obtained by the condensation of (VII) with benzaldehyde indisputably indicates the formation of (VII). For the pyrazole derivative (VIII), the IR spectra likewise have the absorption band of an NH group in the 3360-cm^{-1} region.

Compound (I) was converted by the action of hydroxylamine into the isoxazole (XI).

The retention of the benzothiazole residue in the reactions mentioned is confirmed by the IR spectra of the derivatives (I-XI) in which the characteristic absorption bands of the benzothiazole ring are present [10]. Thus, due to the high reactivity of (I), it has been possible easily and with good yields to effect the synthesis of a large series of extremely difficultly accessible benzothiazole derivatives containing aromatic and heterocyclic substituents.

Preliminary investigations of the perchlorate (I) have shown the presence of a selective suppression of the growth of bacteria of the dysentery group in a dose of 10 γ/ml.

EXPERIMENTAL

The IR spectra of all the compounds obtained were recorded on a UR-20 instrument in paraffin oil. The UV spectra were taken on a Specord UV-Vis spectrophotometer in methanol.

4-(Benzothiazol-2-yl)-2,6-dimethylpyrylium Perchlorate (I). Benzothiazole (2.9 g, 0.02 mole) was metallated with the butyllithium, obtained from 0.3 g (0.04 g-atom) of lithium and 3.84 g (0.028 mole) of butyl bromide, in dry ether at −75°C for 10-15 min. The 2-lithiobenzothiazole formed was brought to reaction with 2.05 g (0.016 mole) of 2,6-dimethyl-γ-pyrone. The reaction was performed for 1 h 30 min at −75°C, and then the temperature was brought up to that of the room over 1 h. After the end of the reaction, 10 ml of water and 20 ml of 28% perchloric acid were added. The precipitate of perchlorate that deposited was filtered off, washed with ether, and dried in the air. Yield 55-81%. Yellow crystals with mp 215-216°C (decomp.). IR spectrum, cm^{-1}: 725, 770, 810, 940, 1110, 1510, 1595, 1635. Found, %: C 48.8; H 3.5; Cl 10.4; S 9.8. $C_{14}H_{12}ClNO_5S$. Calculated,%: C 49.2; H 3.5; Cl 10.4; S 9.4.

2-(2,6-Dimethylpyridin-4-yl)benzothiazole (II). An excess of 25% aqueous ammonia was added to 1 g (0.003 mole) of the perchlorate (I), giving 0.63 g (90%) of (II). It was purified on a column of alumina [benzene−chloroform 3:2)]. mp 105-106°C. A mixture of (II) with an authentic sample [11] gave no depression of the melting point.

4-(Benzothiazol-2-yl)-1-butyl-2,6-dimethylpyridinium Perchlorate (III). To 1 g (0.003 mole) of the perchlorate (I) in 10 ml of ethanol was added 0.73 g (0.01 mole) of n-butylamine dropwise, and the mixture was heated at 90-95°C for 2 h. Then it was cooled and diluted with ether. The yield of the salt (III) was 0.61 g (53%). mp 123-125°C (from a mixture of acetone and ether). IR spectrum, cm^{-1}: 720, 770, 810, 930, 1090, 1315, 1575, 1625. Found, %: C 55.0; H 5.4; Cl 8.9; N 6.9; S 8.2. $C_{18}H_{21}ClN_2O_4S$. Calculated,%: C 54.5; H 5.3; Cl 8.9; N 7.0; S 8.1.

4-(Benzothiazol-2-yl)-2,6-dimethyl-1-phenylpyridinium perchlorate (IV) was obtained similarly. Yield 0.98 g (80%). IR spectrum, cm^{-1}: 720, 770, 805, 950, 1100, 1250, 1315, 1580, 1630. mp 255-256°C. Found, %: C 57.3; H 4.3; Cl 8.5; N 6.8; S 7.1. $C_{20}H_{17}ClN_2O_4S$. Calculated, %: C 57.6; H 4.1; Cl 8.5; N 6.7; S 7.1.

2-[5-(Diethylamino)-3-methylphenyl]benzothiazole (V). A mixture obtained by the addition of 0.22 g (0.003 mole) of diethylamine to a suspension of 1 g (0.003 mole) of (I) in 10 ml of ethanol was boiled for 15 min, the solvent was distilled off, the residue was dissolved in 15% hydrochloric acid, and the solution was neutralized with 25% ammonia. Yield 0.6 g (68%), mp 150-152°C. UV spectrum: λ_{max}, nm (log ε): 224 (4.29); 250 (3.90); 347 (3.85). Found, %: C 72.4; H 6.4; N 9.7; S 11.3. $C_{18}H_{20}N_2S$. Calculated, %: C 72.9; H 6.8; N 9.4; S 10.8.

2-(5-Hydroxy-3-methylphenyl)benzothiazole (VI). A solution of 1 g (0.025 mole) of caustic soda in 2 ml of water was added dropwise to a suspension of 1 g (0.003 mole) of (I) in 10 ml of ethanol. The mixture was boiled in the water bath for 6 h. The products that were insoluble in the alkaline medium were extracted with ether. Acidification of the aqueous solution with 10% hydrochloric acid led to the deposition of a gel-like precipitate of (VI), which was washed with water to neutrality. Yield 0.4 g (57%). mp 167-169°C. IR spectrum: 1160, 1270, 1310, 3220. Found, %: C 69.1; H 4.3; N 6.3; S 12.7. $C_{14}H_{11}NOS$. Calculated, %: C 69.5; H 4.6; N 5.8; S 13.2.

1-Amino-4-(benzothiazol-2-yl)-2,6-dimethylpyridinium Perchlorate (VII). A mixture of 0.003 mole of (I) and 0.003 mole of hydrazine hydrate in 3 ml of ethanol was made at 0°C. Then it was heated until the solid matter had dissolved (30 min) and was cooled, and the salt (VII) was filtered off. Yield 0.83 g (80%). mp 217-219°C (from water). IR spectrum: 720, 770, 890, 950, 1090, 1100, 1510, 1590, 1635, 3330, 3415. Found, %: C 47.5; H 4.1; Cl 10.0; N 11.5; S 9.4. $C_{14}H_{14}ClN_3O_4S$. Calculated, %: C 47.3; H 3.9; Cl 9.9; N 11.8; S 9.0.

Reaction of the Perchlorate (I) with an Excess of Hydrazine Hydrate. With stirring, 1.2 ml of 80% hydrazine hydrate was added dropwise to 1 g (0.003 mole) of (I) in 10 ml of ethanol, and the mixture was boiled until the solid matter had dissolved (30 min). After cooling, the perchlorate (VII) was filtered off. Yield 0.3 g. mp 217-218°C (from water). On dilution with water, the mother solution deposited 0.4 g (64%) of 2-(3-methylpyrazol-5-yl)benzothiazole (VIII). mp 144-145°C (from aqueous ethanol). UV spectrum: λ_{max}, nm (log ε): 225 (4.16), 265 (3.73); 300 (3.66). IR spectrum: 730, 770, 890, 915, 1020, 1160, 1260, 1585, 3360. Found, %: C 61.8; H 4.3; S 15.2. $C_{11}H_9N_3S$. Calculated, %: C 61.4; H 3.2; S 14.9.

4-(Benzothiazol-2-yl)-1-benzylideneamino-2,6-dimethylpyridinium Perchlorate. Equimolecular amounts (0.001 mole) of (VII) and benzaldehyde were mixed in ethanol, and the mixture was boiled for 30 min. On cooling, the reaction product deposited. Yield 70%. mp 220-222°C (from ethanol). Found, %: N 9.1. $C_{21}H_{18}ClN_3O_4S$. Calculated, %: N 9.1.

Reaction of the Perchlorate (I) with Phenylhydrazine. With stirring, 4.32 g (0.04 mole) of freshly distilled phenylhydrazine was added dropwise to a suspension of 1 g (0.003 mole) of (I) in 10 ml of ethanol. After 2 h, the yellow precipitate that had deposited was filtered off and was dried in a desiccator over calcium chloride. The yield of 2-(3-methyl-1-phenylpyrazol-5-yl)benzothiazole (X) was 0.58 g (68%). mp 155-156°C (from benzene). UV spectrum: λ_{max}, nm (log ε): 212 (3.84); 234 (3.71); 275 (4.11). IR spectrum: 730, 770, 880, 930, 1020, 1065, 1160, 1260, 1520, 1605 cm^{-1}. Found, %: C 69.6; H 4.18; N 14.8; S 10.2. $C_{17}H_{13}N_3S$. Calculated, %: C 70.0; H 4.9; N 14.4; S 11.0.

On dilution with ether, the mother solution deposited yellow crystals of 1-anilino-4-(benzothiazol-2-yl)-2,6-dimethylpyridinium perchlorate (IX). Yield 0.38 g (30%). mp 180-181°C (from a mixture of acetone and ether). IR spectrum: 730, 870, 945, 1100, 1250, 1590, 1605, 1635, 3350. Found, %: C 55.1; H 4.6; Cl 8.1; N 9.6; S 7.1. $C_{20}H_{18}ClN_3O_4S$. Calculated, %: C 55.6; H 4.6; Cl 8.2; N 9.7; S 7.4.

2-(3-Methylisoxazol-5-yl)benzothiazole (XI). A mixture of 1 g (0.003 mole) of (I) in 10 ml of ethanol, 2.05 g (0.03 mole) of hydroxylamine hydrochloride, and 1.2 g (0.03 mole) of caustic soda was kept at room

temperature for 1 h and was then boiled for 15 min, and the ethanol was distilled off. The residue was treated with hot benzene to give 0.4 g (63%) of (XI). mp 112-113°C (from ethanol). UV spectrum: λ_{max}, nm (log ε): 222 (3.75), 238, infl. (3.51); 325 (3.50). IR spectrum, cm^{-1}: 730, 770, 890, 940, 1080, 1160, 1250. 1595, 1670. Found, %: C 60.8; H 4.1; N 12.9; S 15.1. $C_{11}H_8N_2OS$. Calculated, %: C 61.1; H 3.7; N 12.9; S 14.9.

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