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OXIDATIVE CYCLIZATION OF 2-AMINO-1-ARYLIDENEAMINO-BENZIMIDAZOLES INTO 1,2,4-TRIAZOLO[1,5-*a*]BENZIMIDAZOLES

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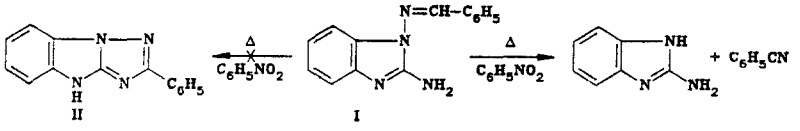
When heated in nitrobenzene, 1-arylideneamino-2-methylaminobenzimidazoles convert in a 20...30% yield into 2-aryl-3-methyl-1,2,4-triazolo[1,5-*a*]-benzimidazoles. In addition, 2-methylaminobenzimidazole and the corresponding benzonitrile are formed as a result of a thermal splitting of the N–N bond. Under the same conditions, 2-amino-1-arylideneaminobenzimidazoles and 1-arylideneamino-3-methylbenzimidazoline-2-imines give only products of spiltting off of the nitrile. In several cases, the subsequent reaction of the nitrile with 2-amino-1-methylbenzimidazole leads to the formation of benzamidines.

2-Aryl-1,2,4-triazolo[1,5-*a*]benzimidazoles are usually synthesized from 1,2-diaminobenzimidazoles and anhydrides or acid chlorides of aromatic acids [1-4]. Another theoretically possible method for the preparation of these compounds could be the oxidative cyclization of 2-amino-1-arylideneaminobenzimidazoles, similar to the transformation of o-phenylenediamine anils into 2-arylbenzimidazoles [5]. It should be noted, however, that an attempt to oxidize 2-amino-1-benzylideneaminobenzimidazole (I) into 2-phenyl-1,2,4-triazolo-[1,5-*a*]benzimidazole (II) by the action of copper acetate [6] was unsuccessful. In the present article, we describe the results of our experiments on the cyclization of 2-amino-1-arylideneaminobenzimidazoles in nitrobenzene medium. This oxidant gives good results in the preparation of 2-arylbenzimidazoles from o-phenylenediamine anils [7].

Boiling compound I in nitrobenzene leads to partial resinification and formation of a complex mixture of compounds, which does not include 2-phenyl-1,2,4-triazolo[1,5-a]-benzimidazole (II). However, an appreciable amount of 2-aminobenzimidazole can be detected in this mixture. This compound is clearly formed as a result of splitting of the N–N bond, as in the case of the N-aminopyridinium hydrazone series [8].



We assumed that this course of reaction can be explained by the lower nucleophilicity of the 2-amino group in compound I, as a result of which the elimination of nitrile, competing with the cyclization, proceeds much more rapidly. To increase the probability of closing the triazole ring, we decided to increase the nucleophilicity of the amino group by introducing a methyl substituent into it, and also by converting it into a fixed imine.

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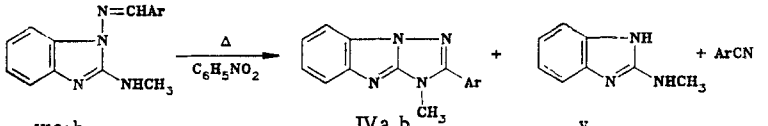
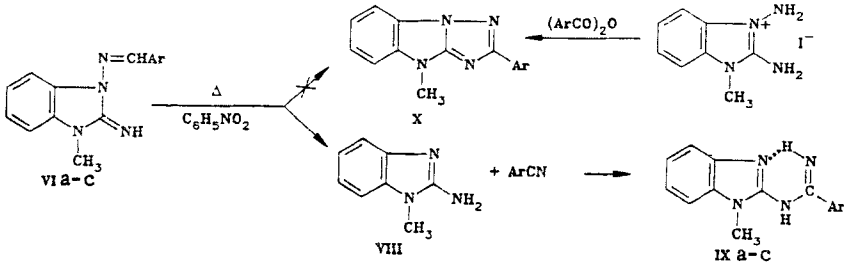
This tactic was partially justified, since when hydrazones III were heated in nitrobenzene, we obtained triazolo[1,5-*a*]benzimidazoles IV in a 20-30% yield. However, also in this case, the formation of nitriles and 2-methylaminobenzimidazole (V) was observed (yield 20...30%).



III, IV a Ar=C_6H_5; b Ar=$C_6H_4NO_2$-*p*

It must be emphasized that compound IVb cannot be obtained by the action of p-nitrobenzoic anhydride on 1-amino-2-methylaminobenzimidazole (cf [3]), and therefore the oxidative transformation of benzimidazole IIIb into triazolobenzimidazole IVb has some synthetic value.

We expected that 1-arylideneamino-3-methylbenzimidazoline-2-imines (VIa-c) would undergo cyclization even more readily than compound III, since the imino group at the 2-position has a high nucleophilicity. We synthesized hydrazones VI from 1-amino-3-methylbenzimidazoline-2-imine (VII), obtained by treating the known 1,2-diamino-3-methylbenzimidazolium iodide [4] with caustic alkali. After brief boiling of compounds VIa,b in nitrobenzene, 2-amino-1-methylbenzimidazole (VIII) was obtained as the only reaction product in both cases in a 50...70% yield. From compound VIc, under the same conditions, besides amine VIII (yield 51%) and p-nitrobenzonitrile (41%), the previously unknown N-(1-methyl-2-benzimidazolyl)-p-nitrobenzamidine (IXc) is also formed. The formation of amidine IXc is, without doubt, the result of the interaction between amine VIII and p-nitrobenzonitrile. We proved this by carrying out a deliberately planned synthesis of compound IXc in this way. As a result of lower electrophilicity of benzonitrile itself and p-methoxybenzonitrile, analogous amidines cannot be formed on short-term heating of hydrazones VIa,b in nitrobenzene. But if a mixture of amine VIII and benzonitrile is heated for 5 h, amidine IXa can be obtained in a 73% yield.



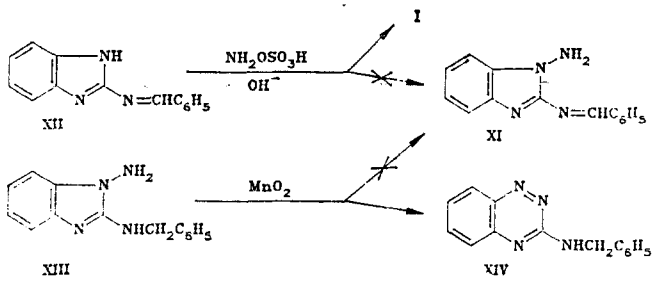
VI, IX, X a Ar=C_6H_5; b Ar=$C_6H_4OCH_3$-*p*; c Ar=$C_6H_4NO_2$-*p*

The reason that compounds VI do not convert into triazolobenzimidazoles is clearly the increased lability of their N–N bond. In fact, the elimination of the corresponding nitrile on heating of compounds VI in nitrobenzene is complete even after 15....20 min, while the same reaction requires several hours to complete with compounds I and III. The instability of the N–N bond in hydrazones VI can be explained by the π-acceptor effect of the imino group at the 2-position, leading to increase in the positive π-charge on the cyclic nitrogen atoms. At the same time, the amino group at the 2-position of compounds I and III is a π-donor, which leads to decrease in the partial positive charge on the hetero atoms and somewhat increases the strength of the N–N bond.

It should be noted that 4-methyl-2-p-nitrophenyl-1,2,4-triazolo[1,5-*a*]benzimidazole (Xc), which could not be obtained from compound VIc, was synthesized by us by an independent method from 1,2-diamino-3-methylbenzimidazolium iodide and p-nitrobenzoic anhydride.

The oxidative cyclization of 1-amino-2-arylideneaminobenzimidazoles XI appeared to be very attractive. The two features of these compounds, namely, the increased nucleophilicity of the N-amino group and the failure to split the nitrile group, clearly favor the ring closure. However, we did not succeed in synthesizing azomethine XI. In an attempt to obtain this compound by amination of 2-benzylideneaminobenzimidazole (XII) using hydroxylamine-O-sulfonic acid in an alkaline medium, only hydrazone I was isolated. It

is possible that under the conditions of this reaction, the benzylideneamino group undergoes hydrolysis and the 1,2-diaminobenzimidazole formed reacts with the liberated benzaldehyde at the N-amino group. In another experiment, we oxidized 1-amino-2-benzylaminobenzimidazole (XIII) using manganese dioxide or lead tetraacetate, in the hope that the intermediately formed compound XI (cf. a similar synthesis of aromatic azomethines [9]) would give 2-phenyltriazolobenzimidazole II under the reaction conditions. However, the only reaction product in these experiments was the previously unknown 3-benzylaminobenzo-1,2,4-triazine (XIV), formed due to the oxidation of the N-amino group to N-nitrene followed by ring expansion therein. A similar reaction has already been observed for 1,2-diaminobenzimidazole [6].



EXPERIMENTAL

The IR spectra were measured on a UR-20 spectrophotometer in mineral oil and the PMR spectra on Tesla BS-487 (80 MHz). Tesla BS-567 (100 MHz) and Bruker WH-90 (90 MHz) spectrometers, using TMS as internal standard. The mass spectra were obtained on a Varian MAT-311 spectrometer with a direct introduction of the sample into the ionic source, at a ionizing voltage of 70 eV. The course of the reactions and the purity of the compounds were monitored by the TLC method on plates with aluminum oxide of grade III activity, using chloroform as eluent and developing with iodine vapors.

2-Amino-1-benzylideneaminobenzimidazole (I). A. A solution of 0.3 g (2 mmoles) of 1,2-diaminobenzimidazole and 0.2 ml (2 mmoles) of benzaldehyde in 5 ml of propanol is boiled for 3 h. After cooling, the precipitate is filtered and washed with ethanol. Yield 0.4 g (85%). Light-yellow fibrous needles, mp 205...206°C (from propanol). IR spectrum: 1555, 1600, 1625, 1650, 2800...3300, 3447 cm^{-1} (NH_2). Found, %: C 71.0, H 5.0, N 23.6. $C_{14}H_{12}N_4$. Calculated, %: C 71.2, H 5.1, N 23.7.

B. A solution of 2.5 g (20 mmoles) of hydroxylamine-O-sulfonic acid, neutralized by dry $NaHCO_3$, in 5 ml of water is added in the course of 2...3 min at 40...45°C to a light yellow solution of 2.2 g (10 mmoles) of 2-benzylideneaminobenzimidazole [10] and 2.0 g (50 mmoles) of NaOH in 30 ml of aqueous alcohol (1:1), whereby the reaction mixture strongly darkens. It is stirred for 50 min at 40...45°C. After cooling, the precipitate is filtered, washed with water, alcohol and ether. Yield, 0.8 g (34%) of compound I. Needles, mp 204...205°C (from alcohol). A sample mixed with material from experiment A does not show depression of the melting point.

Heating Hydrazone I in Nitrobenzene. A solution of 1.18 g (5 mmoles) of hydrazone I in 15 ml of nitrobenzene is boiled for 12 h (to complete disappearance of a spot of the starting compound in TLC). The resinous residue after evaporation of nitrobenzene is boiled with 20 ml of water. The aqueous solution is evaporate to yield 0.31 g (47%) of 2-aminobenzimidazole. Colorless crystals, mp 224°C (from water), which in physicochemical characteristics are identical to an authentic sample.

1-Benzylideneamino-2-methylaminobenzimidazole (IIIa) is obtained by boiling equimolecular amounts of 1-amino-2-methylaminobenzimidazole [3] and benzaldehyde in propanol for 2 h. Yield, 98%. Pale-yellow crystals, mp 109...110°C (from ethyl acetate). IR spectrum: 1630, 3418 cm^{-1} (NH). Found, %: C 71.8, H 5.3, N 22.5. $C_{15}H_{14}N_4$. Calculated, %: C 71.7, H 5.3, N 22.3.

2-Methylamino-1-(p-nitrobenzylidene)aminobenzimidazole (IIIb) is obtained in a similar way as compound IIIa, yield 88%. Orange crystals, mp 249...250°C (from DMFA). IR spectrum: 1642, 3427 cm^{-1} (NH). Found, %: C 59.9, H 4.2, N 23.5. $C_{15}H_{13}N_5O_2$. Calculated, %: C 60.0, H 4.3, N 23.7.

3-Methyl-2-phenyl-1,2,4-triazolo[1,5-*a*]benzimidazole (IVa). A solution of 0.7 g (2.8 mmoles) of azomethine IIIa in 2 ml of nitrobenzene is boiled for 5 h, whereby the reaction mixture strongly darkens. Nitrobenzene is evaporated, the residue is dissolved in 15 ml of chloroform and separated on a column with Al_2O_3 (eluent chloroform). First, 0.06 g (20%) of benzonitrile is eluted, and then a yellow fraction with R_f 0.7, comprising a mixture of 0.2 g (28%) of initial azomethine IIIa and 0.15 g (22%) of compound IVa (separated by grinding with alcohol). Colorless crystals, mp 178...179°C (from ethyl acetate). The material does not show depression of the melting point of a sample mixed with an authentic compound IVa material, obtained by the method in [3]. Alcohol elutes 0.08 g (20%) of 2-methylaminobenzimidazole (V). Colorless prisms, mp 192...193°C (from water), which conforms with the literature data [11].

3-Methyl-2-p-nitrophenyl-1,2,4-triazolo[1,5-*a*]benzimidazole (IVb). A solution of 1.0 g (3.3 mmoles) of aldimine IIIb in 5 ml of nitrobenzene is boiled for 8 h (the course of the reaction is monitored from the disappearance of the starting compound in the TLC). After evaporation of nitrobenzene, the residue is treated with 20 ml of chloroform, and 0.12 g (25%) of amine V are filtered off. Colorless prisms, mp 192...193°C (from water). The chloroform extract is passed through a column with Al_2O_3 (chloroform), whereby a fraction with R_f 0.95 is first collected, which consists of p-nitrobenzonitrile, 0.12 g (24%), and then a yellow fraction with R_f 0.7 – compound IVb, 0.3 g (30%). Yellow crystals, mp 239...241°C (from DMFA). IR spectrum: 1600, 1640 cm^{-1} PMR spectrum (DMSO-D_6, 100 MHz): 3.86 (3H, s, N–CH_3); 7.36 (2H, m) and 7.84 (2H, m) – 5H...8-H protons; 8.28 (2H, d J = 9.0 Hz, 2'-H) and 8.56 ppm (2H, d, J = 9.0 Hz, 3'-H). Mass spectrum, m/z (I/I_{max}, %): $M^{+\cdot}$ 293 (100), $[M - NO]^+$ 263 (15), $[M + H - NO_2]$ 248 (11), $[M - O_2NC_6H_4CN]^+$ 145 (28), 118 (66), 104 (77). Found: C 61.6; H 3.9; N 23.7%. $C_{15}H_{11}N_5O_2$. Calculated: C 61.4; H 3.8; N 23.9%.

1-Amino-3-methylbenzimidazoline-2-imine (VII). A suspension of 2.9 g (10 mmoles) of 1,2-diamino-3-methylbenzimidazolium iodide [4] in 10 ml of 40% KOH solution is stirred for 10 min at 20°C. The precipitate is filtered and washed with 10 ml of ice water. Yield, 1.37 g (84%). Colorless crystals, mp 140...142°C (from water). IR spectrum: 1640, 1660, 2500...3200, 3280 cm^{-1} (NH, NH_2). Found, %: C 59.3, H 6.1, N 34.6. $C_8H_{10}N_4$. Calculated, %: C 59.3, H 6.2, N 34.6.

1-Benzylideneamino-3-methylbenzimidazoline-2-imine (VIa). A solution of 1.13 g (7 mmoles) of imine VII and 0.8 ml (7.9 mmoles) of benzaldehyde in 10 ml of propanol is boiled for 1 h. The solvent is evaporated, the residue is ground with ether, and filtered. Yield 1.5 g (86%). Pale yellow needles, mp 112...113°C (from alcohol). IR spectrum: 1670, 3328 cm^{-1} (NH). Found, %: C 71.7, H 5.4, N 22.3. $C_{15}H_{14}N_4$. Calculated, %: C 72.0, H 5.6, N 22.4.

3-Methyl-1-(p-methoxybenzylidene)aminobenzimidazoline-2-imine (VIb) is obtained in a similar way as compound VIa, yield 92%. Colorless crystals, mp 138...139°C (from alcohol). IR spectrum: 1662, 3317 cm^{-1} (NH). Found, %: C 68.3, H 5.9, N 20.0. $C_{16}H_{16}N_4O$. Calculated, %: C 68.6, H 5.7, N 20.0.

3-Methyl-1-(p-nitrobenzylidene)aminobenzimidazoline-2-imine (VIc) is obtained in a similar way as compound VIa, yield 81%. Bright-orange needles, mp 220...221°C (from DMFA). IR spectrum: 1675, 3250 cm^{-1} (NH). Found, %: C 61.0, H 4.3, N 23.6. $C_{15}H_{13}N_5O_2$. Calculated, %: C 61.0, H 4.4, N 23.7.

Heating Aldimines VIa,b in Nitrobenzene. A solution of 0.8 g (3.2 mmoles) of azomethine VIa in 2 ml of nitrobenzene is boiled for 15 min, whereby the solution darkens strongly. The solvent is evaporated to dryness, the residue is ground with ether and the precipitate of 2-amino-1-methylbenzimidazole (VIII) is filtered. Yield 0.35 g (72%). Colorless prisms, mp 200...201°C (from water). A sample mixed with authentic 2-amino-1-methylbenzimidazole does not show depression of the melting point.

2-Amino-1-methylbenzimidazole (VIII) is also formed when aldimine VIb is boiled in nitrobenzene for 10 min (yield 47%).

N-(1-Methyl-2-benzimidazolyl)-p-nitrobenzamidine (IXc). A solution of 1.0 g (3.3 mmoles) of imine VIc in 5 ml of nitrobenzene is boiled for 20 min. The residue after evaporation of nitrobenzene is treated with 20 ml of chloroform and the yellow precipitate (0.45 g), which is a mixture of 0.25 g (51%) of 2-amino-1-methylbenzimidazole (VIII) (separated by boiling in 30 ml of water, followed by evaporation of water) and 0.2 g (20%) of

amidine IXc, is filtered. The chloroform filtrate is passed through a column with Al_2O_3 (chloroform), whereby the fraction with R_f 0.95 is first collected. The yield of p-nitrobenzonitrile is 0.2 g (41%). Light-yellow leaflets, mp 147-149°C (from alcohol). No depression is observed of the melting point of a sample mixed with authentic p-nitrobenzonitrile. The yellow fraction with R_f 0.4 (0.2 g, 20%), of amidine IXc is then eluted. The overall yield of amidine IXc is 0.4 g (40%). Yellow brilliant crystals, mp 224...225°C (from butanol). IR spectrum: 1600, 1635, 3100...3450 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 90 MHz); 3.87 (3H, s, N–CH_3); 6.3 (1H, m, NH); 7.28 (3H, m) and 7.60 (1H, m) – aromatic protons; 8.16 (2H, d, J = 9.0 Hz, 2'-H); 8.36 (2H, d, J = 9.0 Hz, 3'-H); 11.0 ppm (1H, br. m, NH). PMR spectrum (DMSO-D_6, 90 MHz); 3.82 (3H, s, N–CH_3); 7.16 (2H, m) and 7.50 (2H, m) – aromatic protons; 8.39 (4H, m, 2'-H and 3'-H); 9.02 (1H, m, NH) and 10.54 ppm (1H, m, NH). Mass spectrum, m/z, (I/I_{max}, %): $M^{+\cdot}$ 295 (100), $[M-O]^+$ 279(15), $[M-NO]^+$ 265 (13), $[M-NO_2]$ 249(16), $[O_2NC_6H_4CN]^{+\cdot}$ 148 (18), 132 (13), 119 (51), 105 (21). Found, %: C 61.4, H 3.9, N 23.8. $C_{15}H_{13}N_5O_2$. Calculated, %: C 61.4, H 3.8, N 23.9.

B. A solution of 0.75 g (5 mmoles) of 2-amino-1-methylbenzimidazole (VIII) and 0.75 g (5 mmoles) of p-nitrobenzonitrile is boiled for 3 h. The solvent is evaporated, the residue is boiled with 15 ml of water, and a yellow precipitate is filtered in a hot state, and washed with water and acetone. Yield, 0.9 g (61%). Orange needles, mp 225...226°C (from DMFA). No depression is observed of the melting point of a sample mixed with experiment A material.

N-(1-Methyl-2-benzimidazolyl)benzamidine (IXa) is obtained in a similar way as compound IXc from benzimidazole VIII and benzonitrile in the course of 5 h, yield 73%. Pale-yellow needles, mp 169...170°C (from alcohol). IR spectrum: 1630, 2900...3300, 3490 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 80 MHz): 3.80 (3H, s, N–CH_3); 6.28 (1H, m, NH, disappears after deuteration); 7.23 (3H, m) and 7.45 (4H, m) – aromatic protons; 7.95 (2H, m, o-H, C_6H_5); 10.70 ppm (1H, m, NH, disappears after deuteration). Found, %: C 69.5, H 5.8, N 21.7. $C_{15}H_{14}N_4 \cdot 1/2H_2O$. Calculated, %: C 69.5, H 5.7, N 21.6.

4-Methyl-2-p-nitrophenyl-1,2,4-triazolo[1,5-*a*]benzimidazole (Xc). A mixture of 1.45 g (5 mmoles) of 1,2-diamino-3-methylbenzimidazolium iodide [4] and 0.35 g (2.5 mmoles) of potassium carbonate in 5 g (18 mmoles) of p-nitrobenzoic anhydride is heated with stirring for 2 h at 200°C. After cooling, 20 ml of 5% KOH solution are added, and the mixture is heated for 5 min. It is then cooled, the precipitate is filtered and washed with water, alcohol and ether. The material is purified by chromatography on a column with Al_2O_3 (chloroform). Yield 0.4 g (54%). Pale-yellow prisms, mp 244...246°C (from DMFA) IR spectrum 1610, 1642 cm^{-1}. Found, %: C 61.3, H 3.7, N 24.0. $C_{15}H_{11}N_5O_2$. Calculated, %: C 61.4, H 3.8, N 23.9.

3-Benzylaminobenz-1,2,4-triazine (XIV). A. A suspension of 0.36 g (1.5 mmoles) of 1-amino-2-benzylaminobenzimidazole (XIII) [3] and 1.3 g (15 mmoles) of γ-MnO_2 in 40 ml of benzene is boiled for 2 h with distillation of water. The mixture thereby darkens noticeably. Manganese oxide is separated and washed several times with chloroform. The evaporated solution is passed through a column with Al_2O_3 (chloroform), collecting a yellow fraction with R_f 0.3. Yield 0.08 g (23%). Yellow crystals, mp 143...144°C (from methanol). IR spectrum: 1553, 3430 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 80 MHz): 4.78 (2H, d, J = 7.0 Hz, CH_2, after deuteration – a singlet); 6.40 (1H, m, NH, disappears after deuteration); 7.40 (5H, m, C_6H_5); 7.65 (3H, m) and 8.13 ppm (1H, m) – aromatic protons. Found, %: C 71.1, H 5.1, N 23.6. $C_{14}H_{12}N_4$. Calculated, %: C 71.2, H 5.1, N 23.7.

B. Lead tetraacetate (0.7 g, 16 mmoles) is added in small portions at 0...5°C to a suspension of 0.36 g (1.5 mmole) of compound XIII in 10 ml of methylene chloride. The dark-brown solution is stirred for 1 h at 0...5°C, and then passed through a column with Al_2O_3 (chloroform), collecting a yellow fraction with R_f 0.3. Yield, 0.1 g (28%). Yellow crystals, mp 143...144°C (from methanol). No depression is observed of the melting point of a sample mixed with a material from experiment A.

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ETHYL ESTERS OF 1,4-DIHYDROPYRIDINE-3,5-DICARBOTHIONIC ACIDS

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Methods for the synthesis of the esters of 1,4-dihydropyridine-3,5-dicarbothionic acids by the thionation of the carbonyl analogs with Lawesson's reagent are developed. The influence of the substituents at the nitrogen atom on the course of the thionation reaction is considered. The physicochemical characteristics of this series of substances are analyzed; their reactivity in the reactions of N-alkylation, oxidation, and anion formation is studied.

The 1,4-dihydropyridines (1,4-DHPs), which are hydrogenated nitrogen-containing heterocycles with unusual chemical properties [1, 2] and varied biological activity [3], have recently been widely investigated.

Continuing the investigations into the synthesis of sulfur-containing 1,4-DHPs [4], we set ourselves the objective of developing methods for the isolation of unknown ethyl esters of 1,4-DHP-dicarbothionic acids unsubstituted in the 2 and 6 positions. We previously developed methods for the synthesis of esters of 2,6-dimethyl-1,4-DHP-dicarbothionic acids, studied their physicochemical properties and reactivity [5], and determined the induction and resonance constants of the ethoxythiocarbonyl substituent in the aromatic compounds [6].

Taking into account the possible superimposing of the steric factor of the 2,6-methyl groups on the electronic effects of the ethoxythiocarbonyl substituent in the 1,4-DHP ring, it was expedient to study the physicochemical properties and reactivity of the thione esters of 1,4-DHP-dicarboxylic acids unsubstituted at the 2 and 6 positions.

The 4-aryl-3,5-diethoxythiocarbonyl-1,4-DHPs (IIa-h) are not successfully obtained by cyclocondensation [7], since the corresponding thione esters of propiolic acid are hitherto unknown. Attempts at the thionation of ethyl propiolate with Lawesson's reagent [the dimer of the sulfide of p-methoxyphenylthionophosphine (XI)] were unsuccessful due to the polymerization of the esters of propiolic acid. There is a known method for the thionation of the carbonyl and alkoxycarbonyl groups in aliphatic and aromatic compounds, as well as the keto group in the indene fragment of 5-oxo-4,5-dihydroindenopyridines [8, 9]. We found that the 4-aryl-3,5-diethoxycarbonyl-1,4-DHPs (Ia-h) react readily with Lawesson's reagent, and form the new thione esters (II_a-h).

The thionation was carried out by the prolonged boiling of (Ia-h) with double the molar amount of Lawesson's reagent in dry toluene or xylene in an atmosphere of argon. The

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