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REACTION OF 3-ACYLAMINO- AND 3-ALKOXYBENZO[*c*]PYRILIUM SALTS WITH HYDRAZINE

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The reaction of 3-acylamino- and 3-alkoxybenzo[c]pyrilium perchlorates with hydrazine has been studied. It was discovered that the direction of the recyclization of the pyran ring depends on the type of substituent in position 3 and on the ratio of reactants. Derivatives of isoquinoline and benzo-2,3-diazepine were obtained.

Keywords: benzo-2,3-diazepine, benzo[*c*]pyrilium, hydrazine, isoquinoline, recyclization.

In the whole variety of reactions of benzo[*c*]pyrilium salts with nucleophilic reagents that has been studied a limited number of works has been published on the interaction of them with hydrazine and its derivatives. It is known that benzo[*c*]pyrilium salts may be converted into derivatives of 2-aminoisoquinoline or benzo-2,3-diazepine [1-3]. Previously [4, 5] we reported conversions of benzo[*c*]pyrilium salts with functional substituents in position 4 (ester, cyano group) in the presence of hydrazine and phenylhydrazine, and certain factors determining the direction of recyclization. There are no data in the literature on analogous conversions of benzo[*c*]pyrilium salts containing functional substituents in position 3. The aim of the present work was to study the reactions of 3-acylamino-1-alkylbenzo[*c*]pyrilium salts **1** [6] and 3-alkoxy-1-alkylbenzo[*c*]pyrilium salts **2** [7] with hydrazine and also to search for new possibilities for obtaining nitrogen-containing heterocycles from them.

The structure of the products of reacting salts **1** and **2** with hydrazine is regulated by the substituent at position 3 and by the salt–hydrazine ratio. On interacting perchlorates **1a,b** and hydrazine hydrate in ratios from 1:1 to 1:3 the 1-alkyl-3-hydroxyisoquinolines **3** are formed, previously obtained by the action of ammonia [7]. Probably under these conditions the hydrazine molecule acts as a base and the oxonium cation, as in the case of the interaction with ammonia [7] and inorganic bases [8], undergoes an autorecyclization with the participation of the nitrogen atom of the acylamino group. An increase in the ratio to 1:5 leads to the formation of 1-alkyl-2-aminoisoquinolin-3(2H)-ones **4**. Increasing the amount of nucleophile further does not affect the course of the reaction.

Replacement of the acylamino group in position 3 by an alkoxy substituent changes the character of the conversions of the benzo[*c*]pyrilium cation. On interacting 1-alkyl-3-ethoxybenzo[*c*]pyrilium perchlorates **2a,b** with an equimolar amount of hydrazine hydrate at room temperature, a mixture is formed of compound **4** and the ketoester hydrazone **5**, but on heating only the isoquinolone **4** is obtained, which may be isolated both as the perchlorate and as the base. Compound **4** was also obtained in the reaction of salt **2** with hydrazine

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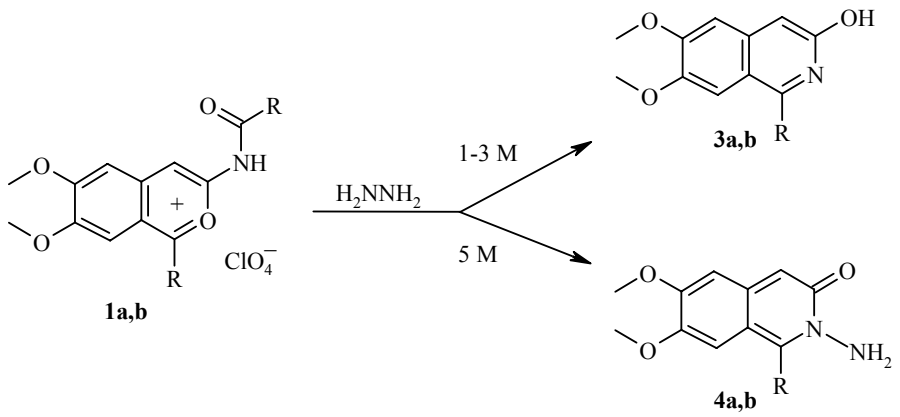
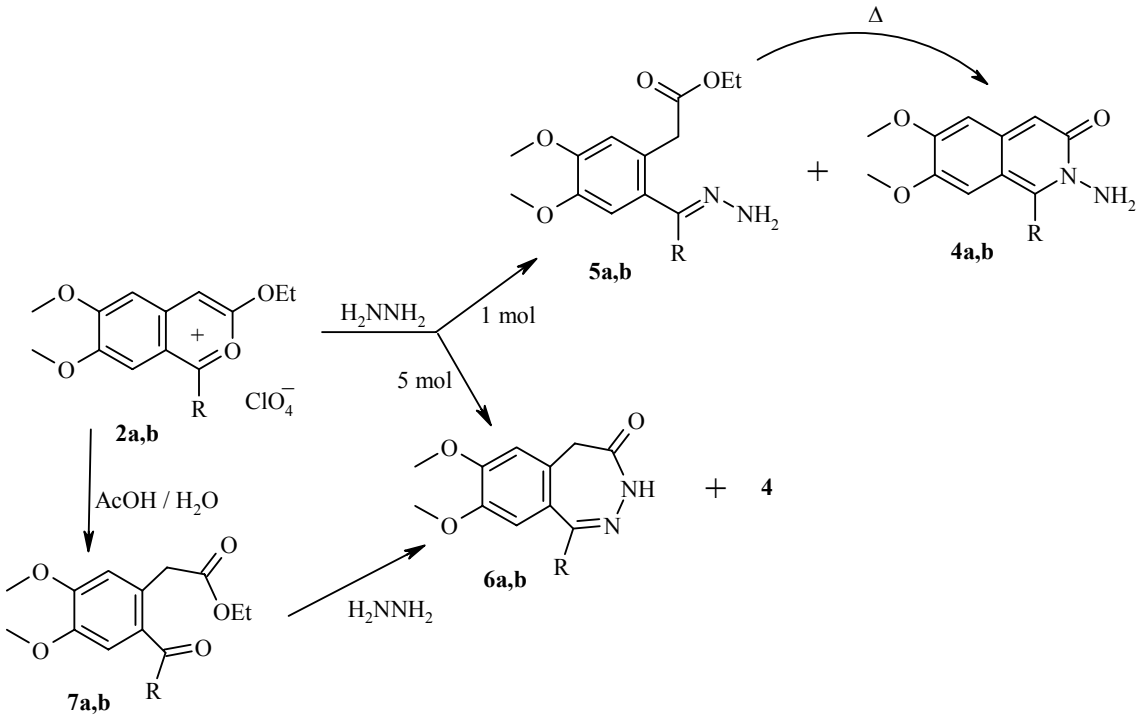


1, **3**, **4 a** R = Me; **b** R = Et

dihydrochloride. Heating perchlorates **2** with an excess of hydrazine hydrate in 2-propanol leads to isoquinolone **4** and 1-alkylbenzo-2,3-diazepin-4(5H)-one **6**. The yield of diazepines grows with an increase in the ratio of pyrilium salt–hydrazine from 1:3 to 1:5. Satisfactory yields of diazepinones **6** were obtained on cyclizing 2-acyl-4,5-dimethoxyphenylacetic acid esters **7** with hydrazine, however in this case also the minor product **4** was present in the reaction mixture at 5-7%.



2, 6, 7 a R = Me; **b** R = Et

According to the experimental data salts **1** and **2** are convenient starting materials for the synthesis of 2-aminoisoquinolin-3(2H)-ones, but not for benzo-2,3-diazepine derivatives. At the same time, it was shown in [4, 9, 10] that the recyclization of 4-substituted derivatives of benzo[*c*]pyrilium proceeds successfully with the formation of derivatives of 5-R-benzo-2,3-diazepine and 5-R-benzo-2,3-diazepin-4(5H)-one. It may be

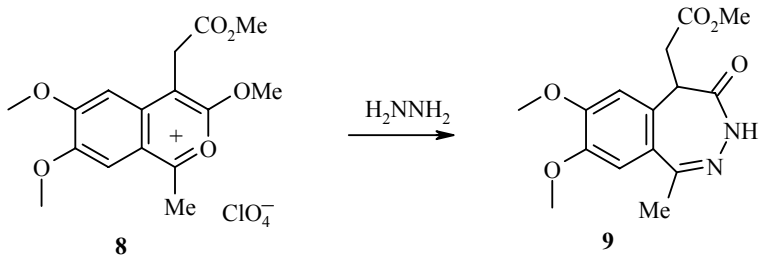
TABLE 1. Physicochemical Characteristics of Compounds **4-6, 9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
4a	$C_{12}H_{14}N_2O_3$	61.4 / 61.5	5.9 / 6.0	12.0 / 12.0	223-225	78
4b	$C_{13}H_{16}N_2O_3$	62.7 / 62.9	6.5 / 6.5	11.4 / 11.3	199-200	73
5a	$C_{14}H_{20}N_2O_4$	59.9 / 60.0	7.0 / 7.2	10.2 / 10.0	127-129	50
5b	$C_{15}H_{22}N_2O_4$	61.0 / 61.2	7.5 / 7.5	9.7 / 9.5	111-113	42
6a	$C_{12}H_{14}N_2O_3$	61.4 / 61.5	5.9 / 6.0	12.0 / 12.0	214-216	47
6b	$C_{13}H_{16}N_2O_3$	62.8 / 62.9	6.4 / 6.5	11.5 / 11.3	187-189	39
9	$C_{15}H_{18}N_2O_5$	59.0 / 58.8	6.0 / 5.9	9.1 / 9.1	167-169	60

suggested that compounds of the benzo-2,3-diazepine series, including benzo-2,3-diazepin-4(5H)-ones, may be obtained in satisfactory yield by reacting hydrazine with benzo[*c*]pyrilium salts with a substituent in the 4 position. Confirmation of this hypothesis for derivatives of 3-alkoxybenzo[*c*]pyrilium salts comes from the recyclization carried out by us of 3,6,7-trimethoxy-4-(methoxycarbonyl)methylbenzo[*c*]pyrilium perchlorate (**8**) [9] into 6,7-dimethoxy-1-methyl-5-(methoxycarbonyl)methylbenzo-2,3-diazepin-4(5H)-one (**9**), isolated after purification in a yield of more than 50%.

TABLE 2. Spectral Characteristics of Compounds **4-7**, **9**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
4a	3250, 3170, 1620	2.78 (3H, s, CH_3); 3.80 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 6.37 (1H, s, H arom.); 6.71 (2H, s, NH_2); 6.73 (1H, s, H arom.); 7.00 (1H, s, H arom.)
4b	3240, 3165, 1620	1.25 (3H, t, CH_3); 3.29 (2H, q, CH_2); 3.82 (6H, s, 2 × OCH_3); 6.38 (1H, s, H arom.); 6.58 (2H, s, NH_2); 6.74 (1H, s, H arom.); 6.93 (1H, s, H arom.)
5a	3360, 3300,1735, 1625	1.12 (3H, t, CH_3); 2.14 (3H, s, CH_3); 3.75 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 3.85 (2H, s, CH_2); 4.01 (2H, q, CH_2); 6.85 (1H, s, H arom.); 7.03 (1H, s, H arom.)
5b	3380, 3300,1730, 1625	1.01 (3H, t, CH_3); 1.26 (3H, t, CH_3); 2.80 (2H, q, CH_2); 3.75 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 3.87 (2H, s, CH_2); 4.02 (2H, q, CH_2); 6.85 (1H, s, H arom.); 6.92 (1H, s, H arom.)
6a	3210, 1635, 1615	2.42 (3H, s, CH_3); 3.21 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 6.87 (1H, s, H arom.); 7.03 (1H, s, H arom.); 10.35 (1H, s, NH)
6b	3200, 1630, 1615	1.14 (3H, t, CH_3); 2.90 (2H, q, CH_2); 3.11 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 7.27 (1H, s, H arom.); 7.51 (1H, s, H arom.); 10.20 (1H, s, NH)
7a	1740, 1685	1.12 (3H, t, CH_3); 2.14 (3H, s, CH_3); 3.75 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 3.85 (2H, s, CH_2); 4.01 (2H, q, CH_2); 6.85 (1H, s, H arom.); 7.03 (1H, s, H arom.)
7b	1730, 1680	1.01 (3H, t, CH_3); 1.36 (3H, t, CH_3); 2.80 (2H, q, CH_2); 3.75 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 3.87 (2H, s, CH_2); 4.02 (2H, q, CH_2); 6.85 (1H, s, H arom.); 6.92 (1H, s, H arom.)
9		2.30 (3H, s, CH_3); 2.75 (1H, dd, J_{AB} = 16.8, J_{AC} = 4.7, H_A); 3.14 (1H, dd, J_{AB} = 16.8, J_{BC} = 10.5, H_B); 4.69 (1H, dd, J_{AC} = 4.7, J_{BC} = 10.5, H_C); 3.58 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 6.81 (1H, s, H arom.); 7.02 (1H, s, H arom.); 8.85 (1H, br. s, NH)



In our opinion, on forming a seven-membered ring the role of the substituent at position 4 of the benzo[*c*]pyrilium cation results in disturbance of the planarity of the intermediate formed on opening the pyran ring with a molecule of hydrazine, which makes possible the formation of the energetically disadvantageous, compared with a six-membered, diazepine ring.

EXPERIMENTAL

The IR spectra were recorded in nujol on a UR 20 spectrophotometer, and the ^{1}H NMR spectra on a Varian Gemini 200 (200 MHz) spectrometer in DMSO-d_6, internal standard was TMS. The physicochemical and spectral characteristics of the synthesized compounds are given in Tables 1 and 2.

Keto ester **7** was characterized only by spectral methods. Procedures providing the best yields are given for compounds **4** and **6**.

2-Amino-1-R-6,7-dimethoxyisoquinolin-3(2H)-ones (4) and Hydrazones of Ethyl 2-Acyl-4,5-dimethoxyphenylacetates (5). Perchlorate **2** (10 mmol) was added to a solution of hydrazine hydrate (20 mmol) in 2-propanol (15 ml), the mixture was stirred until solution was achieved, and then left overnight. The reaction mixture was poured into water and the solid hydrazone **5** filtered off. The filtrate was evaporated to dryness in vacuum, and the residue separated in a mixture of dichloromethane–aqueous sodium bicarbonate solution. The organic layer was washed with water, dried over anhydrous $MgSO_4$, the solvent evaporated, and aminoisoquinolone **4** crystallized from alcohol.

2-Amino-1-R-6,7-dimethoxyisoquinolin-3(2H)-ones (4). A mixture of perchlorate **2** (10 mmol) and hydrazine hydrate (10 mmol) in alcohol (20 ml) was boiled for 2-3 h, and evaporated to dryness in vacuum. The residue was dissolved in water, and sodium acetate (10 mmole) added. The mixture was stirred for 10-15 min, an equimolar amount of Na_2CO_3 was added, and the mixture stirred for a further 30-60 min. The reaction mixture was evaporated to dryness in vacuum, the residue was dissolved in dichloromethane, and the solution washed once with water. The organic layer was dried over anhydrous $MgSO_4$, the solvent evaporated, and isoquinolone **4** crystallized from alcohol.

1-R-7,8-Dimethoxybenzo-2,3-diazepin-4(5H)-ones (6). A mixture of keto ester **7** (10 mmol) and hydrazine hydrate (30 mmol) in 2-propanol was heated for 2-3 h, then left overnight. The precipitated solid diazepinone **6** was filtered off and recrystallized three times from 2-propanol. Isoquinolone **4** was isolated from the alcoholic filtrates.

Ethyl 2-Acyl-4,5-dimethoxyphenylacetates (7). Perchlorate **2** was dissolved with heating in 50% acetic acid. The cooled solution was poured into water, and left overnight. The solid was filtered off, washed with water, and dried.

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