REACTIONS OF HETEROCYCLIC CATIONS WITH N-CONTAINING NUCLEOPHILES. 14.* RECYCLIZATION OF 2,6-DIPHENYLPYRYLIUM PERCHLORATE UNDER THE INFLUENCE OF NUCLEOPHILES WITH AN N—C—N FRAGMENT

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The recyclization of 2,6-diphenylpyrylium perchlorate under the influence of isothioureas, guanidine, 2-aminobenzimidazoles, 2-aminonaphth[1,2-d]imidazole, 2-aminothiazole, 2-aminobenzothiazole, and 2-aminopyridine was studied. The examined reactions lead to monocyclic or condensed pyrimidines.

The reaction of 2,6-diphenylpyrylium perchlorate (I) with the simplest N-containing nucleophiles was recently described [2]. In the present research we studied the reactions of salt I with compounds that contain the N—C—N amidine fragment and compared the investigated transformations with those known for 2,4,6-triphenylpyrylium perchlorate (II) [3].

Quantum-mechanical calculations of the electron-density distributions in the cations of I and II [4] lead one to believe that attack by the nucleophile on salt II is preferable at the $C_{(2)}$ atoms, whereas attack at both the $C_{(2)}$ and $C_{(4)}$ atoms is equally likely, and the electrophilicity of salt II should be higher. When perchlorate II is attacked by the nucleophile at $C_{(2)}$, the ring is opened to give intermediate imino ketone III [5]. If for salt I one of the possible mechanisms will be realized, viz., attack by the nucleophile at the $C_{(2)}$ atom, then in the subsequent opening of the ring it is also logical to assume the formation of intermediate imino ketone IV. Quantum-mechanical calculations of the electron-density distributions in III and IV† demonstrated that the positive charges on the carbon atoms designated by asterisks are equal (see Fig. 1). Consequently, in the case of attack on pyrylium salt I at the 2 position by a nucleophile with an N—C—N group and subsequent recyclization one might expect the formation of a pyrimidine ring, just as in the reactions of perchlorate II with the indicated reagents [3].

In fact, the reaction of salt I with S-benzylisothiourea in a ratio of 1:2 in ethanol leads to the formation of 2-benzylthio-4-phenylpyrimidine (Va). Similarly, the reaction of salt I with S-methylisothiourea gives 2-methylthio-4-phenylpyrimidine (Vb), which is identical to the compound described in [6]. The compositions and structures of Va were confirmed by the results of elementary analysis and IR spectroscopy, as well as by its conversion to a picrate.

The reaction of salt I with guanidine, which occurs at a reagent ratio of 1:2, leads to 2-amino-4-phenylpyrimidine (VI), the structure of which was confirmed by the presence in the IR spectrum of absorption bands of a primary amino group and by acylation to give VII, as well as by comparison with a known sample [7]. It should be noted that salt I, in contrast to salt II, does not react with the resulting amide VI during the reaction with guanidine. Primarily hydrolysis of salt I in the presence of a base to give a mixture of 1,5-diphenylpentene-1,5-dione (VIII) and 2,6-diphenylpyranylidenepentenedione (IX), the structures of which were previously established [8], takes place when the reaction is carried out with dry dimethylformamide (DMF).

*See [1] for communication 13.

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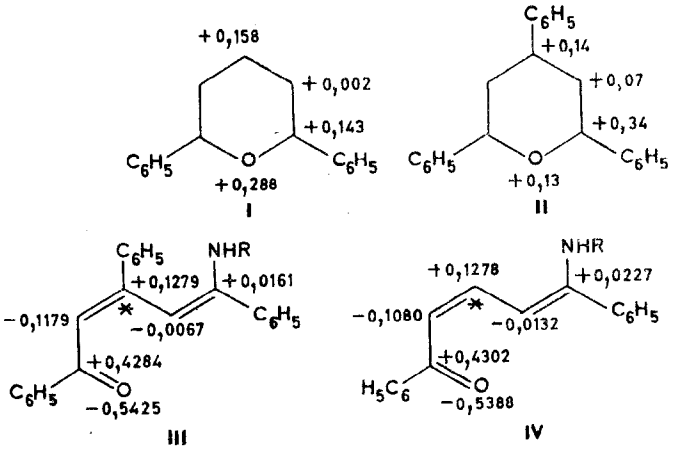
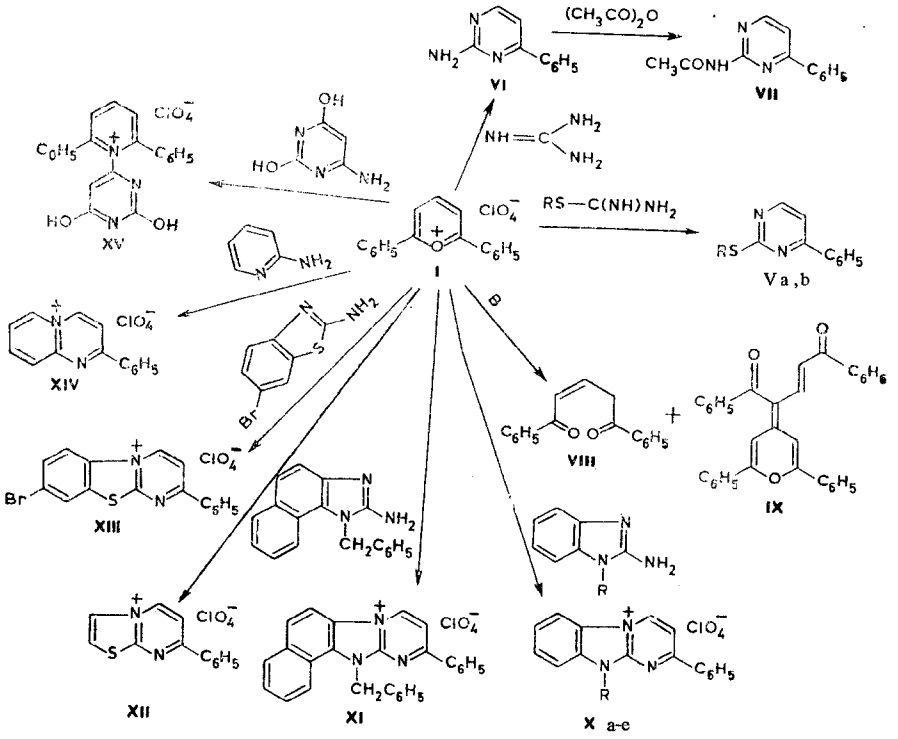


Fig. 1. Electron-density distributions in pyrylium salts I and II and in amino ketones III and IV [calculations by means of the Pariser—Parr—Pople (PPP) method].



V a $R=CH_2C_6H_5$, b $R=CH_3$; X a $R=C_2H_5$, b $R=CH_2C_6H_5$, c $R=C_8H_{17}$, d $R=C_9H_{19}$, e $R=C_{10}H_{21}$

We studied the reaction of salt I with amino-substituted azoles and found that the reaction with 2-aminobenzimidazoles proceeds in the same way as with salt II to give pyrimido[1,2-a]benzimidazolium perchlorates X, the compositions and structures of which were confirmed by the results of **elemental analysis and** IR spectroscopy. The PMR spectrum of Xa contains a triplet at 1.3 ppm (3H of the CH_3 group), a quartet at 4.45 ppm (2H of the CH_2 group), and a multiplet of 11 aromatic protons (7.0-8.1 ppm). The indicated reaction pathway is confirmed by the simultaneous formation of acetophenone. The reaction of salt I with 2-amino-3-benzylnaphth[1,2-d]imidazole is also realized with the formation of pyrimido[1,2-a]naphth[1,2-d]imidazolium perchlorate (XI).

In contrast to perchlorate II, which forms N-hetaryl-substituted pyridinium salts with 2-aminothiazole and 2-amino-6-bromobenzothiazole [9], salt I reacts with these compounds to give condensed compounds XII and XIII. The compositions and structures of the latter were confirmed by the results of **elemental analysis and** IR spectroscopy, and the recyclization pathway was confirmed by the formation of acetophenone.

We also studied the reaction of salt I with amino-substituted azines and found that its reaction with 2-aminopyridine proceeds ambiguously. This reaction gives a mixture of perchlorates, which, owing to their different colors, are clearly visible on chromatographic plates; however, they cannot be separated preparatively. From the reaction mixture we were able to isolate only pyrido[1,2-a]pyrimidinium perchlorate (XIV) (in low yield), the composition and structure of which were confirmed by the results of elemental analysis and IR spectroscopy. Individual salt products could not be isolated at all in the reaction of salt I with 4-phenyl-, 4,6-diphenyl-, and 2-aminopyrimidines. On the other hand, the reaction of salt I with the less basic 6-amino-uracil leads to the corresponding pyridinium perchlorate XV. It should be noted that salt II reacts with 2-aminopyridine and 2-aminopyrimidine to give exclusively N-pyridyl- and N-pyrimidinylpyridinium perchlorates.

On the basis of the results obtained in this research it may be concluded that the absence of a substituent in the 4 position of salt I facilitates attack by it on the "pyridine" atom of the heterocyclic fragment, which, when this atom is sufficiently basic, leads to the synthesis of condensed systems, just as in the case of azoles. Competitive processes, including the formation of condensed systems, pyridinium salts, and others, are observed with the less basic azines.

In all of the investigated reactions one observes simultaneous processes involving the hydrolysis of salt I in the presence of a base; these processes substantially decrease the yields of recyclization products as compared with the yields for salt II. A significant fraction of the hydrolysis of salt I can be explained by removal of diketone VIII from the reaction zone in the equilibrium process owing to Michael condensation of two of its molecules [8], which also becomes possible when there is no substituent attached to the $C_{(4)}$ atom of salt I.

The longer time required for the completion of the reactions of salt I with nucleophiles as compared with salt II and the absence of its reaction with the resulting amine VI in the reaction with guanidine confirm the results of quantum-mechanical calculations regarding the lower electrophilicity of salt I as compared with salt II.

EXPERIMENTAL

The PMR spectrum was recorded with a Tesla BS 467C spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were obtained with a Specord 71-IR spectrometer. The UV spectrum of a solution in acetonitrile was recorded with a Specord UV-VIS spectrophotometer. The purity of the compounds obtained was monitored by means of thin-layer chromatography (TLC) on plates with aluminum oxide or silicon dioxide in a benzene–ethyl acetate system (3:1) or in chloroform. The presence of benzaldehyde was determined by its conversion to the 2,4-dinitrophenylhydrazone.

Reaction of Perchlorate I with S-Benzylisothiourea. A solution (5 ml) of sodium ethoxide, prepared from 0.14 g (6 mmole) of sodium, was added with ice cooling to a suspension of 1.22 g (6 mmole) of S-benzylisothiourea hydrochloride in 5 ml of absolute ethanol, 30 min after which 0.99 g (3 mmole) of salt I was added, and the reaction mixture was refluxed for 2 h. The NaCl was removed by filtration, and the filtrate was concentrated and diluted with ether. The ether layer was separated and washed with water, the solvent was evaporated, and the residue was purified by chromatography with a column packed with aluminum oxide (benzene was the solvent and eluent). The first fraction was collected and worked up to give 0.63 g of 2-benzylthio-4-phenylpyrimidine (Va). The picrate of pyrimidine Va had mp 151-152°C (from ethanol). Found: C 54.7; H 3.7; N 14.1; S 5.9%. $C_{17}H_{14}N_2S \cdot C_6H_3N_3O_7$. Calculated: C 54.5; H 3.4; N 13.8; S 6.3%. Workup of the second fraction, which contained a red product, gave 0.18 g (22%) of pyranylidenepentenedione IX with mp 216°C (from butanol) (mp 216-217°C [2]). No melting-point depression was observed for a mixture of IX with a genuine sample.

The reaction of perchlorate I with S-methylisothiourea was realized similarly starting from S-methylisothiourea sulfate, but the mixture was refluxed for 1 h. The reaction mixture was cooled and diluted with ether, the ether layer was washed with water, and the ether was evaporated. The residue was dissolved in benzene and chromatographed with a column filled with aluminum oxide by elution with petroleum ether. The first fraction was collected and worked up to give 2-methylthio-4-phenylpyrimidine (Vb). The picrate of pyrimidine Vb had mp 171.5-172°C (from ethanol). Found: C 47.6; H 3.1; N 16.4; S 7.0%. $C_{11}H_{10}N_2S \cdot C_6H_3N_3O_7$. Calculated: C 47.3; H 3.0; N 16.2; S 7.4%.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp,[a] deg C	IR spectrum, cm^{-1}	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
V a	53—54	1190, 1345, 1410, 1470, 1540, 1555, 1570, 1600	73,5	5,4	11,1[b]	10,3	$C_{17}H_{14}N_2S$	73,4	5,1	11,5[b]	10,1	76
V b	85—85,5[c]	1210, 1355, 1420, 1475, 1500, 1545, 1560, 1600	65,1	5,3	15,3[b]	14,1	$C_{11}H_{10}N_2S$	65,3	5,0	15,9[b]	13,9	78
VI	160—161[d]	1445, 1475, 1555, 1560, 1650, 3125, 3325	70,4	5,7	—	24,4	$C_{10}H_9N_3$	70,2	5,3	—	24,5	45
VII	215,5—216[e]	1300, 1340, 1425, 1530, 1570, 1600, 1670	67,8	5,2	—	19,5	$C_{12}H_{11}N_3O$	67,6	5,2	—	19,7	94
X a	217	1100, 1440, 1475, 1560, 1590, 1610, 1630	57,6	4,7	9,9	11,1	$C_{18}H_{16}ClN_3O_4$	57,8	4,3	9,5	11,2	34
X b	261	1100, 1440, 1485, 1565, 1600, 1635	63,1	4,3	7,9	9,6	$C_{23}H_{18}ClN_3O_4$	63,4	4,1	8,1	9,6	93
X c	160—161	1100, 1440, 1475, 1600, 1610, 1630	62,7	6,1	8,1	8,9	$C_{24}H_{28}ClN_3O_4$	63,0	6,2	7,7	9,2	41
X d	152—153	1100, 1440, 1475, 1600, 1610, 1630	63,4	6,6	7,1	8,6	$C_{25}H_{30}ClN_3O_4$	63,6	6,4	7,5	8,9	43
X e[f]	158—158,5	1100, 1445, 1480, 1560, 1600, 1615, 1635	64,3	6,8	7,0	8,4	$C_{26}H_{32}ClN_3O_4$	64,3	6,6	7,3	8,7	55
XI	308—309	1100, 1415, 1445, 1475, 1555, 1600, 1640	67,0	4,1	7,7	8,9	$C_{27}H_{20}ClN_3O_4$	66,7	4,2	7,3	8,7	89
XII	233	1100, 1410, 1490, 1550, 1600, 1620	45,8	3,2	10,7[b]	8,8	$C_{12}H_9ClN_2O_4S$	46,1	2,9	10,3[b]	9,0	32
XIII	303	1100, 1400, 1430, 1475, 1530, 1600, 1615	43,8	2,7	7,7[b]	6,6	$C_{16}H_{10}BrClN_2O_4S$	43,5	2,3	7,3[b]	6,3	76
XIV	209—210[g]	1110, 1560, 1600, 1640	54,5	3,9	11,5	9,2	$C_{14}H_{11}ClN_2O_4$	54,8	3,6	11,6	9,1	10
XV	297—297,5	1120, 1490, 1520, 1600, 1640, 1730	56,8	4,0	8,2	9,7	$C_{21}H_{16}ClN_3O_6$	57,1	3,7	8,0	9,5	31
XVI	258	1100, 1410, 1540, 1560, 1580, 1600, 1620	66,8	4,6	7,3	8,5	$C_{27}H_{20}ClN_3O_4$	66,7	4,2	7,3	8,7	98
XVII	226		63,7	4,1	6,2[b]	5,9	$C_{26}H_{19}ClN_2O_4S$	63,6	3,9	6,5[b]	5,7	92

[a]The compounds were recrystallized: Va from aqueous ethanol, Vb from aqueous acetone, VI and VII from benzene, Xa, c-e from ethanol, Xb from acetonitrile, XI and XIII from nitromethane, XII, XIV, and XV from acetic acid, and XVI and XVII from ethanol—acetonitrile. [b]The analysis for S is presented. [c]According to [6], this compound had mp 86.5-87°C. [d]According to the data in [7], this compound had mp 160-161°C. [e]According to the data in [10], this compound had mp 220-221°C. [f]UV spectrum, λ_{max} (log ε): 267 (4.74) and 333 nm (4.90). [g]According to the data in [11], this compound had mp 210-211°C.

2-Amino-4-phenylpyrimidine (VI). A solution of sodium ethoxide, prepared from 0.14 g (6 mmole) of sodium and 5 ml of ethanol, was added to a suspension of 0.58 g (6 mmole) of guanidine hydrochloride in 5 ml of ethanol. After 30 min, the mixture was added to 0.99 g (3 mmole) of salt I in 20 ml of acetone, and the mixture was refluxed for 1 h. It was then cooled, diluted with ether, and filtered, and the filtrate was washed with water and dried over potassium carbonate. The ether was removed by distillation, and the dry residue was treated wih a small amount of benzene and filtered to give 0.23 g of pyrimidine VI. The benzene filtrate contained primarily VIII and IX mixed with other unidentified components.

2-Acetamino-4-phenylpyrimidine (VII). Equimolar amounts of pyrimidine VI and acetic anhydride were refluxed in glacial acetic acid for 20 min, after which the mixture was cooled, and VII was removed by filtration.

Reaction of Perchlorate I with 2-Amino-1-ethylbenzimidazole. A 0.39-g (2.4 mmole) sample of 2-amino-1-ethylbenzimidazole was added to a hot solution of 0.67 g (2 mmole) of salt I in 3 ml of DMF, and the mixture was refluxed for 30 min. It was then cooled, and the mixture was treated with ether to give an oil, which was reprecipitated from acetone by the addition of water. The precipitate was removed by filtration and washed with butanol and ethanol to give 0.25 g of 5-ethyl-3-phenylpyrimido[1,2-α]benzimidazolium perchlorate (Xa). PMR spectrum (in CF_3COOH): 1.3 (3H, t, CH_3), 4.45 (2H, q, CH_2), 7-8.1 ($11H_{arom}$, m), and 8.85 ppm (1H, s, NH). The ether layer was washed three times with water and dried over potassium carbonate. The ether was removed by distillation, and the residue was recrystallized from butanol to give 0.13 g (19%) of pyranylidenepeptenedione IX, which was identical to a genuine sample.

5-Benzyl-, 5-octyl-, 5-nonyl-, and 5-decyl-3-phenylpyrimido[1,2-α]benzimidazolium perchlorates (Xb,c,d,e, respectively) and 5-benzyl-3-phenylpyrimido[1,2-α]naphth[1,2-d]imidazolium perchlorate (XI) were similarly obtained; salts Xb-e and XI were isolated from the reaction mixtures with ether and were obtained in the form of yellow precipitates.

7-Phenylpyrimido[1,2-b]thiazolium Perchlorate (XII). This compound was obtained from salt I and 2-aminothiazole by a method similar to that used to prepare X. The oil that formed when the mixture was treated with ether was separated and mixed with a small amount of chloroform, and undissolved perchlorate XII was removed by filtration and washed with acetone.

8-Bromo-2-phenylpyrimido[1,2-b]benzothiazolium Perchlorate (XIII). This compound was obtained from salt I and 2-amino-6-bromobenzothiazole by a method similar to that used for salts X, except that the mixture was refluxed for 45 min. The product was isolated by means of ether in the form of an oil, which was reprecipitated from acetone by the addition of water.

Reaction of Salt I with 2-Aminopyridine. This reaction was carried out with a reagent ratio of 1:1.2 in refluxing DMF for 30 min. The mixture was then cooled and treated with ether, and the liberated oil was reprecipitated from chloroform by the addition of ether, after which the precipitate was treated with a small amount of acetone and removed by filtration to give colorless 2-phenylpyrido[1,2-α]pyrimidinium perchlorate (XIV). A complex mixture of perchlorates that could not be separated was precipitated from the filtrate by means of ether. The ether layers were combined and washed with water, the ether was evaporated, and the residue was dissolved in benzene and chromatographed with a column filled with aluminum oxide by elution with petroleum ether. The yellow fraction was collected and worked up to give VIII, with mp 153°C (from ethanol) (mp 152°C [8]), in 12% yield. A red fraction containing pyranylidenepentenedione IX was then separated by elution with benzene.

1-(2,4-Dihydroxy-6-pyrimidinyl)-2,6-diphenylpyridinium Perchlorate (XV). This compound was obtained by the reaction of salt I and 6-aminouracil in a ratio of 1:1.2 in refluxing DMF for 40 min. The reaction mixture was filtered without cooling, and bright-yellow perchlorate XV was precipitated from the filtrate by the addition of ether.

The reactions of perchlorate II with 2-aminopyrimidine and 2-aminothiazole have not been carried out previously, and they are therefore given below. The reactions of salt II with the indicated amines were carried out as in the preceding method. 1-(2-Pyrimidinyl)-2,4,6-triphenylpyridinium perchlorate (XVI) and 1-(2-thiazolyl)-2,4,6-triphenylpyridinium perchlorate (XVII) were precipitated from the reaction mixtures by the addition of ether.

Data on the compounds obtained in this research are presented in Table 1.

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SYNTHESIS AND PROPERTIES OF 3-OXA-7,11-DIAZASPIRO[5.6]DODECANES

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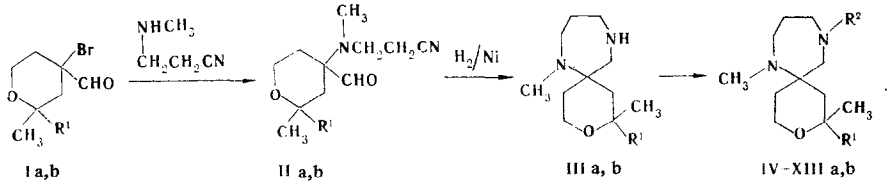
A method for the synthesis of 2,2-dialkyl-3-oxa-7,11-diazaspiro[5.6]dodecanes was developed on the basis of 4-bromo-4-formyltetrahydropyrans. The products were alkylated at the nitrogen atom in the 11 position by means of alkyl halides and acrylic acid derivatives, and the alkoxycarbonyl groups in the side chain were reduced.

In recent years considerable attention has been paid to methods for the synthesis and study of the biological properties of spiro biheterocyclic compounds [1-4]. Having an accessible method of synthesis of 4-bromo-4-formyltetrahydropyrans [5] at our disposal, we have developed a method for the synthesis of a new spiro biheterocyclic system in which the tetrahydropyran and perhydrodiazepine rings are spiro-bonded via the scheme



I a,b — II a,b — III a, b — IV-XIII a,b

I—XIII a $R^1=CH_3$; b $R^1=C_2H_5$; R^2 see Table 1.

Halo aldehydes Ia,b react smoothly with β-methylaminopropionitrile [6] to give formyl nitriles IIa,b, which undergo hydrogenation with cyclization to give spiro amines IIIa,b in good yields at a hydrogen pressure of 110 atm (technical) at 90°C in the presence of Raney nickel. The N-monosubstituted perhydrodiazepine ring makes it possible to obtain numerous derivatives of this spiro biheterocycle (Table 1), some of which we synthesized with the aid of ethyl bromoacetate (IVa,b), propargyl bromide (Va, b), α-chloroacetamide (VIa,b), 5-phenyl-1-chloro-2-hexene (VIIa,b), methyl acrylate (VIIIa,b), and acrylamide (IXa,b) as the reagents. We also obtained several alcohols (Xa,b, XIa) by hydrogenation of IVa,b and VIIIa with lithium aluminum hydride.

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