REACTIONS AND MASS-SPECTROMETRIC STUDY OF AZA ANALOGS OF 2-AMINOCHROMONE

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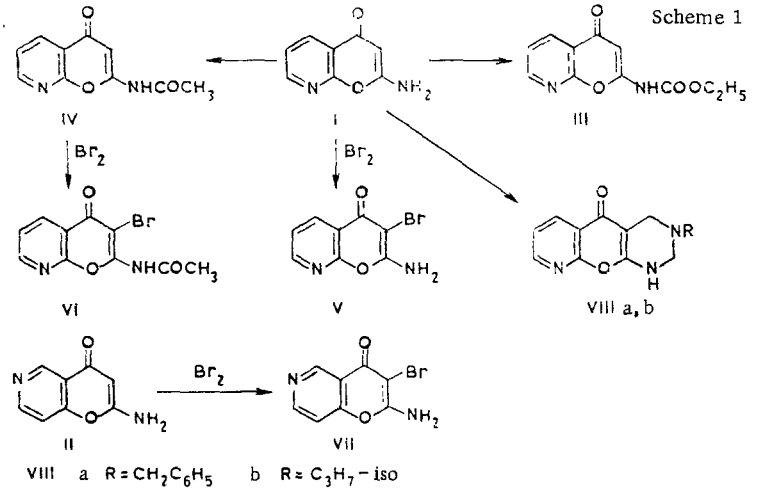
Electrophilic substitution reactions at the C and $N_{(2)}$ atoms of 2-amino-4-oxo-4H-pyrano[2,3-b]pyridine were studied. 2-Aminoazachromones were subjected to a mass-spectroscopic study in comparison with 2-aminochromenes, and fundamental differences in their fragmentation were established.

We have previously [1] synthesized 2-aminoazachromones (AZC): 2-amino-4-oxo-4H-pyrano[2,3-b]pyridine (I) and 2-amino-4-oxo-4H-pyrano[3,2-c]pyridine (II). The presence of pyridine and 4-pyrone heteroaromatic rings in I and II opens up additional possibilities in the search for biologically active substances and in the study of the reactivity of the condensed pyrone–pyridine system, in which the mutual effect of the atoms should be realized in a rather complex manner. We have studied some electrophilic substitution reactions of I and II.

Scheme 1



2-Acyl derivatives III and IV are formed by the action of $ClCOOC_2H_5$ on I in dimethylsulfoxide (DMSO) in the presence of triethylamine or acetic anhydride in pyridine. In analogy with 2-acylaminochromones [2], the absorption bands at 1710-1760 and 1615 and 1635 cm^{-1} in the IR spectra of III and IV should be assigned to the stretching vibrations of the amide and pyrone carbonyl groups, respectively. The PMR spectrum of IV is also in agreement with the assigned structure. The action of bromine on I in acetic acid initially gives an adduct that is converted to 2-amino-3-bromopyrono[2,3-b]pyridine (V) on treatment with sodium sulfite. 2-Acetamido-3-bromopyrono[2,3-b]pyridine (VI) and 2-amino-3-bromopyrono[3,2-c]pyridine (VII) were similarly obtained. A 3-H signal at 5-7 ppm is absent in the PMR spectra of V-VII.

5-Oxo-1,2,3,4-tetrahydro-5H-pyrido[3',2':5,6]pyrano[2,3-b]pyrimidine derivatives (VIIIa, b), which give monohydrochlorides, were obtained by reaction of I with primary amines and excess formaldehyde.

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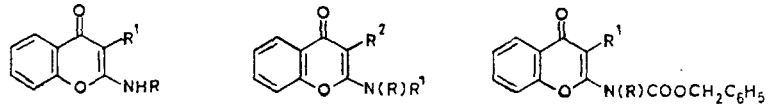
Thus electrophilic substitution in 2-aminopyronopyridines I and II may proceed at the 2-amino group or at the C_3 atom of the pyrone ring, as is also observed in the case of 2-aminochromones (AC) [3].

Compounds I-IV were subjected to a mass-spectroscopic study. For a more profound understanding of the fragmentation processes of these compounds, the data obtained are compared with the mass spectra of various AC (IX-XXIII), which were previously synthesized in [2-5].



IX-XI XII-XX XXI-XXIII

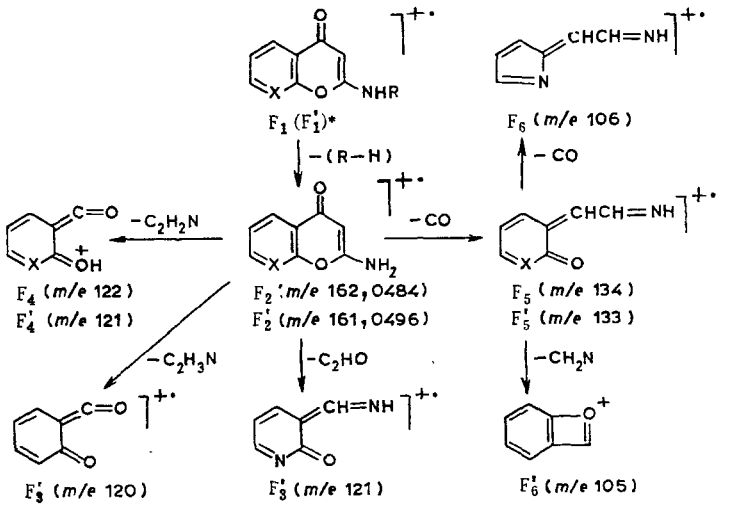
IX $R=R^1=H$; X $R=H$, $R^1=Br$; XI $R=CH_3$, $R^1=H$; XII $R=COCH_3$, $R^1=R^2=R^3=H$; XIII $R=COC_6H_5$, $R^1=R^2=R^3=H$; XIV—XIX $R=COOC_2H_5$; XIV $R^1=R^2=R^3=H$; XV $R^1=R^3=H$, $R^2=Br$; XVI $R^1=R^2=H$, $R^3=CH_3$; XVII $R^1=R^2=H$, $R^3=Cl$; XVIII $R^1=R^2=H$, $R^3=NO_2$; XIX $R^1=CH_3$, $R^2=R^3=H$; XX $R=CONC_4H_8$, $R^1=R^2=R^3=H$; XXI $R=R^1=H$; XXII $R=H$, $R^1=Br$; XXIII $R=CH_3$, $R^1=H$

The principal pathways of fragmentation of AZC and AC under the influence of electron impact are presented in Scheme 2. The fragmentation of molecular ions F_1 and F'_1 of N-acyl derivatives of AZC and AC involves the loss of R—H (where $R=COCH_3$ or $COOC_2H_5$), which is accompanied by migration of a hydrogen atom of the alkyl group to the nitrogen atom in the 2 position to give, respectively, F_2 (m/e 162) and F'_2 (m/e 161) ions, which, with respect to their structures, are evidently analogous to the molecular ions of unsubstituted I and IX. This process is probably similar to the formation of the ion of an aromatic amine in the fragmentation of acetanilides (for example, see [6]) or ethyl carbamates (see below).

One of the chief differences in the fragmentation of AZC is the absence of simple retrodiene fragmentation of the F_2 ion — the fragmentation characteristic for chromones.

In the case of the AC, retrodiene fragmentation of the F'_2 ion leads to the formation of the F'_3 ion typical for chromones [7-10] with m/e 120 (see Scheme 2).

Scheme 2



*For F'_n, X=CH; for F_n, X=N.

In the spectra of AZC one observes low-intensity (< 1-8%) F_3 ions with m/e 121, which (according to the high-resolution mass-spectral data; see the experimental section) are products of (F_2-CH_2O) fragmentation rather than products of normal retrodiene reaction of ion F_2.

Another peculiarity in the fragmentation of AZC consists in successive loss from ion F_2 of two CO groups (this was confirmed by the presence of the corresponding metastable ions and the high-resolution mass spectrum; see the experimental section) to give ions F_5 (m/e 134) and F_6 (m/e 106). The fragmentation of AC in this direction proceeds through decarbonylation of ion F'_2 to ion F'_5, with m/e 133, and subsequent loss of CH_2N to give ion F'_6 with m/e 105.

The structure of ion F_5 (m/e 134) or F'_5 (m/e 133) can be represented as a condensed 2-substituted furan, but a structure with an open furan ring must be preferred.

Retrodiene fragmentation of ions F_2 and F'_2 with migration of a hydrogen atom, which leads to the formation of, respectively, ions F_4 (m/e 122) and F'_4 (m/e 121), is characteristic for the fragmentation of AZC

and AC. One cannot exclude fragmentation of molecular ions F_1 and F'_1 directly to ions F_4 and F'_4 or to ion F'_3, but the corresponding metastable peak is detected only in the spectrum of XIV.

It should be noted that the structure of ion F'_3 was assigned to the products of fragmentation of 2-alkylchromones and some hydroxyflavones [10]. An ion of the F_4 (F'_4) type may correspond to yet several other structures, for example, those with an aldehyde group in which the hydrogen atom is attached to the ring carbon atoms, in which case structures with a single bond between the carbonyl group and the ring are unlikely, since ion F'_4 formed from XIV with an O^{18} label (33%) at the pyrone carbonyl group retains its label practically completely (30%).

Ion F_4 (F'_4) is also present in the mass spectra of 3-substituted V and X. Consequently, the hydrogen atom attached to C_3 does not necessarily participate in the formation of ion F_4 (F'_4), and a hydrogen atom of the amino group evidently migrates. Nitrogen-deuterated XIV and XV give an F'_4 ion containing deuterium (m/e 122). Hydrogen migration from the amino group is also confirmed by comparison of the ratios of the intensities of the peaks of the F'_4/F'_1 ions of IX and its N-methyl derivative XI (in all cases the intensity of F'_1 is 100%): for IX, F'_4/F'_1 is 0.68, as compared with 0.40 for XI, i.e., almost half. A comparison of the intensities of ions* F_4 and F_2 (m/e 162) in the spectra of I and III and of the intensities of ions F'_4 and F'_2 (m/e 161) in the spectra of IX and XIV shows that replacement of a hydrogen atom of the amino group by a carbethoxy group leads to an increase in the intensity ratio of ion F_4 and those with m/e 162 for III (0.72), as compared with I (0.44), and of the $I_{F_4'}/I_{161}$ ratio for XIV (2.2) as compared with IX (0.68). These results can be explained by the fact that in the case of III and XIV (and also XV-XIX) ions F_4 and F'_4 are also formed by another pathway, for example, through migration of a hydrogen atom of the alkyl group.

The unusual character of the fragmentation of AZC should be explained by the increased electron-acceptor properties of the pyridine ring as compared with the benzene ring. The same reason evidently also affects the character of the fragmentation of the ethyl carbamate grouping in AZC and AC. It is known [11-16] that the fragmentation of ethyl carbamates consists in the formation of $[M-44]^{+\cdot}$, $[M-45]^{+}$, $[M-46]^{+\cdot}$, $[M-59]^{+}$, $[M-72]^{+\cdot}$ and $[M-74]^{+\cdot}$ ions, and this corresponds to the elimination of CO_2. CO_2H (or C_2H_5O), C_2H_5OH, (CO_2+CH_3), ($CO_2+C_2H_4$), and (C_2H_5OH+CO). All of these ions are present in the mass spectrum of III, whereas there are practically no $[M-44]^{+\cdot}$ and $[M-45]^{+\cdot}$ ions in the spectrum of XIV. Consequently, processes involving hydrogen migration toward the aromatic system are manifested less markedly in AZC.

In the case of XIX, the formation of $[M-C_2H_5OH]^{+\cdot}$ and $[M-C_2H_5OH-CO]^{+\cdot}$ ions is excluded, and ion F'_4 may arise both from the ion with m/e 175 $[M-CO_2-C_2H_4]^{+\cdot}$ and from the molecular ion. Evidence in favor of this is provided by the high-intensity ratio of ions F'_4 and those with m/e 175 in the mass spectrum of XIX (0.72) as compared with XI (0.40). Carbobenzoxy derivatives of 2-amino chromone (XXI-XXIII) give low-intensity molecular ions (0.15, 0.3, and 13%, respectively), which undergo fragmentation with ejection of a molecule of benzyl alcohol in the case of XXI and XXII or CO_2 in the case of XXIII. The former successively eliminate a bromine atom (XXII) or CO_2 or undergo fragmentation to give ions with m/e 120 (XXI and XXII); the $[M-CO_2]^{+}$ ion (XXIII) undergoes fragmentation to give ion F'_4.

Like other 2-acylaminochromones, amide XX forms ions F'_2, F'_3, and F'_4, and, through the loss of pyrrolidine, is evidently converted to the corresponding isocyanate [m/e 187 (100%)], which subsequently successively loses two CO molecules or undergoes retrodiene fragmentation to give F'_3. N-benzoyl derivative XIII differs markedly from the other N-acyl substituted compounds with respect to the instability of M^+ (7%), the fragmentation of which includes the successive formation of $[C_6H_5CO]^+$ (100%) and $[C_6H_5]^+$ ions.

Thus we have established the principal differences in the mass spectra of AZC and AC: The absence of normal retrodiene fragmentation and the presence of two successive decarbonylation processes in the case of AZC. We have shown that the amino group in the 2 position of chromones is in turn responsible for a number of rearrangement processes that are absent in the mass spectra of chromone and its simplest derivatives. Moreover, the degree of the occurrence of the indicated processes increases on passing from AC derivatives to their aza analogs.

The fragmentation of 2-amino-6-azochromone (II) is similar to that of I; only small differences in the relative intensities of the ions are observed (the M^+ peak is also the maximum peak).

EXPERIMENTAL

The IR spectra of mineral-oil suspensions or chloroform solutions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were obtained with a Varian T-60 spectrometer on the δ scale.

*Here and elsewhere, the peak intensities are expressed in percent relative to the maximum.

TABLE 1. Intensities of the Most Important Peaks in the Mass Spectra of 2-Amino-8-azachromones and 2-Aminochromones

Ions	Ion intensities							
	I	III	IV	V	IX	X	XI	XIV
F_1 or F'_1		27	9	100		100	100	60
F_2 or F'_2	100	100	100		100	38	2	45
F_3 or F'_3	0	8	0	8	29	14	12	86
F_4 or F'_4	44	72	44	24	68	55	40	100
F_5 or F'_5	29	22	23		10		5	12
F_6 or F'_6	10	10	4	18	4	7	12	10
F_1-CO_2		16						
$F_1-C_2H_5OH$		14						
$F_1-C_2H_5OH$		13						90
$F_1-CO_2-CH_3$		7						14
$F_1-CO-C_2H_4$		See F_2						See F'_2
$F_1-CO-C_2H_5OH$		4						25
$F_1-C_6H_5CH_2OH$								

TABLE 1. (continued)

Ions	Ion intensities							
	XV	XVI	XVII	XVIII	XIX	XXI	XXII	XXIII
F_1 or F'_1	38	58	13	38	100(M^+)	0,3	0,3	13(M^-)
F_2 or F'_2		4		15				
F_3 or F'_3	42			8	17	47	30	1
F_4 or F'_4	86			20	49			3
F_5 or F'_5		61						5
F_6 or F'_6		14		14	16	8		3
F_1-CO_2								19
$F_1-C_2H_5OH$				15	12			
$F_1-C_2H_5OH$	100	40	21					
$F_1-CO_2-CH_3$	20	21	37	12				
$F_1-CO-C_2H_4$	58	35	18	52	68			19
$F_1-CO-C_2H_5OH$	78	7	12		23			
$F_1-C_6H_5CH_2OH$						65	80	

The mass spectra were recorded with an MKh-1303 mass spectrometer with a system for direct introduction of the samples into the ion source at ionizing voltages of 50 and 20 eV and an ionization chamber temperature of 250°. The following metastable transtions are observed in the mass spectra:

III, 234 (M^-) →190+CO_2 (m^* 154,2); 190→162+C_2H_4 (m^* 138); 134→106 (m^* 84); 122→94 (m^* 72.5); IV, 204 (M^+)→162 (m^* 128,5), 162→134 (m^* 111), 134→106 (m^* 84,0), 162→122 (m^* 92,0), 122→94 (m^* 72,5); V, 242/240 (M^+)→214/212+CO (m^* 188.5), 242/240→161+ +Br (m^* 107,5), 161→133+CO (m^* 109,5), 122→94+CO (m^* 72,5); IX, 121→93 (m^* 71,5); X, 241/239 (M^+)→160+Br (m^* 106,5), 160→132+CO (m^* 108,5), 241/239→ →213/211+CO (m^* 187), 213/211→132+Br (m^* 82,5), 121→93+CO (m^* 71,5); XI. 121→93 (m^* 71,5); XII, 203 (M^+)→161 (m^* 127,8), 161→121 (m^* 91,5), 121→93 (m^* 71,5); XIII, 265 (M^+)→105+160 (m^* 41.6), 105→77+CO (m^* 56,6), XV, 313/311 (M^+)→232+Br (m^* 173); XVI, 247 (M^+)→175 (m^* 124,0); XIX, 247 (M^+)→121 (m^* 59,5), 121→93 (m^* 71,5); XX, 258 (M^+)→187+81 (m^* 135,5), 187→159+CO (m^* 135), 187→120+67 (m^* 77,0).

The high-resolution mass spectra were recorded with a Jeol JMS 01SG-2 spectrometer at an ionizing voltage of 75 eV.* The fundamental data of the high-resolution mass spectra were as follows (the ion and its composition and mass are listed):

I, F_1 (M^+). $C_8H_6N_2O_2$, 162,0484; F_5, $C_7H_6N_2O$, 134,0509; F_4, $C_6H_4NO_2$, 122,0206; F_3, $C_6H_5N_2O$, 121,0378; F_6, $C_6H_5N_2$, 106,0495; IX, F'_1 (M^+), $C_9H_7NO_2$, 161,0484; F'_5, C_8H_7NO, 133.0531; F'_4, $C_7H_5O_2$, 121,0304; F'_3, $C_7H_4O_2$, 120,0209; F'_6, C_7H_5O, 105,0337.

2-Carbethoxyamino-4-oxo-4H-pyrano[2,3-b]pyridine (III). A 1.09 g (0.01 mole) sample of $ClCOOC_2H_5$ was added with cooling to a solution of 1.62 g (0.01 mole of I in 30 ml of DMSO and 1.52 ml of triethylamine, and the mixture was heated for 1 h on a boiling-water bath. The resulting precipitate was removed by filtration, and the filtrate was vacuum evaporated. A small amount of water was added to the residue, and the mixture was allowed to stand for three days. The resulting precipitate was removed by filtration to give 1.2 g

*The high-resolution mass spectra were recorded by A. B. Belikov for which the authors express their gratitude.

(51%) of III with mp 202-203° (dec., from ethanol). Found: C 56.6; H 4.2; N 12.3%. $C_{11}H_{10}N_2O_4$. Calculated: C 56.4; H 4.3; N 12.0%. IR spectrum ($CHCl_3$, c 0.01 M, d 1 mm): 3425 (ν_{NH}), 1760 (ν_{CO}), 1635 (ν_{CO}), and 1602 (ring double bond ν) cm^{-1}.

2-Acetamido-4-oxo-4H-pyrano[2,3-b]pyridine (IV). A mixture of 0.81 g (5 mmole) of I, 20 ml of acetic anhydride, and 5 ml of pyridine was heated at ~100° for 5 h, after which it was vacuum evaporated, and the residue was treated with a small amount of water to give 0.55 g (54.5%) of IV with mp 260-263° (dec., from ethanol). Found: C 58.7; H 4.0; N 13.7%. $C_{10}H_8N_2O_3$. Calculated: C 58.8; H 4.0; N 13.7%. IR spectrum (in oil): 1712 (ν_{CO}) and 1615 (ring and ν_{CO}) cm^{-1}. PMR spectrum (in DMSO), δ: 2.1 (3 H, s,* CH_3), 6.8 (1 H, s, 3-H), 7.5 (1 H, two d, $J_1 = 8$ Hz, $J_2 = 5.6$ Hz, 6-H), 8.35 (1 H, two d, $J_1 = 8$ Hz, $J_2 = 2$ Hz, 5-H), and 8.6 ppm (1 H, two d, $J_1 = 5$ Hz, $J_2 = 2$ Hz, 7-H).

2-Amino-3-bromo-4-oxo-4H-pyrano[2,3-b]pyridine (V). A 1.6-g (0.01 mole) sample of bromine was added to a solution of 1.62 g (0.01 mole) of I in 50 ml of glacial acetic acid, and the mixture was allowed to stand overnight. The resulting precipitate was removed by filtration, treated with a solution of 7 g of Na_2SO_3 in 150 ml of water, and washed with water to give 1.5 g (63%) of V with mp 233-234° (dec., from acetic acid). Found: C 39.7; H 2.2, Br 33.2; N 11.3%. $C_8H_5BrN_2O_2$. Calculated: C 39.9; H 2.1; Br 33.2; N 11.6%. IR spectrum (in oil): 3300-3400 (ν_{NH}) and 1620 (ν_{CO} and ring double bonds) cm^{-1}. PMR spectrum (in DMSO), δ: 7.43 (1 H, two d, $J_1 = 9$ Hz, $J_2 = 4.5$ Hz, 6-H), 8.13 (2 H, broad signal, NH_2), 8.3 (1H, two d, $J_1 = 9$ Hz, $J_2 = 2$ Hz, 5-H), and 8.5 ppm (1 H, two d, $J_1 = 4.5$ Hz, $J_2 = 2$ Hz, 7-H).

2-Amino-3-bromo-4-oxo-4H-pyrano[3,2-c]pyridine (VII). This compound, with mp > 270° (dec.), was obtained in 67% yield from II by the method used to prepare V. Found: C 39.8; H 2.0; Br 32.1; N 11.5%. $C_8H_5BrN_2O_2$. Calculated: C 39.9; H 2.1; Br 32.2; N 11.6%. IR spectrum (in oil): 3280-3300 (broad ν_{NH_2} band), 1668 (δ_{NH_2}), and 1610 (ν_{CO} and ring double bonds) cm^{-1}. PMR spectrum (in CF_3COOH), δ: 7.60 (1 H, d, $J = 8$ Hz, 8-H), 8.55 (1 H, d, $J = 8$ Hz, 7-H), and 9.2 ppm (1 H, s, 5-H).

2-Acetamido-3-bromo-4-oxo-4H-pyrano[2,3-b]pyridine (VI). This compound, with mp 194-195° (dec., from ethanol), was obtained in 46% yield from IV by the method used to prepare V. Found: C 42.4; H 2.6; Br 28.5; N 10.0%. $C_{10}H_7BrN_2O_3$. Calculated: C 42.4; H 2.5; Br 28.2; N 9.9%. IR spectrum (in $CHCl_3$, c 0.01 M, d 1 mm): 3480 (ν_{NH}), 1720 (ν_{CO}), 1660 (ν_{CO}), 1620 and 1600 (ν_{ring}) cm^{-1}. PMR spectrum (in DMSO), δ: 2.05 (3 H, s, CH_3), 7.67 (1H, two d, $J_1 = 9$ Hz, $J_2 = 4.5$ Hz, 6-H), 8.23 (1 H, NH), 8.43 (1 H, two d, $J_1 = 7$ Hz, $J_2 = 2$ Hz, and 5-H), 8.7 ppm (1 H, two d, $J_1 = 5$ Hz, $J_2 = 2$ Hz, 7-H).

3-Benzyl-5-oxo-1,2,3,4-tetrahydro-5H-pyrido[3',2':5,6]pyrano[2,3-b]pyrimidine (VIIIa) Hydrochloride. A mixture of 0.81 g (5 mmole) of I, 1.5 ml of 32% formaldehyde, 0.6 g (5.5 mmole) of benzylamine, and 30 ml of alcohol was heated to the boiling point, after which it was allowed to stand overnight. It was then vacuum evaporated, and the residue was washed with ether and dissolved in a small amount of absolute alcohol. A saturated alcohol solution of HCl was added to the alcohol solution, and absolute ether was added to precipitate 1.2 g (73%) of the hydrochloride of VIIIa with mp 188-189° (dec., from ethanol). Found: C 61.9; H 5.1; Cl 10.4; N 12.8%. $C_{17}H_{15}N_3O_2 \cdot HCl$. Calculated: C 61.9; H 4.9; Cl 10.8; N 12.8%. IR spectrum: 3250 (ν_{NH}) and 1630 and 1608 (ν_{CO} and ring) cm^{-1}. PMR spectrum (in D_2O), δ: 4.6, 4.82, 5.18 (three s, CH_2 groups), 7.8 (7-H and C_6H_5), 8.75 (1 H, two d, $J_1 = 8$ Hz, $J_2 = 2$ Hz, 6-H), 8.90 (1 H, two d, $J_1 = 4.5$ Hz, $J_2 = 2$ Hz, 8-H). The base had mp 205-206° (dec., from ethanol). Found: C 69.3; H 5.2; N 14.3%. $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.2; N 14.7%.

3-Isopropyl-5-oxo-1,2,3,4-tetrahydro-5H-pyrido[3',2':5,6]pyrano[2,3-d]pyrimidine (VIIIb) Hydrochloride. This compound, with mp 209-210° (dec., from absolute ethanol) was obtained in 61% yield by the method used to prepare the hydrochloride of VIIIa. Found: Cl 12.6; N 14.9%. $C_{13}H_{15}N_3O_2 \cdot HCl$. Calculated: Cl 12.6; N 14.9%.

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*Abbreviations: s is singlet and d is doublet.

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REACTION OF METHYL-SUBSTITUTED PYRYLIUM SALTS WITH TERTIARY AMINES

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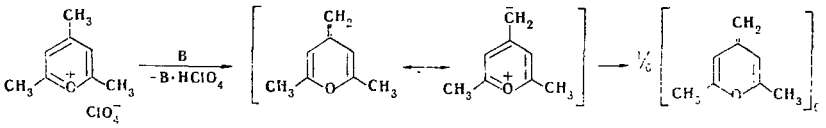
UDC 547.81

2,4,6-Trimethylpyrylium perchlorate reacts with heterocyclic compounds containing a pyridine nitrogen atom and having basicities higher than 9 pK_a units (in acetonitrile) through a step involving the formation of a methylenepyran. 4-Methyl-2,6-diphenyl- and 2-methyl-4,6-diphenylpyrylium perchlorates react with benzimidazole to give 1,2-ethanediylidenebispyrans. Methyl-substituted pyrylium salts react with 2,6-diphenylpyrylium and flavylium perchlorates in the presence of benzimidazole to give methylidynecyanines and with acetic anhydride to give trimethylidynecyanines.

We have observed that triethylamine and many heterocyclic compounds (Table 1) containing a tertiary (pyridine) nitrogen atom split out of a molecule of perchloric acid from 2,4,6-trimethylpyrylium perchlorate (I) to give 2,6-dimethyl-4-methylenepyran (II), which, as previously shown in [1], is subsequently converted to hexamer III:



I II III

It follows from Table 1 that a decrease in the basicity of the amine leads to a decrease in the yield of hexamer III, and bases with pK_a values below 9 do not split out perchloric acid from salt I. The basicity constant of methylenepyran II evidently should range from 8 to 9 pK_a units, and weaker bases therefore cannot remove a proton from the conjugate acid I.

It is known [4, 5] that 4-methylflavylium perchlorate (IV), under the influence of pyridine, is converted to methylene base V, which reacts with the starting salt to give 1,2-ethanediylidenebis(4-H-flavene) (VI), prob-

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