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MASS-SPECTROMETRIC STUDY OF THE CYCLIZATION OF DIAZO KETONES.

5.* CYCLIZATION OF PHTHALOYL DIPEPTIDE DERIVATIVES OF DIAZOMETHANE

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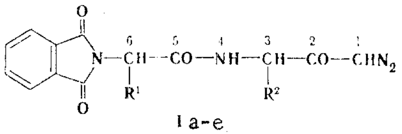
UDC 543.51:547.867.2

An analysis of the electron-impact mass spectra of phthaloyl dipeptide derivatives of diazomethane made it possible to conclude that a certain percentage of the $[M - N_2]^+$ ions have the 1,3-oxazin-5-one structure, while some of them undergo fragmentation without cyclization. The Wolff rearrangement does not occur. Alkyl substituents in the 4 position of the resulting heterocycle hinder cyclization. Under chemical-ionization conditions the $[MH - N_2]^+$ ions exist in similar forms. The cyclization process is hindered in this case by the introduction of a benzyl substituent in the chain.

We have previously shown [1-4] that some types of diazo ketones eliminate a molecule of nitrogen under the influence of electron impact (EI) and under chemical-ionization (CI) conditions, and the resulting fragment cyclizes to a certain extent without undergoing the Wolff rearrangement [5, 6]. This sort of cyclization process is similar to the chemical transformation of these diazo ketones in the condensed phase under the influence of acidic agents. In the present research in order to predict the possible cyclization reactions in solutions we studied the EI and CI mass spectra of a series of phthaloyl dipeptide derivatives of diazomethane (I), the chemical transformations of which have not been investigated.



I a-e

I a $R^1=R^2=H$; b $R^1=CH_3$, $R^2=H$; c $R^1=CH_2C_6H_5$, $R^2=H$; d $R^1=R^2=CH_3$; e $R^1=CH_3$, $R^2=CH_2C_6H_5$

As expected [1-4], peaks of molecular ions (M^+) of diazo ketones I are completely absent in the EI mass spectra; however, a peak of $[M - N_2]^+$ ions, the relative intensity of which is considerably higher in the mass spectra of Ia-c, in which $R^2 = H$, is observed in

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*See [1] for Communication 4.

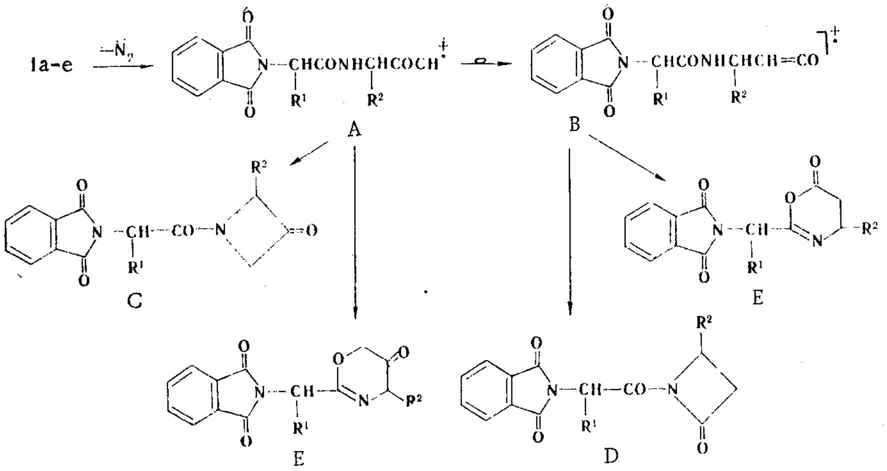
M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 623-629, May, 1983. Original article submitted April 27, 1982.

TABLE 1. Intensities of the Peaks of the Characteristic Fragment Ions in the Electron-Impact Mass Spectra

Compound	$[M-N_2]^+$	F_1	F_2	F_3	F_4	F_5	F_6	F_7	Σ1–13	X
Ia	3,3	1,0	0,3	0,6	4,0	7,0	0,1	0,7	49,2	0,18
Ib	2,6	0,5	0,3	0,6	2,0	4,4	1,2	0,7	60,0	0,23
Ic	4,0	0,3	0,3	0,6	0,3	1,0	6,3	1,2	42,3	0,03
Id	1,2	—	0,6	2,8	3,3	1,0	0,3	0,3	51,5	2,33
Ie	0,4	—	0,3	0,8	2,0	0,3	1,0	1,0	41,0	2,00
If	0,2	—	0,3	0,3	3,0	0,7	0,3	0,3	43,1	1,50
Ig	0,2	—	—	—	—	—	—	—	30,0	—

all cases. The $[M-N_2]^+$ ion may have different structures (see Scheme 1): A) a linear structure that retains the structure of the starting molecule; B) a linear structure after the Wolff rearrangement (a ketone); C) an N-substituted azetidin-3-one structure [in the case of cyclization with the formation of a new bond between the $C_{(1)}$ and $N_{(4)}$ atoms]; D) an N-substituted azetidin-2-one structure (in the case of similar cyclization after the Wolff rearrangement); E) a 1,3-oxazin-5-one structure [in the case of cyclization with the formation of a new bond between the $C_{(1)}$ atom and the oxygen atom of the carbonyl group attached to the $C_{(5)}$ atom]; F) a 1,3-oxazin-6-one structure [in the case of similar cyclization after the Wolff rearrangement].

Scheme 1



One also might have assumed the formation of nine-membered heterocycles in the case of cyclization at the phthalimide oxygen atom; however, this sort of cyclization evidently does not occur, since the principal peaks in the mass spectra of all of the investigated compounds are due to ions that contain an unsubstituted phthalimide fragment and ions that are characteristic for the fragmentation of N-substituted phthalimides [7-9]. The overall intensity (Σ1-13) of such characteristic ions is due primarily to the current of ions of the 1-13 type and amounts to 60% of the total ion current.

Specific fragmentation of the 1 ions, which consists in the ejection of a molecule of water, is observed in the case of Ic,f, in which $R^1 = CH_2C_6H_5$. This process probably takes place via the scheme

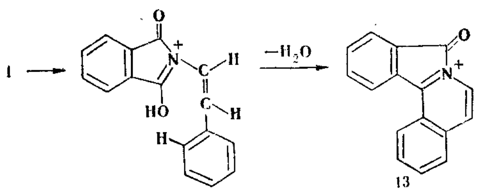
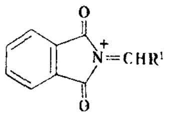
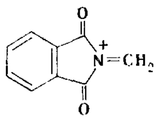


TABLE 2. Intensities of the Peaks of the Characteristic Fragment Ions in the Chemical-Ionization Mass Spectra

Compound	MH^+	$[MH-N_2]^+$	Σ_{frag}	F_4	F_5	$[F_4+H_2]$	F_8	$[F_8+H]$	$[F_8+H_2]$	$[F_8+H_3]$	F_9	F_{10}	$[F_{10}+H]$	F_{11}	Y
Ia	0,1	60,0	2,4	0,6	0,2	0,1	0,8	0,2	0,4	0,8	1,5	2,3	1,2	0,1	0,04
Ib	0,1	90,0	3,0	0,5	0,1	0,1	1,5	0,1	0,1	0,1	0,6	0,6	0,4	0,2	0,01
Ic	0,1	5,9	0,8	0,4	0,8	0,4	1,1	0,1	0,1	0,1	4,0	9,0	1,5	0,2	1,50
Id	0,1	67,2	2,0	2,0	0,4	—	4,0	—	0,1	—	0,6	0,5	0,1	0,3	0,01
Ie	0,1	7,4	0,4	1,0	0,2	0,2	2,3	0,2	0,4	0,4	2,7	16,5	2,7	0,4	2,25
If	0,1	28,1	1,1	1,0	0,2	0,8	0,4	—	0,5	0,5	6,4	3,0	0,4	0,2	0,12
Ig	0,1	14,5	0,2	—	0,1	—	0,4	—	0,2	—	8,5	3,4	0,5	0,2	0,25

1) 
maximum peak

2) 
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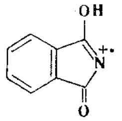
3) 
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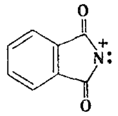
4) 
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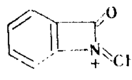
5) 
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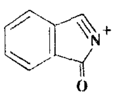
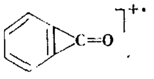
6) 
130

7) $O=C=\overset{+}{N}=CHR$

8) $C_6H_5CO^+$

9) 
104

10) 103

11) 102

12) 76

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*Here and subsequently in the text, the numbers that characterize the ions are the mass-to-charge ratios (m/z).

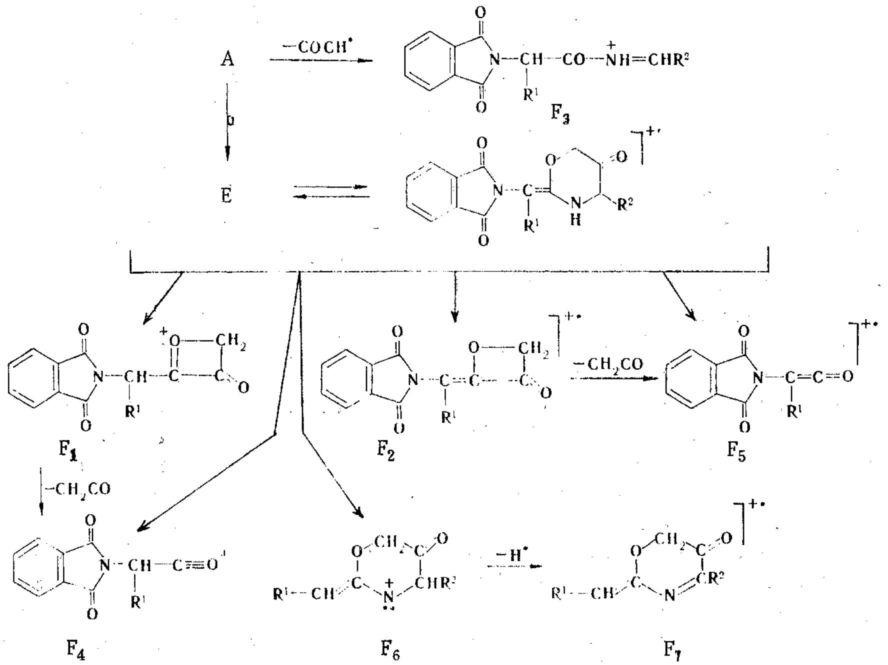
To establish the structure of the $[M-N_2]^+$ ions we made a thorough study of the mass spectra of the diazo ketones in the region of high m/z values. In the case of Ia-c (R^2 = H) the $[M-N_2]^+$ ions eliminate fragments with 28, 29, and 41 amu, which leads to F_1, F_2, and F_3 ions, respectively (see Scheme 2). The low intensities of the signals of these ions made it impossible to determine their elementary compositions by high-resolution mass spectrometry. The peaks of F_1 ions vanish completely in the mass spectra of Id,e, while the magnitude of the F_2 ions remains unchanged, i.e., the eliminated particle includes the R^2 radical, which is possible only in the case of cyclic oxazinone structures E and F [1]. This fact and the absence in the mass spectra of intense peaks of $[M-N_2, -CO]^+$ and $[M-N_2, CH_2CO]^+$ ions constitute evidence that azetidinone structures C and D can be excluded from consideration [2]. Consequently, some of the $[M-N_2]^+$ ions exist in the form of oxazinones. It is known from the literature data [11, 12] that 1,3-oxazin-6-ones eliminate a molecule of CO_2. This process was not observed in this case, and this makes it possible to reject structure F. Linear structure B, in all likelihood, also is not realized, since otherwise peaks of characteristic ions formed in the fragmentation of the products of intramolecular cyclization of ketone would be observed in the mass spectra. It follows from the information set forth above that a certain percentage of the $[M-N_2]^+$ ions have 1,3-oxazin-5-one structures. The F_1 ions are then formed as a result of elimination by the $[M-N_2]^+$ ions of an $NCH_2^{\cdot}$ radical, whereas their absence when a substituent is introduced in the 4 position of the heteroring has already been noted [13]. In addition, low-intensity peaks of $[M-N_2, -C_2H_2O_2]^+$ (1.0 and 1.2%) and $[M-N_2, -C_3HO]^+$ (1.8 and 1.5%, respectively, of the total ion current) ions, which are characteristic for the fragmentation of 4-unsubstituted 2-phenyl-5,6-dihydro-4H-1,3-oxazin-5-ones [13], are observed in the mass spectra of Ia,b. Intense peaks of F_4 and F_5 ions, which are also characteristic for the fragmentation of the previously studied oxazinones [13], although in this case they may also be formed from $[M-N_2]^+$ ions with linear structure A, are present in all of the EI mass spectra.

TABLE 3. Mass Spectra of Ia-g

Compound	m/z values (relative intensities of the ion peaks in percent of the maximum peak)
	Electron impact
Ia	258 (10,1), 188 (15,1), 187 (22,6), 161 (18,4), 160 (100), 133 (9,3), 105 (7,7), 104 (14,9), 77 (18,1), 76 (14,5)
Ib	272 (8,2), 202 (7,7), 201 (14,4), 175 (16,0), 174 (100), 147 (25,8), 131 (8,3), 130 (24,5), 76 (13,0), 69 (27,6)
Ic	348 (40,1), 250 (100), 232 (77,3), 202 (70,3), 131 (42,4), 130 (30,8), 104 (38,4), 103 (62,2), 91 (38,4), 77 (41,3)
Id	202 (15,2), 175 (15,9), 174 (100), 147 (25,8), 130 (28,4), 77 (20,9), 76 (18,0), 69 (13,6), 52 (13,7), 51 (15,5)
Ie	175 (16,0), 174 (100), 147 (19,2), 130 (20,9), 91 (18,1), 78 (54,6), 77 (22,2), 69 (23,5), 57 (25,4), 55 (21,6)
If	250 (26,0), 103 (27,0), 77 (98,6), 76 (100), 75 (28,9), 74 (90,1), 73 (27,9), 63 (42,1), 57 (67,6), 56 (37,2)
Ig	202 (38,1); 174 (42,8), 160 (90,2), 91 (41,2), 81 (49,0), 78 (44,8), 71 (47,9), 69 (92,3), 57 (83,5), 55 (100)
	Chemical ionization
Ia	297 (2,6), 261 (3,8), 260 (18,3), 259 (100), 258 (4,0), 206 (2,6), 205 (4,9), 160 (1,5), 148 (2,9), 71 (2,8)
Ib	311 (2,2), 275 (3,8), 274 (19,5), 273 (100), 272 (5,1), 219 (0,8), 174 (2,0), 148 (0,9), 89 (4,0), 61 (1,9)
Ic	350 (15,3), 349 (59,3), 296 (42,8), 295 (100), 148 (52,5), 71 (45,8), 70 (15,3), 69 (25,4), 67 (16,9), 61 (28,8)
Id	325 (1,6), 289 (3,7), 288 (22,0), 287 (100), 286 (3,9), 219 (1,0), 202 (1,4), 174 (2,7), 71 (1,1), 61 (2,5)
Ie	363 (38,6), 259 (47,2), 220 (37,0), 219 (100), 206 (13,4), 205 (40,2), 174 (14,2), 148 (16,5), 71 (22,0), 61 (14,2)
If	365 (29,8), 364 (28,6), 363 (100), 296 (11,9), 295 (26,8), 148 (73,8), 91 (12,5), 71 (30,4), 69 (11,3), 61 (20,2)
Ig	365 (5,7), 364 (28,6), 363 (100), 219 (11,4), 149 (5,0), 148 (27,9), 122 (5,0), 91 (5,7), 71 (7,9), 61 (14,5)

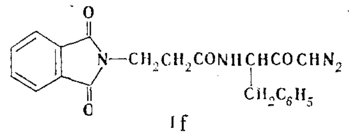
The primary processes involved in the fragmentation of the $[M - N_2]^+$ ions can be represented by the general scheme

Scheme 2

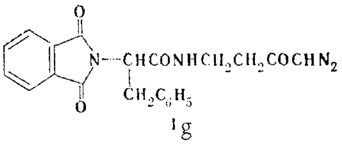


The F_3 ions are characteristic for the fragmentation of diazo ketones [1-4]. They may arise from both the M^+ ions as a result of the ejection of a $COCHN_2$ particle and from the $[M - N_2]^+$ ions with linear structure A in the case of splitting out of a $CHCO^•$ radical. The presence of a peak of this ion in the mass spectra of the investigated compounds constitutes evidence that a certain percentage of the $[M - N_2]^+$ ions have linear structure A. The magnitude of the ratio of the intensities of the peaks of the F_3 and $[M - N_2]^+$ ions ($I_{F_3}/I_{[M - N_2]^+} = X$) may evidently reflect to some extent the relative percentage of $[M - N_2]^+$ ions with linear structure A. It is apparent from Table 2 that X increases sharply when substituent R^2 is introduced, i.e., the percentage of $[M - N_2]^+$ ions with structure A increases. Consequently, alkyl substituent R^2 hinders cyclization. Substituents R^1 does not have a substantial effect on the cyclization; this should have been expected in the case of the formation of a six-membered heteroring that does not include a $C_{(6)}$ atom.

For a more nearly complete study of diazo ketones of this type we investigated the mass spectra of If,g.



If



Ig

Whereas all of the peaks of the F_1-F_7 primary fragment ions are observed in the mass spectrum in the case of If, they are completely absent in the mass spectrum of diazo ketone Ig. Consequently, the $[M - N_2]^+$ ions formed in the fragmentation of If undergo a certain amount of cyclization to 1,3-oxazin-5-ones, i.e., lengthening of the carbon chain in this case does not hinder this process. A seven-membered heteroring should have been formed in the cyclization of the $[M - N_2]^+$ ion in the case of Ig; however, it was not possible to confirm its formation from the mass spectrum. At the same time, a low-intensity peak of an ion with m/z 84, which is characteristic for the fragmentation of N-substituted pyrrolidin-3-ones [3], is present in the mass spectrum of Ig. It is possible in this case that the electrophilic $C_{(1)}$ atom attacks the peptide nitrogen atom to give a pyrrolidinone ring rather than the oxygen atom.

Thus a study of the EI mass spectra of phthaloyl dipeptide derivatives of diazomethane (Ia-e) showed that a certain percentage of the $[M - N_2]^+$ ions formed in the first step of the fragmentation undergo cyclization to 1,3-oxazin-5-one derivatives, i.e., without Wolff rearrangement, whereas some undergo fragmentation directly from the linear form. Alkyl substituent R^1 does not affect the degree of cyclization, while substituent R^2 slows this process down substantially. Lengthening of part of the carbon chain by one methylene group that is not included in the composition of the resulting heteroring does not affect the cyclization process, while removal of the carbonyl group from the electrophilic carbon atom excludes cyclization at the oxygen atom and possibly directs it to the nitrogen atom with the formation of a pyrrolidin-3-one.

As one should have expected [1-4], the principal peaks in the CI mass spectra are the peaks of $[MH - N_2]^+$ ions; however, their relative intensities differ significantly from one another. With respect to the intensities of the peaks of this ion, the investigated compounds can be divided into two groups. The first group includes diazo ketones Ia,b,d ($I[MH - N_2]^+ =$ 60-90%), while the second group includes Ic,e (6-10% of the total ion current).* A comparison of the intensities of the peaks of the cluster ions makes it possible to divide the investigated diazo ketones into the same groups. The first group includes compounds that do not contain benzyl substituents R^1 or R^2, i.e., the introduction of this substituent into the molecule lowers the intensity of the $[MH - N_2]^+$ ion peak by a factor of almost 10.

The CI mass spectra of all of the investigated compounds contain low-intensity peaks of protonated molecular ions (MH^+); however, they do not convey specific information regarding the structure of the $[MH - N_2]^+$ ions, since all of the recorded fragments are N-substituted phthalimide fragments that are formed in profound stages of the fragmentation, primarily as a result of ion-molecular reactions [1-4]:

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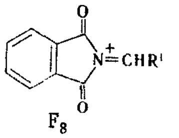
*The intensities of the peaks of these ions in the mass spectra of If, g have intermediate values.

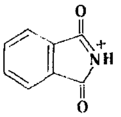
F_4 $[F_4 + 2H]^+$ F_5



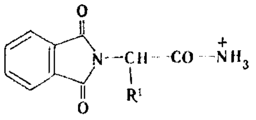
F_8

$[F_8 + H]^+$ $[F_8 + 2H]^+$

$([F_8 + 3H]^+)^*$



F_9†



F_{10}

$([F_{10} + H]^+)^*$

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*These ions are formed, in all likelihood, as a result of ion-molecular reactions involving reduction of the carbonyl group to a hydroxy group [14, 15].
†The structure of this ion was established in [16].

It has been previously shown [1-4] that ions of the F_{10} type are formed only from $[MH - N_2]^+$ ions with noncyclic structures. It is apparent from Table 2 that the relative intensities of the F_{10} ion peaks are increased markedly in the case of Ic, e, in which R^1 or R^2 are benzyl groups. The ratio of the relative intensities of the peaks of F_{10} and $[MH - N_2]^+$ ions ($I_{F_{10}}/I[MH - N_2]^+ = Y$) changes extremely markedly in this case. It might be assumed that the Y value is an approximate estimate of the relative numbers of diazo ketone molecules that undergo fragmentation without cyclization and, consequently, that benzyl substituents hinder cyclization under chemical ionization conditions, possibly as a consequence of steric factors but more likely as a consequence of electronic factors; however, the solution of this problem requires additional study. It should be noted that a similar regularity is not observed under electron impact.

Thus an analysis of the CI mass spectra of phthaloyl dipeptide derivatives of diazomethane does not make it possible to draw an unambiguous conclusion as to whether or not the $[MH - N_2]^+$ ion undergoes cyclization; however, it might be assumed that cyclization occurs in the absence of benzyl substituents in the molecule, for otherwise virtually the entire fragmentation pattern is due to $[MH - N_2]^+$ ions with linear structures and, possibly, MH^+ ions directly.

EXPERIMENTAL

The mass spectra were obtained with a Varian MAT-44S spectrometer. The electron-impact mass spectra were recorded at 50-150°C and an ionizing-electron energy of 75 eV (and an emission current of 0.5 mA). The chemical-ionization mass spectra were recorded at a pressure in the ionization chamber of 33.3 Pa and an electron energy of 160 eV; the gas-reactant was isobutane.

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REACTION OF 10-FORMYL-3-METHYL-1,2,3,4-TETRAHYDROPYRIMIDO [1,2-a]INDOLE AND ITS DIMETHYLIMINIUM SALT WITH NUCLEOPHILIC AGENTS

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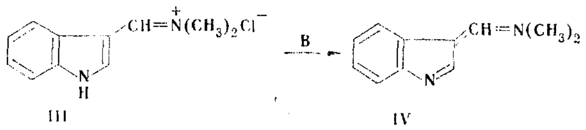
The reaction of 10-dimethyliminium-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a] indole chloride and the protonated form of 10-formyl-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole with some N- and C-nucleophiles leads to the formation of products of condensation at the carbonyl carbon atom. Condensation with the potassium enolate of cyanoacetic ester is accompanied by subsequent cyclization to give compounds of the α-carboline series. Acidic hydrolysis of the aldehyde gives 3-methyl-1,2,3,4-tetrahydropyrimido[1,2]indole hydrochloride.

We have previously shown [1] that the reaction of 1-acetyl-2-phenyl-4-methylpyrazolidine with iminium salts leads to 10-methylenedimethyliminium-3-methyl-1,2,3,4-tetrahydropyrimido-[1,2-a]indole chloride (I) in high yield; alkaline hydrolysis of I gives 10-formyl-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (II). The virtually complete lack of data on the synthesis and properties of such compounds compelled us to investigate the reactivities of these bifunctional indole derivatives.

It is known that 3-indolyldimethyliminium chloride (III), which is formed in the formylation of indole under the conditions of the Vilsmeier reaction, in the presence of bases (pyridine, triethylamine) gives enamine IV, which reacts readily with nucleophilic agents [2, 3]:



We have shown that iminium salt I reacts with p-toluidine in pyridine to give azomethine Va. Azomethine Vb was similarly obtained even with a weak nucleophile such as p-nitroaniline. The reaction of I with hydroxylamine leads to the formation of nitrile VI as a consequence of dehydration of the initially formed oxime, which also takes place readily in the case of oximes of 3-formylindoles themselves [4, 5]. Intense absorption at 2210 cm^{-1}, which corresponds to the cyano group, is observed in the IR spectrum of VI; the PMR spectrum does not contain the weak-field signals of azomethine and hydroxy protons that are characteristic for oximes.

For iminium salt I we also found that the reaction with active C-nucleophiles, viz., nitromethane in the presence of sodium ethoxide and the potassium enolate of cyanoacetic

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