ACETALS OF LACTAMS AND ACID AMIDES.

36.* SOME REACTIONS OF ENAMINES OF THE ISOQUINOLINE SERIES AND SYNTHESIS OF PYRIMIDO[4,3-a]ISOQUINOLINES

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The reactions of 1-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives with acyl chlorides were investigated. 2-Oxopyrimido[4,3-a]isoquinoline derivatives were obtained by the reaction of 1-carbamidomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with dimethylformamide and dimethylacetamide diethylacetals. The reaction of the latter with phosphorus oxychloride and then with primary amines was used to synthesize a number of hydrochlorides that are derivatives of 2-iminopyrimido[4,3-a]isoquinoline.

It has been previously established [2] that secondary enamino amides, the NH group and α-carbon atom of which are included in a ring, are capable of reacting with dimethylformamide diethylacetal (I) to give condensed pyrimidines. Within the framework of the search for methods for the synthesis of condensed heterocycles that include an isoquinoline fragment we investigated some properties and transformations of 1-cyanomethylene- (II) and 1-carbamidomethylene-6,7-dimethoxy-1,2,3-tetrahydroisoquinolines (III) [3]. The reaction of enamines II and III with benzoyl chloride takes place at the "enamine" β position, just as in the case of enamines [4], to give β,β-disubstituted enamines IV and V. The reaction of cyanomethylene derivative II with acetyl chloride proceeds similarly, as a result of which, 1-(cyanoacetylmethylene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI) was isolated.

However, VII, which according to the results of elementary analysis contains two acetyl groups, is formed in the reaction of amide III with acetyl chloride. The absence in the PMR spectrum of VII of a signal of a vinyl proton indicates that one acetyl group is located in the "enamine" β position. The other acetyl group may be attached to the ring or amide nitrogen atom. Its position was established by means of PMR spectroscopy on the basis of the change in the multiplicity of the signals of the C_3—2H protons (4.06 ppm, $CDCl_3$) when alcohol is added: the multiplet due to coupling of the C_3—2H protons with the NH and C_4—2H protons is converted to a distinct triplet when CD_3OD is added, which indicates the presence in the investigated compound of a cyclic NH group. It follows unambiguously from these data that the acetyl residues in VII are attached to the β-carbon atom of the enamine and the NH-carbamide substituent (see Table 1 for the PMR spectra of IV-VII).

In the next step of our research we studied the possibility of obtaining pyrimido[4,3-a]isoquinolines on the basis of enamino amide III. We were unable to accomplish the formation of a pyrimidine ring by the reaction of amide III with ethyl orthoformate. However, the reaction with dimethylformamide acetal I and dimethylacetamide acetal VIII proceeds smoothly, and 9,10-dimethoxy-6,7-dihydropyrimido[4,3-a]isoquinol-2-one (IX) and its 4-methyl derivative (X), respectively, are formed as a result.

It should be noted that despite the absence of an electron-acceptor substituent in the 1 position of three-ring system IX (the 5 position of the pyrimidine ring), heating IX with alkali leads to opening of the pyrimidine ring to give the starting enamino amide. We have previously observed [1] similar opening of the pyrimidine ring in 5-cyano derivatives of pyrimidine to give the corresponding enamino amides.

*See [1] for Communication 35.

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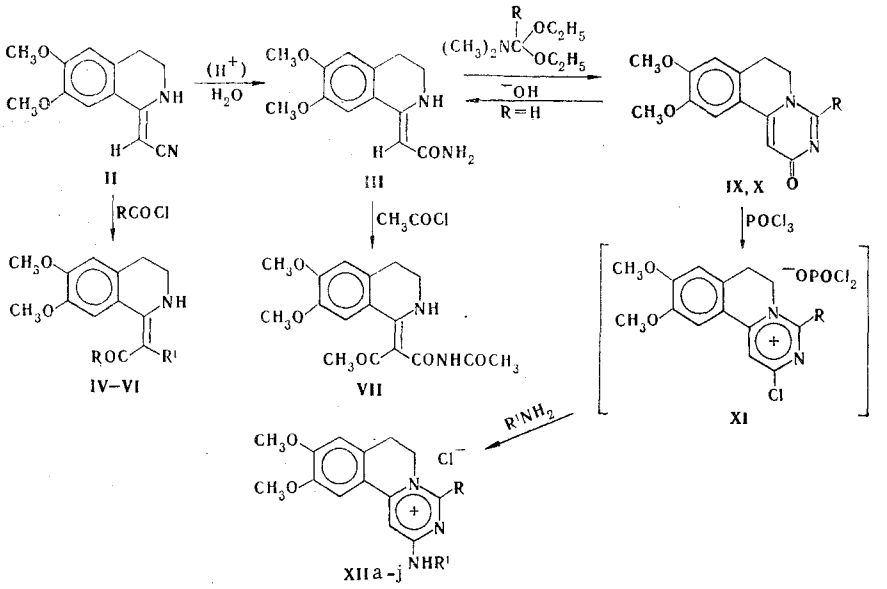
TABLE 1. PMR Spectra of IV-VII in $CDCl_3$

Compound	Chemical shifts, ppm (multiplicity)							
	OCH_3 (s)	CH_3 (s)	C_4—2-H (t)	C_3—2-H (m)	C_5—H, C_8—H (s)	Ring NH	C_6H_5 (m)	Amide NH
IV	3,95 3,98	—	2,89	3,52	6,74 8,06	12,89	7,25	—
V	3,92 3,96	—	2,85	3,44	7,50 7,52	10,22	7,72	6,71 8,74
VI	3,94 3,96	2,44	2,84	3,51	6,72 7,97	12,44	—	—
VII	3,90 3,94	2,15 2,38	2,88	4,06	6,61 7,2	8,85	—	6,9

For the synthesis of 2-imino derivatives of pyrimido[4,3-a]isoquinoline on the basis of IX and X we needed to accomplish activation of the amide function of the latter by the production of a complex with phosphorus oxychloride.



IV R=Ph, R^1=CN; V R=Ph, R^1=$CONH_2$; VI R=Me, R^1=CN; IX R=H; X R=CH_3; XII a-j R=H; a R^1=H; b R^1=$PhCH_2CH_2$; c R^1=4-$MeOC_6H_4$; d R^1=4-$NO_2C_6H_4$; e R^1=4-MeC_6H_4; f R^1=4-C_6H_4COOEt; g R^1=4-ClC_6H_4; h R^1=4-$C_6H_4SO_2NH_2$; i R^1=4-BrC_6H_4; j R^1=Ph; XIII R=Me, R^1=H

We found that pyrimidoisoquinolines IX and X react readily with phosphorus oxychloride to give intermediate amide chlorides (XI), which, without special purification, were subjected to reaction with ammonia and aliphatic-aromatic and aromatic amines. As a result, we synthesized a number of 2-amino derivatives of pyrimido[4,3-a]isoquinoline (XIIa-j, XIII). It follows from the structures of salts XII and XIII that the bases corresponding to them are 2-imino derivatives and that a significant gain in energy due to aromatization should occur during salt formation. On this basis, it may be concluded that imines XIV should be strong bases. To confirm this, we measured the ionization constants for a number of compounds of the series obtained (XIIa-i).* It is apparent from Table 2 that the investigated compounds are actually extremely strong bases and that when R = H or $PhCH_2CH_2$ they are so strong that their ionization constants in alcohol cannot be measured.

A comparison of the pK_a values obtained for XII with the corresponding σ_p constants of the para substituents of the benzene ring (presented in Table 2) shows that a linear relationship, which is described by the following equation, exists between these parameters:

$$pK_a = 10.08 - 1.43\sigma_p;\ r = 0.97,\ S = 0.15.$$

*We were unable to measure the pK_a value for XIIj because of its low solubility in 50% alcohol, in which we determined the ionization constants for the remaining members of the series.

TABLE 2. Ionization Constants for XIIa-i in 50% Alcohol

Compound	R	pK_a[a]	σ_p
XIIa	H	>12	—
XIIb[b]	$PhCH_2CH_2$	>12	—
XIIc	4-$MeOC_6H_4$	10,35	-0,268
XIId	4-$NO_2C_6H_4$	8,73	0,778
XIIe	4-MeC_6H_4	10,12	-0,17
XIIf	4-C_6H_4COOEt	9,48	0,45
XIIg	4-ClC_6H_4	9,88	0,227
XIIh	4-$C_6H_4SO_2NH_2$	9,20	0,57
XIIi	4-BrC_6H_4	9,8	0,232

[a]The error in the determination does not exceed 0.04 pK_a units.
[b]The constant was determined in 96% alcohol.

The overall correlation for the electron-donor and electron-acceptor substituents makes it possible to conclude that, in contrast to cyclic amidines [5], in this case the benzene ring is coplanar with the C=N bond.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with Perkin-Elmer 457 and UR-10 spectrometers. The UV spectra of solutions in ethanol were recorded with a Hitachi EPS-3T spectrometer. The PMR spectra were obtained with an XL-100 spectrometer with tetramethylsilane as the internal standard. The ionization constants were determined in 50 and 96% (by volume) solutions of ethanol with a Radiometer apparatus by the method described in [6].

The melting points of the substances were determined with an apparatus of the MP-1 type from the Yamato Scientific Co. Ltd. The purity of the substances was monitored by chromatography on UV-254 plates.

(1'-Benzoyl-1'-cyano)methyleno-6,7-dimethoxy-3,4-dihydroisoquinoline (IV). A 0.44-g (4.3 mmole) sample of triethylamine and 0.61 g (4.3 mmole) of benzoyl chloride were added successively dropwise to a solution of 1 g (4.3 mmole) of isoquinolineacetonitrile II in 10 ml of chloroform, and the mixture was refluxed for 2 h. It was then cooled, and the chloroform solution was washed with water and dried with sodium sulfate. The solvent was removed by distillation to give 1 g (79%) of IV with mp 183-186°C (from acetonitrile) (Table 3).

(1'-Carbamido-1'-benzoyl)methyleno-6,7-dimethoxy-3,4-dihydroisoquinoline (V) was similarly obtained in 29% yield from isoquinolineacetamide III (Table 3).

(1'-Cyano-1'-acetyl)methyleno-6,7-dimethoxy-3,4-dihydroisoquinoline (VI). A 0.88-g (8.6 mmole) sample of triethylamine and 0.68 g (8.6 mmole) of acetyl chloride were added successively dropwise to a solution of 1 g (4.3 mmole) of isoquinolineacetonitrile II in 10 ml of chloroform, and the reaction mixture was stirred at room temperature for 3 h, after which it was washed with water and dried with sodium sulfate. Removal of the solvent by distillation gave 0.9 g (77%) of VI (Table 3).

(1-Acetyl-1-acetylcarbamido)methyleno-6,7-dimethoxy-3,4-dihydroisoquinoline (VII) was similarly obtained from isoquinolineacetamide (III) (Table 3).

2-Oxo-9,10-dimethoxy-2,5,6,7-tetrahydropyrimido[4,3-a]isoquinoline (IX). A 0.61-g (4.2 mmole) sample of acetal I was added to a solution of 0.7 g (3 mmole) of isoquinolineacetamide III in 15 ml of dry toluene, and the reaction mixture was refluxed for 5 h with monitoring of the course of the process from the liberation of dimethylamine. It was then cooled and filtered to give 0.44 g of IX. UV spectrum (in alcohol), λ_{max} (log ε): 242 (4.38) and 324 nm (4.23). PMR spectrum ($CDCl_3$): 3.92 and 3.94 (3H, s, OCH_3 group), 3.09 and 4.08 (2H, t, C_6—2H and C_7—2-H), 6.51 (1H, s, C_1—H), 6.75 and 7.15 (1H, s, C_8—H and C_{11}—H), and 8.18 ppm (1H, s, C_4—H).

TABLE 3. Characteristics of the Synthesized Compounds

Compound	mp,[a] °C	Found, %					Empirical formula	Calculated, %					Yield, %
		C	H	Cl	N	H_2O		C	H	Cl	N	H_2O	
IV	183—186	71,7	5,2	—	8,5	—	$C_{20}H_{18}N_2O_3$	71,9	5,4	—	8,4	—	79
V	208—210	68,1	5,7	—	7,9	—	$C_{20}H_{20}N_2O_4$	68,2	5,7	—	8,0	—	29
VI	225—228	66,1	5,9	—	10,2	—	$C_{15}H_{16}N_2O_3$	66,2	5,9	—	10,3	—	77
VII	214—215	61,3	6,1	—	8,3	—	$C_{17}H_{20}N_2O_5$	61,5	6,0	—	8,4	—	30
IX	263—265	65,2	5,3	—	10,8	—	$C_{14}H_{14}N_2O_3$	65,1	5,4	—	10,9	—	57
X	255—257	66,1	6,0	—	10,4	—	$C_{15}H_{16}N_2O_3$	66,2	5,9	—	10,3	—	79
XIIa	275—277	51,0	6,2	10,7	12,9	10,9	$C_{14}H_{15}N_3O_2 \cdot HCl \cdot 2H_2O$	51,0	6,1	10,8	12,8	10,9	78
XIIb	225—228	63,4	6,3	8,5	10,0	4,2	$C_{22}H_{23}N_3O_2 \cdot HCl \cdot H_2O$	63,5	6,3	8,5	10,1	4,3	62
XIIc	295—297	63,0	5,6	8,5	10,5	—	$C_{21}H_{21}N_3O_3 \cdot HCl$	63,1	5,5	8,9	10,5	—	87
XIId	298—300	54,1	4,8	8,3	12,4	6,5	$C_{20}H_{18}N_4O_4 \cdot HCl \cdot H_2O$	54,4	5,0	8,0	12,6	6,1	93
XIIe	266—268	65,8	5,5	9,7	10,8	—	$C_{21}H_{21}N_3O_2 \cdot HCl$	65,7	5,7	9,3	11,0	—	97
XIIf	276—277	62,4	5,5	7,9	9,3	—	$C_{23}H_{23}N_3O_4 \cdot HCl$	62,5	5,5	8,0	9,5	—	76
XIIg	>300	59,3	4,8	17,5	10,5	—	$C_{20}H_{18}ClN_3O_2 \cdot HCl$	59,4	4,7	17,6	10,4	—	85
XIIh[b]	>300	53,4	4,7	7,9	12,5	—	$C_{20}H_{20}N_4SO_4 \cdot HCl$	53,5	4,7	7,9	12,5	—	77
XIIi[c]	299—301	53,8	4,2	7,9	9,5	—	$C_{20}H_{18}BrN_3O_2 \cdot HCl$	53,5	4,2	7,9	9,4	—	94
XIIj[d]	287—290	54,5	5,3	—	9,7	2,2	$C_{20}H_{19}N_3O_2 \cdot H_3PO_4 \cdot 0{,}5H_2O$	54,6	5,0	—	9,6	2,1	70
XIII	>300	56,9	5,9	11,4	13,2	2,2	$C_{15}H_{17}N_3O_2 \cdot HCl \cdot 0{,}5H_2O$	56,9	6,0	11,2	13,2	2,8	76

[a]The compounds were crystallized: IV and IX from acetonitrile, V from benzene, VI from toluene, VII and XIII from methanol, X and XIIa, e from ethanol, XIIb from isopropyl alcohol, XIIc, d, h-j from DMF, and XIIf, g from DMSO. [b]Found: S 6.8%. Calculated: S 7.1%. [c]Found: Br 17.8%. Calculated: Br 17.8%. [d]Found: P 7.1%. Calculated: P 7.1%.

2-Oxo-4-methyl-9,10-dimethoxy-2,5,6,7-tetrahydropyrimido[4,3-a]isoquinoline (X) was similarly synthesized by reaction with dimethylacetamide diethylacetal (Table 3).

Reaction of Tetrahydropyrimidine (IX) with Alkali. A suspension of 0.77 g (3 mmole) of IX in 8 ml of 0.1 N NaOH was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration to give 0.42 g (61%) of III with mp 162-163°C (163-164°C [3]). With respect to the IR spectral data and the melting point, the compound obtained was identical to a genuine sample of III.

2-Imino-9,10-dimethoxy-2,5,6,7-tetrahydropyrimido[4,3-a]isoquinoline Hydrochloride (XIIa). A suspension of 1 g (3.9 mmole) of pyrimido[4,3-a]isoquinoline IX in 6 ml of phosphorus oxychloride was refluxed for 30 min, after which the $POCl_3$ was removed by vacuum distillation, and the residual complex was washed with dry benzene and suspended in 12 ml of chloroform. A 1.2-ml (8.1 mmole) solution of ammonia in alcohol was added dropwise to the resulting suspension, and the reaction mixture was stirred at room temperature for 1 h. The solid material was removed by filtration and washed with water to give 1 g of IX. UV spectrum, λ_{max} (log ε): 245 (4.37) and 338 nm (4.26). IR spectrum: 3100-3450 (NH, H_2O); 1720, 1680 cm^{-1} (C=N).

2-Imino-4-methyl-9,10-dimethoxy-2,5,6,7-tetrahydropyrimido[4,3-a]isoquinoline hydrochloride (XIII) was similarly obtained from 2-oxo-4-methyl-9,10-dimethoxy-2,5,6,7-tetrahydropyrimido[4,3-a]isoquinoline (X) (Table 3). Compounds XIIb-j were obtained by a similar method. It should be noted that XIIb was isolated from chloroform solution, while the synthesis of XIIc-j was carried out in refluxing chloroform, and hydrochlorides XIIe, j-i were obtained in the presence of triethylamine (Table 3).

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MOLECULAR AND CRYSTAL STRUCTURE OF ACETONE N-METHYL-N-(4-CHLORO-1-PHTHALAZINYL)HYDRAZONE AND ITS BISULFATE

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Acetone N-methyl-N-(4-chloro-1-phthalazinyl)hydrazone and its bisulfate salt were subjected to x-ray diffraction study. Rotation of the fragments about the C–N (23.5°) and N–N (59.4°) bonds occurs in the hydrazone. The amino nitrogen atom is pyramidal. Protonation of the hydrazone leads to the formation of a three-ring cation, viz., the 1,3,3-trimethyl-2,3-dihydro-1,2,4-triazolo[3,4-a]-phthalazinium cation.

Data from the UV and PMR spectra constitute evidence that acetone N-methyl-N-(4-chloro-1-phthalazinyl)hydrazone (I) has a nonplanar structure (rotation about the C_{ring}–N and N–N bonds) [1] and behaves anomalously upon protonation, during which the amidrazone fragment undergoes ring closure to give the 1,3,3-trimethyl-2,3-dihydro-1,2,4-trazolo[3,4-a]phthalazinium cation [2]. In order to determine the precise geometry of hydrazone I and its bisulfate II we subjected them to x-ray diffraction study.

The general form of the molecule and the bond lengths and angles in hydrazone I are presented in Fig. 1.

The phthalazine system is planar within the limits of 0.050 Å. The Cl, N_3, and C_9 atoms virtually lie in the same plane, but the N_4 and C_{10}–C_{12} atoms deviate considerably from it (Table 1), and, upon the whole, the molecule is not planar.

The pyridazine (P2) and benzene (P3) rings are planar within the limits of 0.020 Å, and the P2/P3 dihedral angle is 3.5° (P1/P2 1.83°), which is somewhat less than the bending of the phthalazine system in 1-dimethylamino-4-chlorophthalazine (III) (5.02°) [3] but greater than in salts of phthalazine derivatives that are protonated at the ring N_2 atom (1.4 and 1.6°) [4, 5].

The endocyclic bond angles are the same as in amine III [3] and with the same differences from unsubstituted phthalazine [6]. The exocyclic N_1C_1Cl and C_1C_1Cl angles are unequal because of short intramolecular nonvalence Cl···H_3 [2.73(4) Å] and Cl···C_3 [3.09(1) Å] contacts, whereas the $N_2C_8N_3$ and $C_7C_8N_3$ angles are unequal because of N_3···H_6 (2.71 Å), N_3···C_6 (2.97 Å), and N_2···C_9 (2.62 Å) contacts (the peri effect). This factor also explains the certain increase in the $C_6C_7C_8$ angle as compared with the analogous angle in amine III and phthalazine [3, 6].

The N_3 atom has a compact trigonal-pyramidal conformation. The sum of the bond angles at N_3 is 340.2°, and the degree of pyramidal character [3] C_P^N = 0.495, which is higher than in amine III (C_P^N = 0.327). The N_3 atom deviates 0.375 Å from the $C_8C_9N_4$ plane.

The deviations of the C_9 and N_4 atoms from the P2 plane (Table 1) and the torsion angles (Table 2) constitute evidence for an angle of rotation of the hydrazone fragment about the C_8–N_3 bond from the position that is optimal for conjugation of the N_3 atom with the ring. A θ value of −25.8° is obtained from an analysis of the torsion angles from the Newman pro-

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