ACETALS OF LACTAMS AND ACID AMIDES.

34.* SYNTHESIS AND PROPERTIES OF ENAMINES OF THE ISOQUINOLINE SERIES

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The reactions of 1,2,3,4-tetrahydro-3-isoquinolone derivatives with dimethylformamide acetal and the hydrolysis and transamination of the resulting enamino amides — 1,2,3,4-tetrahydro-4-dimethylaminomethylene-3-isoquinolone derivatives — were studied. It is shown that 1,2,3,4-tetrahydro-1-phenyl-6,7-dimethoxy-3-isoquinolone can be converted to the corresponding lactim ether. The reactions of the latter with dimethylformamide acetal and hydrazine and the dehydrogenation of this lactim ether in the presence of sodium ethoxide were studied.

It is known that dimethylformamide diethylacetal (I) reacts readily with various carbonyl compounds to give the corresponding enamino ketones. However, the α-methylene link in the simplest lactams turns out to be insufficiently active for condensation with acetal I, and the production of the corresponding α-dimethylaminomethylene derivatives of butyro-, valero-, and caprolactams is possible only when stronger electrophilic reagents, viz., aminal ethers [2], are used.

Nevertheless, in undertaking our study of the properties of 1-phenyl-3-oxo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) [3] we had in mind that the protons of the CH_2 group in the 4 position should be more labile than, for example, in 2-piperidone and that the condensation of acetal I at this link is likely under certain conditions. In fact, the corresponding enamine, viz., 1-phenyl-3-oxo-4-dimethylaminomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III), is formed in high yield when I and II are heated in dimethylformamide (DMF).

Signals at 2.95 (NMe_2), 3.75 and 3.90 (OCH_3 groups, 6.44 and 6.58 (C_5H and C_8H), 7.65 (=CH—N), and 7.34 ppm (C_6H_5), as well as characteristic (for compounds of this type) signals of a methylidyne proton in the 1 position at 5.42 ppm (doublet) and a broad doublet of an NH group at 6.24 ppm, are observed in the PMR spectrum of III in $CDCl_3$.

Compound III has properties that are typical for substituted enamines. In particular, it is hydrolyzed readily and in high yield in an acidic medium to the corresponding hydroxymethylene derivative IV. It should be noted that a signal of the proton of an OH group is observed in the PMR spectrum of the latter at 13.78 ppm (see the experimental section), which indicates a strong intramolecular hydrogen bond between the OH group and the lactam carbonyl group. When IV is heated in alkali, it readily undergoes ketone cleavage to give lactam II. At the same time, enamino amide III, in contrast to activated enamino ketones, remains unchanged even in the case of prolonged heating in alkali. Also of interest is the fact that, in contrast to the simplest lactams [5], lactam II is completely resistant to alkaline hydrolysis.

Enamine III also readily undergoes transamination to give secondary enamines V and VI, which are characterized by an intramolecular hydrogen bond between the enamine NH group and the lactam carbonyl group (δ_{NH} for V and VI 9.14 and 9.40 ppm, respectively).

6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinolone (VII), like lactam II, undergoes condensation with dimethylformamide acetal (I). Signals of protons at 2.92 (NMe_2) and 3.83 and 3.87 ppm (OCH_3 groups), two doublets at 4.13 and 5.05 ppm (protons in the 1 position,

*See [1] for Communication 33.

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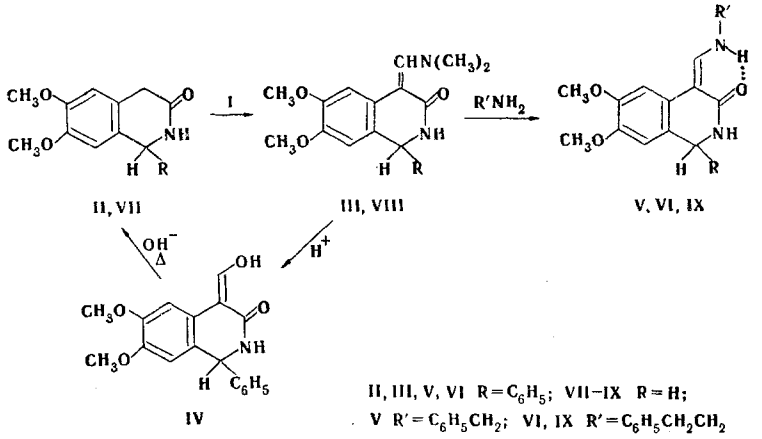
TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
III	185—187[a]	71,0	6,7	8,1	$C_{20}H_{22}N_2O_3$	71,0	6,6	8,3	87
IV	181—184[a]	69,5	5,5	4,3	$C_{18}H_{17}NO_4$	69,4	5,5	4,5	88
V	142—145[a]	74,9	5,7	6,8	$C_{25}H_{24}N_2O_3$	75,0	6,0	7,0	73
VI	193—196[b]	75,7	6,2	6,6	$C_{26}H_{26}N_2O_3$	75,3	6,3	6,8	82
VIII	237—240[c]	64,0	6,7	10,7	$C_{14}H_{18}N_2O_3$	64,1	6,9	10,7	68
IX	210—213[b]	70,7	6,6	8,0	$C_{20}H_{22}N_2O_3$	71,0	6,6	8,3	82
X	111—113[d]	72,2	7,4	7,5	$C_{22}H_{26}N_2O_3$	72,1	7,2	7,6	66[e]
XI	120—122[f]	72,1	7,2	7,6	$C_{22}H_{26}N_2O_3$	72,1	7,2	7,6	90[e]
XII	188—191[g]	61,0	4,0	4,0	$C_{17}H_{13}NO_2Cl_2$[h]	61,1	3,9	4,2	20
XIII	84—86[f]	73,5	6,9	4,4	$C_{19}H_{21}NO_3$	73,3	6,8	4,5	63
XIV	259—262[c]	71,4	5,7	7,9	$C_{40}H_{38}N_4O_6$	71,6	5,7	8,4	15

[a]From isopropyl alcohol. [b]From benzene. [c]From DMF. [d]From ethanol. [e]By method A. [f]From hexane. [g]From methanol. [h]Found: Cl 21.0%. Calculated: Cl 21.2%.

J_{gem} = 13.5 Hz), signals of aromatic protons at 6.60 and 6.58 ppm, and the signal of a vinyl proton at 7.65 ppm are observed in the PMR spectrum of enamine VIII (in $CDCl_3$). However, on the basis of such data one cannot solve the problem of the location of the dimethylaminomethylene fragment — the 1 or 4 position of the isoquinoline ring. A comparison of the IR spectra of enamines III and VIII with the spectra of the corresponding lactams II and VII shows that additional conjugation of the C=O group with the enamine fragment leads to an approximately identical shift of the absorption band of the carbonyl group to the low-frequency side (the ν_{CO} values in the spectra of II, III, VII, and VIII are, respectively, 1673, 1655, 1680, and 1663 cm^{-1}). Since the noted conjugation is absent in the condensation of acetal I in the 1 position of the isoquinoline ring, it may be assumed that III and VIII have similar structures, i.e., condensation takes place in the 4 position.

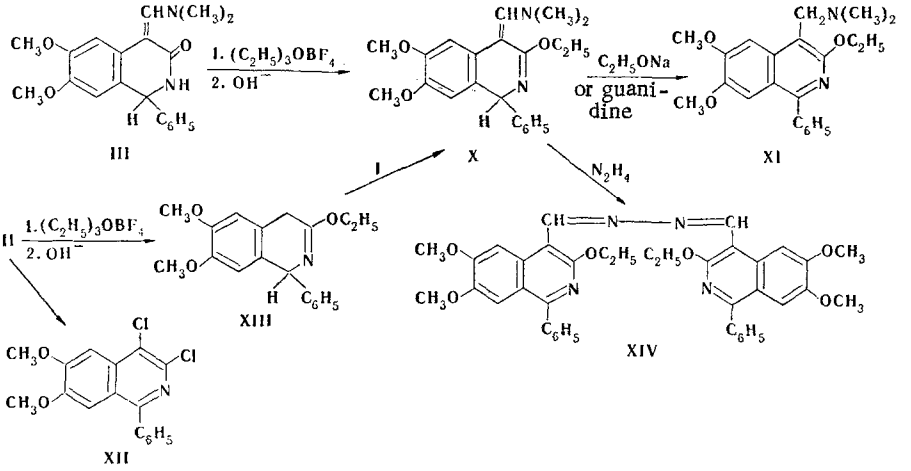
Evidence for a 4-substituted structure of VIII was obtained by its transamination. Signals (in $CDCl_3$) of chelate NH bonds at 9.00 ppm (similar to the analogous signals in the spectra of enamines V and VI) are observed in the PMR spectrum of enamine IX obtained in this way; the frequency of the carbonyl band in the IR spectra undergoes an additional decrease to 1640 cm^{-1} due to hydrogen bonding.



The presence in III of enamino carbonyl and amide fragments ensures the possibility of its selective O-alkylation. Enamino imino ester X was synthesized by reaction of enamine III with triethyloxonium tetrafluoroborate with subsequent decomposition of the resulting tetrafluoroborate complex with a solution of potassium carbonate. We found that X can be readily aromatized to isoquinoline derivative XI; however this does not occur under ordinary conditions (the characteristic signal of a proton in the 1 position of the ring is observed in the PMR spectrum at 5.66 ppm). The mass spectrum of X contains a molecular-ion peak with mass number 366 and peaks due to detachment of side substituents, particularly the intense $[M - Ph]^+$ peak at m/e 289. It should be noted that an $[M - Ph]^+$ fragment is not observed in the mass spectrum of aromatic 1-phenyl-3,4-dichloro-6,7-dimethoxyisoquinoline (XII), which was obtained by heating lactam II with phosphorus oxychloride.

However, the aromatization of X proceeds readily when an alcohol solution of it is heated in the presence of sodium ethoxide. This reaction gives 1-phenyl-3-ethoxy-4-dimethylaminomethyl-6,7-dimethoxyisoquinoline (XI), the structure of which was proved by means of the PMR and mass spectra (see the experimental section); the PMR spectrum does not contain the signal of a proton in the 1 position, while in the mass spectrum one does not observe a peak corresponding to an $[M - Ph]^+$ fragment. The most intense peak in the spectrum is the peak with m/e 322, which is formed due to elimination of NMe_2 from the molecular ion.

It is interesting that XI can also be obtained via an alternative path, viz., by reaction X of acetal I with lactim ether XIII, which is synthesized by reaction of lactam II with $Et_3O^+BF_4^-$. Insofar as we know, this is the first example of the condensation of dimethylformamide acetal in the α position of lactim ethers.



In conclusion, we made an attempt to use an enamine and lactim ether function to construct heterocycles that are condensed with an isoquinoline ring. However, neither of these functions became involved in the reaction with guanidine carbonate, and XI was isolated as the principal product. The reaction with hydrazine leads to a compound that, judging from the results of elementary analysis and the mass spectrum, is an azine (XIV). A low-intensity molecular-ion peak with m/e 670 is observed in the mass spectrum of XIV in the large mass-number region. The principal fragmentation of the molecular ion proceeds through cleavage of the N–N bond. The subsequent fragmentation of the resulting ion takes place with the detachment of CH_3 and C_2H_5 groups. The absence of elimination of C_6H_5 confirms the aromatic structure of XIV. These data indicate the relatively low reactivity of the imino ester function in enamino imino ester X.

EXPERIMENTAL

The PMR spectra of solution of the compounds in $CDCl_3$ were recorded with an XL-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil pastes of the compounds were recorded with an MAT-112 spectrometer with direct introduction of the samples into the ion source; the ionizing-electron energy was 70 eV, and the temperature of the ionization chamber was 180°C. The melting points of the compounds were determined with an MP-1 apparatus (Yamato Scientific Co. Ltd.). The purity of the substances was monitored by chromatography on Silufol UV-254 plates.

1-Phenyl-3-oxo-4-dimethylaminomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III). A mixture of 28.3 g (100 mmole) of II and 37.7 g (240 mmole) of dimethylformamide diethylacetal (I) was heated at 100°C for 4 h in 113 ml of DMF. The reaction mixture was cooled, and the precipitate was removed by filtration and washed with ether to give 30.1 g of III in the form of a crystalline light-yellow powder that was soluble in benzene, alcohols, acetone, and chloroform but insoluble in water, 2 N HCl and 2 N NaOH. 3-Oxo-4-dimethylaminomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII) was similarly obtained from VII and I (Table 1).

1-Phenyl-3-oxo-4-hydroxymethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV). A 1.5-g (4.5 mmole) sample of III was dissolved in 15 ml of 50% acetic acid, and the mixture was stirred at 20°C for 2 h. The solid material was removed by filtration and washed with water to give 1.2 g of IV in the form of a white powder that was soluble in acetone,

alcohols, chloroform, and 2 N NaOH. PMR spectrum, δ: 5.59 [broad s, 1H (C1H)], 6.47 [broad s, 1H (NH)], 6.32 and 6.81 (s, 2H, aromatic protons, C_5—H and C_6—H), 7.28 (broad s, 5H, protons of a phenyl ring attached to C_1), 7.80 broad s, 1H (C_4H)], 13.78 (broad s, 1H, OH).

Alkaline Hydrolysis of 1-Phenyl-3-oxo-4-dimethylaminomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. A 0.67-g (2.5 mmole) sample of III was dissolved in 10 ml of 1 N NaOH, and the mixture was stirred at 20°C for 7 h. It was then refluxed for 2 h, after which the solid product was removed by filtration and washed with water to give 0.7 g (100%) of 1-phenyl-3-oxo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) with mp 196-198°C (from DMF).

1-Phenyl-3-oxo-4-benzylaminomethyleno-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V). A 1.7-g (5 mmole) sample of III was suspended in 17 ml of toluene, 0.6 g (5.6 mmole) of benzylamine was added, and the mixture was refluxed for 3 h with monitoring of the reaction from the liberation of dimethylamine. The mixture was then cooled, washed with ether, and worked up to give 1.45 g of V as a crystalline yellow powder that was soluble in chloroform, alcohols, acetone, and benzene but insoluble in ether, water, 2 N NaOH, and 2 N HCl. Compounds VI and IX were similarly obtained (Table 1).

1-Phenyl-3-ethoxy-4-dimethylaminomethylene-6,7-dimethoxy-1,4-dihydroisoquinoline (X). A) An 11.7-g (34.6 mmole) sample of III was suspended in 50 ml of dry methylene chloride, and a solution of 8.53 g (44.9 mmole) of triethyloxonium tetrafluoroborate in 10 ml of methylene chloride was added dropwise with stirring. The mixture was then stirred for 6-8 h, after which the solvent was removed by distillation *in vacuo*, and the residual oil was triturated with dry ether to give 14 g (89.3%) of the tetrafluoroborate complex of X as a green powder with mp 165-167°C. A 6.7-g (14.8 mmole) sample of this complex was dissolved in 70 ml of chloroform, the solution was cooled with ice, and 10 ml of a saturated solution of potassium carbonate was added dropwise. The chloroform layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed by vacuum distillation, and the residue was triturated with dry ether to give 4 g of white crystals that were quite soluble in organic solvents and 2 N HCl but insoluble in 2 N NaOH, water, and hexane.

B) A 1.6-g (5.1 mmole) sample of XIII was dissolved in 4 ml of DMF, 1.2 g (7.6 mmole) of dimethylformamide diethylacetal (I) was added, and the mixture was heated at 125°C for 12-14 h. The DMF and excess acetal were removed by vacuum distillation, and the residue was triturated with dry ether to give 0.47 g (25%) of X.

1-Phenyl-3-ethoxy-4-dimethylaminomethyl-6,7-dimethoxyisoquinoline (XI). A) A 0.73-g (2 mmole) sample of X was sprinkled into a solution of sodium ethoxide in ethanol, prepared from 0.23 g (10 mmole) of Na and 10 ml of alcohol, and the mixture was refluxed for 6 h. The solvent was removed by distillation *in vacuo*, and the residue was treated with water. The aqueous mixture was extracted from chloroform, and the chloroform layer was washed with water, dried with potassium carbonate, and evaporated *in vacuo*, The resulting oil was triturated with hexane to give 0.66 g of XI in the form of orange crystals that were soluble in organic solvents. PMR spectrum, δ: 1.40 (t, 3H, $C_{3a}H_3$), 2.34 [s, 6H, $N(CH_3)_2$], 3.8 (s, 5H, OCH_3 and $C_{4a}H_2$), 4.02 (s, 3H, OCH_3), 4.5 (q, 2H, C_{3a}, H_2), 7.41 and 7.29 (s, 2H, aromatic protons), 7.15, 7.8 ppm (m, 5H, phenyl ring protons).

B) A 1.83-g (5 mmole) sample of X was sprinkled into a suspension of 0.9 g (5 mmole) of guanidine carbonate in 9 ml of dry DMF, and the mixture was refluxed for 20 h. The solvent was removed by distillation *in vacuo*, and the residue was triturated with water. The aqueous mixture was extracted with chloroform, and the extract was washed with an additional amount of water and dried with potassium carbonate. The solvent was removed by distillation, and the residue was triturated with dry ether to give 0.95 g (52%) of XI.

1-Phenyl-3,4-dichloro-6,7-dimethoxyisoquinoline (XII). A 5.6-g (20 mmole) sample of II was sprinkled into a cooled (to 0°C) suspension of 12.6 g (60 mmole) sample of PCl_5 in 3.3 ml of phosphorus oxychloride, and the mixture was heated at 80°C for 1 h. The $POCl_3$ was removed by distillation, 50 g of ice water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was washed successively with a 10% solution of Na_2CO_3 and water, dried with sodium sulfate, and worked up to give 1.34 g of XII in the form of shiny yellow plates that were soluble in organic solvents but insoluble in water, 2 N NaOH, 2 N HCl, hexane, and petroleum ether. Mass spectrum: intense molecular-ion peak (m/e 333)*; the ratio of the isotope peaks in the group of the molecular ion corresponded to

*The value for the ion that contains the ^{35}Cl isotope is presented.

the presence of two Cl atoms in the molecule. The principal fragmentation pathways include the elimination of H^+ (m/e 332), CH_2O (303), and CH_3O (302).

1-Phenyl-3-ethoxy-6,7-dimethoxy-1,4-dihydroisoquinoline (XIII). A 15.4-g (54.9 mmole) sample of II was suspended in 60 ml of dry methylene chloride, and a solution of 15 g (79.03 mmole) of triethyloxonium tetrafluoroborate in 20 ml of methylene chloride was added dropwise with stirring. The mixture was then stirred at 20°C for 6-8 h, after which it was cooled to 0°C with ice, and the resulting white precipitate was removed by filtration. The tetrafluoroborate complex was suspended in 80 ml of chloroform, and 15 ml of a saturated solution of potassium carbonate was added dropwise at 5°C. The reaction mixture was stirred at 20°C for 40 min, and the chloroform layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed by vacuum distillation, and the residue was triturated with hexane to give 8.4 g of XIII in the form of white crystals that were quite soluble in organic solvents and 2 N HCl and had mp 84-86°C (from hexane). Workup of the mother liquor containing the tetrafluoroborate complex yielded 3.3 g of starting II. Mass spectrum: intense peak with m/e 311. The following ions were observed in the mass spectrum: $[M - CH_3]^+$ 296, $[M - C_2H_4]^+$, 283 $[M - C_2H_5]^+$, 282 $[M - OMe]^+$ 280, $[M - Ph]^+$ 234, and $[M - Ph - C_2H_4]^+$ 206. PMR spectrum, δ: 1.26 (t, 3H, CH_3), 3.72 and 3.84 (s, 3H and 3H, OCH_3), 3.40 (d, 2H, C_4H), 4.04 (q, 2H, $C_{3a}H$), 5.76 (t, 1H, C1H), 6.54 and 6.64 (s, 2H aromatic protons), 7.00, 7.40 ppm (broad m, 5H, phenyl ring protons).

(1-Phenyl-3-ethoxy-6,7-dimethoxy-4-isoquinolyl)azine (XIV). A 0.12-g (3.4 mmole) sample of hydrazine hydrate was added to 1.2 g (3.3 mmole) of Xa in 12 ml of toluene, and the mixture was stirred at 87°C for 10 h. It was then cooled, and the resulting precipitate was removed by filtration to give 0.16 g of XIV in the form of a yellow powder that was insoluble in alcohols, chloroform, and water but soluble in DMF and DMSO.

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