ACETALS OF LACTAMS AND ACID AMIDES.

XXVI.* SYNTHESES OF HETEROCYCLES FROM ENAMINO KETONES AND ENAMINO AMIDES

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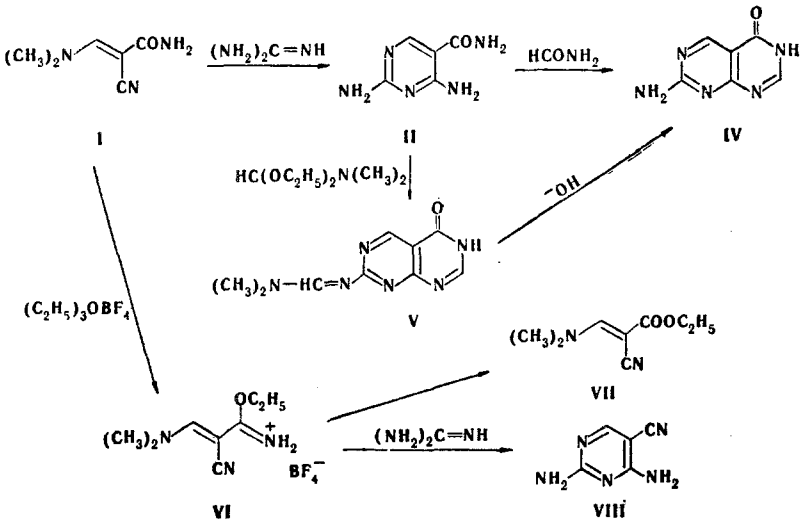
UDC 547.859.07

A new approach to the synthesis of one-, two-, and three-ring compounds from enamides and enamino ketones was investigated. Thus the reaction of α-cyano-β-dimethylaminoacrylamide with guanidine gave 2,4-diamino-5-carbamidopyrimidine, the cyclization of which with dimethylformamide acetal and subsequent hydrolysis gave 2-amino-5,6-dihydro-5-oxopyrimido[4,5-d]pyrimidine. An enamino ketone — 1-benzoyl-2-dimethylamino-2-methylethylene — was subjected to condensation with guanidine, thiourea, and acetamidine, as a result of which 2-substituted 4-phenyl-6-methylpyrimidines were synthesized. The reaction of 1-benzoyl-2-dimethylamino-2-methylethylene with acryloyl chloride leads to 3-dimethylamino-4-benzoyl-Δ^2-cyclohexenone, which was converted to the corresponding diethylacetal. A new synthesis of an acridine derivative was realized by reaction of the latter with ethyl anthranilate.

Enamines have found extensive application in the synthesis of various heterocyclic compounds [2]. In particular, enamino ketones and enamino amides are used as starting compounds for the preparation of indole, quinoline, and benzazepine [3] derivatives and condensed pyrimidines [4] and pyridines [5, 6]. The present paper is devoted to the development of new approaches to the synthesis of one-, two-, and three-ring compounds from enamines.

α-Cyano-β-dimethylaminoacrylamide (I) [7] reacts relatively readily with guanidine to give 2,4-diamino-5-carbamidopyrimidine (II) in high yield, from which 2-amino-5,6-dihydro-5-oxopyrimido[4,5-d]pyrimidine (IV) and 2-dimethylaminomethylazo-5-oxo-5,6-dihydropyrimido-[4,5-d]pyrimidine (V), respectively, were obtained by cyclization with formamide or dimethylformamide diethylacetal (III). Compound V is hydrolyzed smoothly to IV in alkaline media.



*See [1] for communication XXV.

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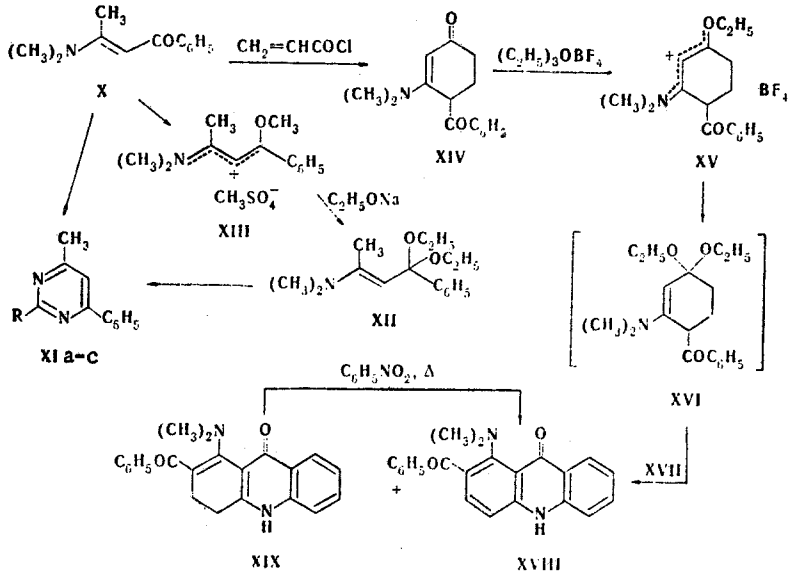
We have established that, in contrast to other vinylogous ureas [5], the ethylation of amine I with triethyloxonium tetrafluoroborate proceeds selectively at the amide carbonyl group; this is confirmed by the PMR spectra of tetrafluoroborate VI and by its hydrolysis to ethyl α-cyano-β-dimethylaminoacrylate (VII). 2,4-Diamino-5-cyanopyrimidine (VIII) was synthesized by reaction of VI with guanidine.

As we noted in [4], an enamino ketone — 3-oxo-4-(N,N-dimethylamino)methylenecaprolactam (IX) reacts readily with various "amidine components" to give pyrimido[4,5-c]azepine derivatives. To compare the reactivity of IX with the reactivity of a more simply constructed enamino ketone — 1-benzoyl-2-dimethylamino-2-methylethylene (X) [9] — we subjected the latter under the same conditions to condensation with guanidine, thiourea, and acetamidine. In all cases we isolated the corresponding 2-R-4-phenyl-6-methylpyrimidines (XIa-c), but the yields were considerably lower than in the analogous reactions of IX. This fact confirms the considerable activating effect of the lactam carbonyl group in enamino ketone IX [4]. Attempts to activate the "enamino ketone" carbonyl group in X by conversion to vinylogous acetal XII [10] through methyl sulfate complex XIII did not lead to positive results.

Another pathway used in the present research for the synthesis of heterocycles was based on the previously studied [3, 11] reaction of enamino ketones with acryloyl chloride. The reaction of X with CH_2=CHCOCl gave 3-dimethylamino-4-benzoyl-Δ^2-cyclohexenone (XIV), the alkylation of which with triethyloxonium tetrafluoroborate leads to tetrafluoroborate XV. The latter was converted to diethylacetal XVI, which was subjected, without isolation, to reaction with ethyl anthranilate (XVII).



XI a R=NH_2; b R=SH; c R=CH_3

However, the reaction did not yield an individual substance but rather a mixture of acridines XIX and XVIII, as evidenced by the PMR spectrum, in which signals of an $N(CH_3)_2$ group (~2.90 ppm), aromatic protons, and an NH group (7.09-8.10 ppm) and a multiplet at 4.95-5.26 ppm with an intensity of two proton units were observed; this indicates the formation of a mixture of acridines XIX and XVIII in a ratio of 1:1. Molecular-ion peaks at 344 and 342* were also present in the mass spectrum. Refluxing of this mixture in nitrobenzene was accompanied by oxidation of XIX to acridine XVIII, as evidenced by the data from the PMR spectra (see the experimental section) and the mass spectra. A molecular-ion peak (342) is observed in the mass spectrum of acridine XVIII. The most intense peak is affiliated with the $(M - OH)^+$ ion and is evidently due to fragmentation of the hydroxy form of the molecular ion. The elimination of a carbonyl group from the molecular ion (28a, f) that would correspond to fragmentation of the oxo form is not observed in the spectrum. The low-intensity peaks at 310, 298, and 265 can be assigned to $(M - OH - CH_3)^+$, $[M - (CH_3)_2]^+$, and $(M - C_6H_5)^+$ ions.

*Here and subsequently, the m/e values are presented for the ion peaks.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. Deuterodimethyl sulfoxide was used as the solvent for VI, VIII, and XVIII, and deuterochloroform was used as the solvent for XIa, b. The IR spectra of mineral oil suspensions of the compounds were obtained with a Perkin–Elmer 457 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 30 eV and an ionization-chamber temperature of 125°C.

3-Dimethylamino-4-benzoyl-Δ^2-cyclohexenone (XIV). A solution of 7.5 g (0.08 mole) of acryloyl chloride in 200 ml of benzene was added dropwise in the course of 5.5 h to a refluxing solution of 14 g (0.09 mole) of X in 630 ml of dry benzene, after which 31.3 ml (0.3 mole) of triethylamine was added, and the mixture was refluxed for another 30 min. It was then cooled and filtered, and the residue from the filtration was treated with chloroform and water and made alkaline to pH 9 with triethylamine. The chloroform layers were combined and dried with Na_2SO_4, and the solvent was removed by evaporation to give 0.7 g of XIV. The benzene solution was evaporated, and the residue was triturated with ethyl acetate to give 7.4 g of XIV. The ethyl acetate was removed by distillation, and the residual oil was passed through a column filled with silica gel (elution with chloroform). The chloroform was removed from the eluate by distillation to give another 0.9 g of cyclohexenone XIV. The overall yield of product with mp 193-194°C (from acetone) was 9 g (42%). Found: C 74.6; H 7.1; N 5.7%. $C_{15}H_{17}NO_2$. Calculated: C 74.1; H 7.0; N 5.7%.

3-Dimethylamino-4-benzoyl-Δ^2-cyclohexenone Tetrafluoroborate (XV). A solution of 3.5 g (0.02 mole) of triethyloxonium tetrafluoroborate in 15 ml of dry methylene chloride was added dropwise to a solution of 4 g (0.02 mole) of cyclohexenone XIV in 40 ml of dry methylene chloride, and the mixture was stirred at room temperature for 6 h, after which it was allowed to stand overnight. The methylene chloride was removed by distillation, and the residue was treated with hexane and ether to give 6 g (98.5%) of tetrafluoroborate XV with mp 118-119°C (from ethyl acetate). Found: C 56.9; H 6.0; N 3.9%. $C_{17}H_{21}NO_2BF_4$. Calculated: C 57.0; H 5.9; N 3.9%.

7-Benzoyl-8-N,N-dimethylamino-9-acridone (XVIII). A solution of 10 g (0.03 mole) of tetrafluoroborate XV in 80 ml of absolute ethanol was added at 0°C to a solution of 0.53 g (0.02 mole) of sodium metal in 20 ml of ethanol, and the mixture was allowed to stand for 30 min. The resulting precipitate was removed by filtration, and the filtrate was vacuum evaporated. Dry toluene (40 ml) and 3.4 g (0.02 mole) of ethyl anthranilate were added to the residue (8.55 g of XVI), and the mixture was refluxed for 4 h. It was then cooled, and the toluene was removed by distillation. The residue was triturated with ether and hexane and washed with acetone. The mixture was filtered, and the solid material was dried to give 1.25 g of a mixture of XVIII and XIX, refluxing of which in nitrobenzene for 2 h with subsequent cooling gave 1 g (10.7% based on XV) of acridone XVII with mp >300°C (from DMF). Found: C 76.8; H 5.8; N 8.2%. $C_{22}H_{18}N_2O_2$. Calculated: C 76.7; H 5.8; N 8.1%. PMR spectrum: 2.83 [s, $N(CH_3)_2$], 6.73 (s, NH), and 7.17-8.15 ppm (m, aromatic protons).

2,4-Dimethyl-6-phenylpyrimidine (XIc). A 0.044-mole sample (1 g of sodium metal in 20 ml of alcohol) of sodium ethoxide was added to a solution of 4.54 g (0.04 mole) of guanidine hydrochloride in 50 ml of absolute ethanol, 6.4 g of X was added to the resulting suspension, and the mixture was refluxed for 1.5 h. It was then cooled, and the precipitate was removed by filtration and washed with alcohol and water. The alcohol was evaporated, and the residue was distilled to give 2.05 g (35%) of XIc with bp 112°C (2 mm). Found: C 78.0; H 6.4%. $C_{12}H_{12}N_2$. Calculated: C 78.3; H 6.2%.

Pyrimidines XIa, b were similarly obtained. Compound XIa, with mp 198-200°C [12], was obtained in 37% yield. PMR spectrum: 2.38 (s, CH_3), 6.68 (s, 3H), 7.40-7.95 (m, C_6H_5), and 5.40 ppm (broad s, NH_2). Compound XIb, with mp 173-174°C [13], was obtained in 63% yield. PMR spectrum: 2.52 (s, CH_3), 7.00 (s, 3H), and 7.50-8.06 ppm (m, C_6H_5).

2,4-Diamino-5-carbamidopyrimidine (II). A solution of sodium ethoxide (0.25 g of Na in 5 ml of ethanol) and 1.39 g (0.01 mole) of I were added to a solution of 0.95 g (0.01 mole) of guanidine hydrochloride in 10 ml of ethanol, and the mixture was allowed to stand at room temperature for 1 h. It was then refluxed for 4 h, after which it was cooled, and the precipitate was removed by filtration and washed successively with alcohol, water, and acetone and dried to give 1.35 g (88%) of II with mp 271-272°C (from water). Found: C 38.6; H 4.7; N 46.0%. $C_5H_7N_5O$. Calculated: C 39.2; H 4.6; N 45.8%.

2-Amino-5-oxo-5,6-dihydropyrimido[4,5-d]pyrimidine (IV). Formamide (8 ml) was added to 1.5 g (0.01 mole) of II, and the mixture was heated at 140°C for 4 h. It was then cooled, and the precipitate was removed by filtration, washed with acetone, and dried to give 1.45 g (82%) of pyrimidine IV with mp >300°C (from water). Found: C 43.9; H 3.1; N 43.4%. $C_6H_5N_5O$. Calculated: C 44.2; H 3.1; N 42.9%.

2-Dimethylaminomethylazo-5-oxo-5,6-dihydropyrimido[4,5-d]pyrimidine (V). Dimethylformamide (8 ml) and 4.4 g of dimethylformamide acetal were added to 1.5 g (0.01 mole) of II, and the mixture was refluxed for 4 h. It was then cooled, and the precipitate was removed by filtration, washed with acetone, and dried to give 1.85 g (94%) of pyrimidine V with mp >300°C. A 50-ml sample of dilute ammonium hydroxide (1:1) was added to 0.65 g of V, and the mixture was allowed to stand for 16 h. The water was removed by distillation to give 0.51 g (94%) of pyrimidine IV.

Ethyl 2-Cyano-2-dimethylaminomethyleneimidate Tetrafluoroborate (VI). A solution of 6.65 g (0.035 mole) of triethyloxonium tetrafluoroborate in 20 ml of CH_2Cl_2 was added to a solution of 4.8 g (0.03 mole) of I in 40 ml of methylene chloride, and the precipitate that formed after 16 h was removed by filtration to give VI with mp 136-137.5°C (from isopropyl alcohol). Found: C 37.7; H 5.9; N 16.4%. $C_{18}H_{14}N_3OBF_4$. Calculated: C 37.6; H 5.5; N 16.5%. PMR spectrum: 1.25 and 4.48 (t and q, $COOC_2H_5$), 3.32 [s, $N(CH_3)_2$], and 7.97 ppm (s, =CH).

2,4-Diamino-5-cyanopyrimidine (VIII). A solution of sodium ethoxide (0.5 g of Na in 10 ml of ethanol) and 2.55 g of VI were added to a solution of 0.95 g (0.01 mole) of guanidine hydrochloride in 10 ml of ethanol, and the mixture was allowed to stand at room temperature for 1 h. It was then refluxed for 4 h, after which it was cooled, and the precipitate was removed by filtration, washed with alcohol, water, and acetone, and dried to give 1 g (74%) of VIII with mp >300°C. IR spectrum: 2200 (CN); 3300, 3430, and 3100 cm^{-1} (NH_2). The mass spectrum contains an intense peak at 135. PMR spectrum: 7.43 (s, NH_2) and 8.45 ppm (s, 6H).

Ethyl α-Cyano-β-dimethylaminoacrylate (VII). Water (20 ml) was added to 2.55 g (0.007 mole) of VI, and the mixture was refluxed for 13 h. It was then cooled, and the precipitate was removed by filtration and dried to give 0.26 g of ester VII. The filtrate was evaporated, the minimum amount of water was added (up to pH 7), and the mixture was extracted with $CHCl_3$. The chloroform layer was dried with Na_2SO_4 and filtered, and the filtrate was evaporated to give another 0.15 g of VII with mp 70-73°C. No melting-point depression was observed for a mixture of this product with a sample of VII obtained by a different method.

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