TWO PATHS FOR THE FORMATION OF PYRIMIDINES FROM sym-TRIAZINE

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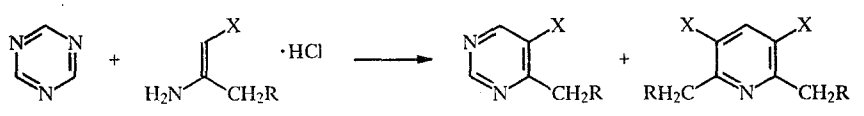
The reaction of sym-triazine with the hydrochlorides of N-unsubstituted enaminones gives mixtures of 4-alkyl-5-acyl(ethoxycarbonyl)pyrimidines and 2,6-dialkyl-3,5-diacyl(ethoxycarbonyl)pyridines. The reaction mechanism was studied by means of the ^{15}N-labelled compounds.

The addition of nucleophiles to azines and their quaternary salts can lead to ring opening, enlargement, and contraction and also to the substitution of one heteroatom by another [1,2]. The sym-triazine ring is opened by the action of hydroxide ion, amide ion, or amines, and this usually leads to hydrolytic cleavage of recyclization of the triazine ring [2,3]. We suggested that the main direction in the transformation of sym-triazine under the influence of N-substituted enaminones to 4-aminopyridines was opening of the sym-triazine ring by an electrocyclic mechanism after addition of a nucleophile [4]. Thermal cycloaddition reactions involving the aromatic sextet of azines are encountered rarely [1,5]. We were able to detect the product from cycloaddition of methylaminocrotonic ester to sym-triazine by NMR, and this provided evidence for the formation of the second reaction product, i.e., the pyrimidine derivative, by the cycloaddition mechanism [4].

Enaminones unsubstituted at the nitrogen atom [6] can be regarded both as heteroanalogs of the allyl anion and as alkenes containing a donating amino group, for which reactions with sym-triazine both by a cycloaddition mechanism and with participation of the β-carbon atom in an electrocyclic mechanism are possible.

However, it was found that the reaction did not occur even when the aminocrotonic ester was heated for a long time with sym-triazine in acetonitrile or benzene. This can be explained by the insufficient nucleophilicity of the β-carbon atom of the enaminone. Accordingly, in order to realize the reaction it is necessary to increase the nucleophilicity of the β-carbon atom by introducing the appropriate substituent at the β position of the enaminone or by increasing the electrophilicity of the triazine ring.

In fact, we established that readily separable mixtures of the pyrimidines (IIIa-d) and pyridines (IVa-d) are formed when sym-triazine (I) is heated with the hydrochlorides of enaminones (IIa-d) unsubstituted at the nitrogen atom in acetonitrile (Table 1).



I IIa-d IIIa-d IVa-d

II—IV a X=COOEt, R=H; b X=COMe, R=H; c X=COOEt, R=Me; d X, R=CH_2CH_2CO

In order to confirm the probable schemes for the formation of the products from the transformation of sym-triazine we synthesized the hydrochloride of ^{15}N-aminocrotonic ester, which we obtained for the first time by the reaction of acetoacetic

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TABLE 1. Characteristics of the Synthesized Compounds (III, IVa-d, Xa, b)

Compound	Molecular formula	mp, °C (hexane)	λ_{max}, nm (log ε)	IR spectrum, ν, (CO), cm^{-1} (vaseline oil)	Mass spectrum, m/z (I, % of maximum peak)	IR spectrum, δ, ppm*	Yield, %
IIIa	$C_8H_{10}N_2O_2$	Oil [4]	217 (3,79); 248 (3,07)	1735	166 (31) M^+, 149 (70), 121 (38), 97 (40), 83 (56), 73 (47), 71 (58), 69 (70), 56 (100), 54 (83)	9,30 (2H, s, 2-, 6-H), 4,47 (2-H, q, *J*=7 Hz, CH_2CH_3), 2,95 (3H, s, 4-CH_3), 1,45 (3H, t, *J*=7 Hz, CH_2CH_3)	54
IVa	$C_{13}H_{17}NO_4$	72 [10]	—	—	251 (34) M^+, 207 (6), 206 (100), 205 (13), 195 (9), 179 (7), 178 (29), 177 (6), 151 (8), 150 (8)	—	7
IIIb	$C_7H_8N_2O$	Oil	222 (5,21); 340 (3,47)	1695	136 (67) M^+, 122 (9), 121 (100), 120 (9), 94 (20), 93 (58), 67 (20), 66 (67), 53 (67), 51 (17)	9,20 (2H, s, 2-, 6-H), 2,67 and 2,60 (6H, 2s, 4-CH_3, CH_3CO)	36
IVb	$C_{11}H_{13}NO_2$	69...72 [13]	217 (4,32); 245 (3,90); 278 (3,63)	1700**	191 M^+	8,33 (1H, s, 4-H), 2,83 and 2,67 (12H, 2s, 2-, 6-CH_3 and 3-, 5-CH_3CO)	8
IIIc	$C_9H_{12}N_2O_2$	Oil [4]	215 (4,50); 247 (3,89)	1735	180 (11) M^+, 152 (9), 151 (100), 135 (16), 133 (13), 108 (13), 107 (16), 80 (16), 79 (11), 78 (9)	9,40 and 9,33 (2H, 2s, 2-, 6-H), 4,46 and 3,23 (4H, 2q, *J*=7Hz, 4-CH_2, OCH_2), 1,43 and 1,33 (6H, 2t, *J*=7 Hz, 4-CH_2CH_3, OCH_2CH_3)	66
IVc	$C_{15}H_{21}NO_4$	Oil	202 (4,27); 232 (3,76); 271 (3,36)	1680	279 M^+	8,60 (1H, s, 4-H), 4,35 and 3,20 (8H, 2q, *J*=7 Hz, 3-, 5-$COOCH_2$ and 2-, 6-CH_2CH_3), 1,40 and 1,27 (12H, 2t, *J*=7Hz, 3-, 5-$COOCH_2CH_3$ and 2-, 6-CH_2CH_3)	6
IIId	$C_8H_8N_2O$	0·1	228 (4,07); 285 (3,79); 335 (3,17)	1700	148 (35) M^+, 121 (100), 120 (57), 99 (49), 93 (48), 71 (50), 69 (35), 66 (62), 65 (35), 58 (100)	9,23 (2H, s, 2-, 6-H), 2,23...3,40 (6H, m, $CH_2CH_2CH_2$)	35
IVd	$C_{13}H_{13}NO_2$	145...148	223 (4,78); 246 (4,41); 289 (4,16); 299 (4,13); 328 (3,43)	1700	215 M^+	8,80 (1H, s, 4-H), 3,33 (12H, m, $CH_2CH_2CH_2$)	45
Xa	$C_{20}H_{18}N_2O_2$	69...71	260 (4,74)	1730	318 M^+	8,18 (10H, m, C_6H_5), 4,30 (2H, q, *J*=7Hz, OCH_2), 2,72 (3H, s, CH_3), 1,06 (3H, t, *J*=7Hz, CH_2CH_3)	80
Xb	$C_{19}H_{16}N_2O$	105...106	261 (4,83)	1700	288 M^+	8,18 (10H, m, C_6H_5), 2,61 and 2,08 (6H, 2s, 6-CH_3, CH_3CO)	60

*The PMR spectra of compounds (IIIc, d, IVb-d, Xb) were recorded in deuterochloroform, those of compounds (IIIa, Xa) in acetone-d_6, and the spectrum of compound (IIIb) in carbon tetrachloride. **The IR spectrum was recorded in films.

ester with a 24% aqueous solution of ammonium carbonate, containing 98% of the ^{15}N isotope. After the reaction between sym-triazine and ^{15}N-aminocrotonic ester under conditions identical with those described for the whole series of enamines (see the experimental section) the respective 4-methyl-5-ethoxycarbonylpyrimidine (IIIa) and 2,6-dimethyl-3,5-diethoxycarbonylpyridine (IVa) were isolated from the reaction mixture.

It was assumed that the pyridine (IIIa) can be formed in two ways, i.e., as a result of cycloaddition and by an electrocyclic mechanism by analogy with the previously proposed schemes for the transformation of sym-triazine during the action of enaminones substituted at the nitrogen atom [4]. It could be expected in this connection that the contribution from each of the alternative paths for the reaction of the enaminone with sym-triazine, i.e., by the electrocyclic mechanism and by the cycloaddition mechanism, would also correspond as a whole to the yields of 4-aminopyridine and pyrimidine in the previously described experiment.

We used mass spectrometry to determine the content of the ^{15}N label in the initial enaminone and in the reaction products. It was found that according to the mass spectrum the content of the ^{15}N isotope in the enaminone amounted to 100% within the experimental error limits, and this naturally corresponds to the content of the isotope in the initial labeled ammonium carbonate. As basis for determination of the ^{15}N content in the obtained pyrimidine and in the pyrimidine with the natural content of the isomer we used the changes in the intensities of the peaks for the ions with m/z 166 $[M^+]$ and the fragmentation ions $[M - 45]^+$ $[M - 46]^+$.

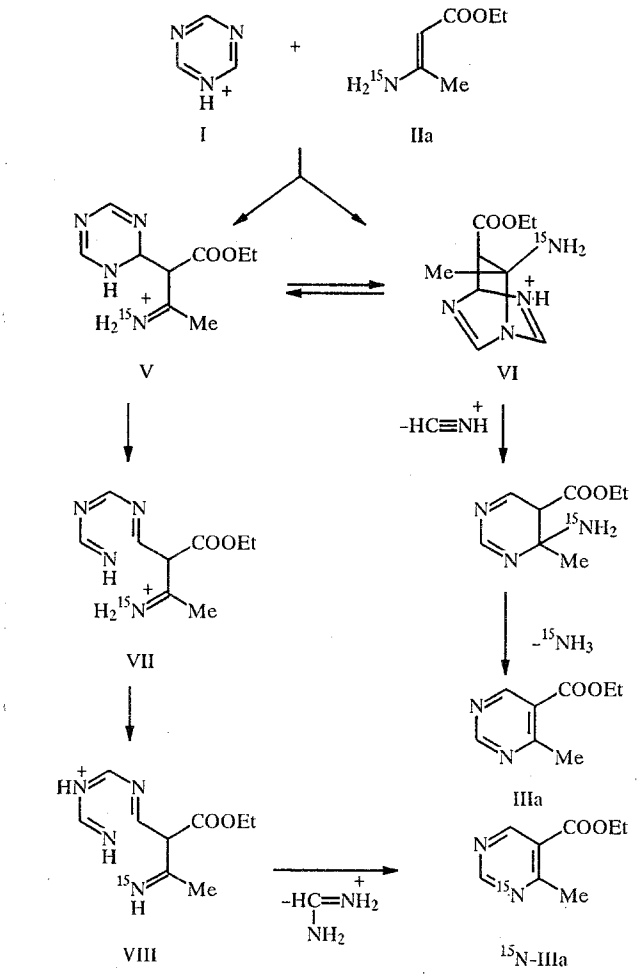
It was found that the content of the ^{15}N label in the pyrimidine was 63%. This means that the pyrimidine (IIIa) is formed to the extent of 37% by the cycloaddition mechanism and 63% by the electrocyclic mechanism. Consequently, the ratio of the reaction paths by the electrocyclic mechanism and the cycloaddition mechanism in this reaction with due regard to the effect of the substituents at the nitrogen atom is in fact similar to the corresponding ratio of the reaction paths in the reaction of sym-triazine with the hydrochlorides of the N-substituted enaminones [4].

On the basis of these data we proposed the following scheme for the formation of 4-methyl-5-ethoxycarbonylpyrimidine (IIIa) from sym-triazine (I) and ^{15}N-aminocrotonic ester (IIa). Sym-Triazine is protonated by the action of the enaminone hydrochloride, and as a result its ring is activated both to nucleophilic attack by the β-carbon of the enaminone (IIa) and to cycloaddition in a reverse Diels—Alder reaction.

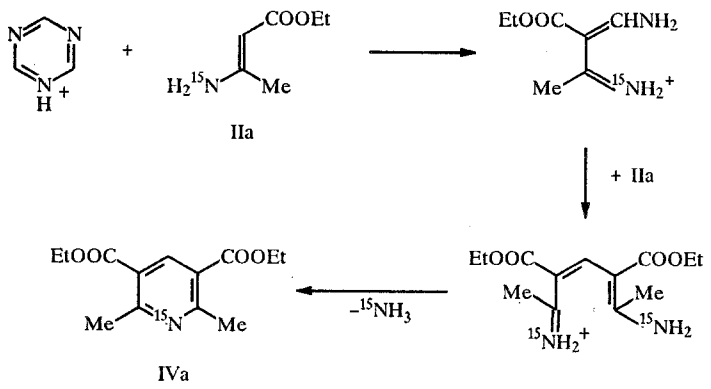
The first stage, i.e., the reaction of the protonated sym-triazine and enaminone (IIa), probably leads to an equilibrium mixture of the two intermediates (V) and (VI). The product (V) from addition of the enaminone to the sym-triazinium cation then undergoes electrocyclic opening to the heteropolyene (VII). Its subsequent closure with the elimination of the formamidinium cation leads to the pyrimidine (IIIa) containing the isotopic label. At the stage of the intermediate (VIII) there are two alternative paths for closure of the heteropolyene, i.e., at the nitrogen atom of the enaminone or at the β'-carbon atom of the enamine fragment of the intermediate, which can be formed from the heteropolyene (VII) or (VIII) by a tautomeric transition. Closure takes place at the nitrogen atom, as confirmed by the absence of 4-aminopyridine in the reaction products. As we already suggested earlier [4], the bicyclic adduct (VI) is transformed in parallel with the elimination of the hydrocyanic acid and ^{15}N-ammonia fragments to the pyrimidine (IIIa). Unusual for this reaction is the ability of the enaminone to react with the inclusion of the C—C—N triad of atoms or the two C—C carbon atoms during the formation of the pyrimidine ring, and this does not have analogies among the transformation of heterocycles [1,2].

The transformation of sym-triazine (I) into 2,6-dimethyl-3,5-diethoxycarbonylpyridine (IVa) takes place simultaneously with the formation of the pyrimidine (IIIa). Compound (IVa) is not formed in the absence of sym-triazine when the hydrochloride of the aminocrotonic ester (IIa) is simply boiled in acetonitrile. Moreover, the degree of inclusion of the ^{15}N isotope in the symmetrical pyridine (IVa), amounts to 98%. (For the calculations we used the changes in the peak intensities for the ions with m/z 251 in the labeled and unlabeled pyridines.) In view of these results and also of the fact that sym-triazine can be used for aminomethylation in a Mannich-type reaction [7,8] it can be supposed that the first stage of the reaction in our case is also aminomethylation of the ^{15}N-aminocrotonic ester (IIa). Condensation with a second molecule of the enaminone (IIa) and cyclization to the symmetrical pyridine (IVa) probably then occur.

The reaction depends substantially on the nature of the substituent at the β position of the enaminone. Thus, the yield of the pyrimidines (IIIa-d) decreases in the transition from the ethoxycarbonyl group to the acetyl group from 55-65% to 35% (Table 1). Conversely, the effect of the substituent R proved insignificant. The yield of the pyridine derivatives (IVa-d), formed as a result of the reaction, depends little as a whole on the change in the substituents R and X and varies between 6% and 15%. (See Scheme at the top of the next page.)

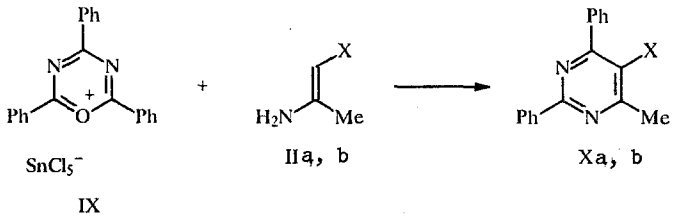


The obtained data provide an argument in favor of the proposed reaction scheme, according to which the substituent at the β-carbon atom of the enaminone could have the strongest effect.



The introduction of three phenyl groups into the triazine ring completely prevents reaction under the influence of the enaminones. In this case reaction does not go even with prolonged heating in a sealed tube. The inertness of 2,4,6-triphenyl-sym-triazine can probably be explained by the high degree of conjugation between the phenyl groups and the heterocycle and by the large size of the substituents.

However, the triphenyldiazapyrylium cation (IX) readily forms the pyrimidines (Xa, b) with the enaminones (IIa, b) unsubstituted at the nitrogen atom.



II, X a X=COOEt; b X=COMe

The enhanced electron deficiency of the diazapyrylium cation compared with triphenyltriazine clearly predominates over the steric effect and the conjugation effects of the phenyl groups, which hinder the reaction.

As was shown with the use of the ^{15}N label, our investigated reaction of sym-triazine with enaminones takes place with participation of the N—C—C triad or the two C—C carbon atoms of the enaminone and leads mainly to the pyrimidine derivatives. The dual reactivity of the enaminones with heteroaromatic compounds has not been observed before and may be of both theoretical and practical interest as a convenient method for the synthesis of difficultly obtainable pyrimidines with accepting substituents at position 5 [9].

The structure of the obtained products from the transformation of sym-triazine was proved by UV spectroscopy, PMR, GLC, mass spectrometry, and comparison of the physicochemical characteristics of the synthesized compounds with the previously described characteristics for compounds (VIIa, c, VIIIa, b) [4,10,11]. The pyrimidines (VIIa-d) and (Xa, b) with accepting substituents at position 5 mainly give one clearly defined absorption band in the UV spectrum in the region of 220-270 nm. In the UV spectrum the pyridines (VIIIb-d), like the 4-aminopyridines [4], give three absorption band but in a more short-wave region. In the IR spectra of all the obtained compounds there are absorption bands with frequencies corresponding to the carbonyl group. In the PMR spectra of the pyrimidines, in addition to the signals for the ethoxycarbonyl groups, there is either a slightly split singlet or two resolved singlets from the 2-H and 6-H protons. As in many aromatic ketones and esters, ejection of the carbonyl group was detected in the mass spectra of our synthesized compounds. The main fragmentation path of the molecular ion in the obtained heteroaromatic ketones is the successive loss of Me or Et and CO groups, while in the esters it is loss of C_2H_4, OEt, and COOEt, as confirmed by the corresponding metastable transitions.

EXPERIMENTAL

The PMR spectra were recorded in deuterochloroform on a Varian T-60 instrument with HMDS as internal standard. The IR spectra were recorded in Vaseline oil and in films on a UR-10 instrument. The UV spectra were recorded on a Cary 219 spectrophotometer in ethanol. The mass spectra were recorded on a Finnigan 4000 instrument at 50 eV with an emission current of 1.5 Ma and with injection into the ionization zone. Gas-liquid chromatography was conducted on an LKhM-8M (model 1) chromatograph with a katharometer as detector (2000 × 3-mm column, Carbowax 4000 on Chromaton N-AW-HMDS, helium, 20 ml/min). The reactions and the purity of the compounds were monitored by TLC on Silufol.

The hydrochlorides of the enaminones (IIa-d) were obtained as described earlier [4,12,13] by direct reaction of the enaminones [14-16] with hydrogen chloride. Triphenyldiazapyrylium pentachlorostannate (IX) was obtained by the reaction of benzonitrile with benzoyl chloride in the presence of tin tetrachloride by the method in [17].

The characteristics of the obtained compounds are given in Table 1. The elemental analyses and also the M^+ values of compounds (III, IVa-d, Xa, b) corresponded to the calculated data.

Ethyl β-^{15}N-Aminocrotonate. Acetoacetic ester was heated at 100°C in a sealed tube for 12 h with a 24% aqueous solution of ammonium carbonate containing 98% of ^{15}N. The reaction was monitored by GLC. The yield of ethyl β-^{15}N-aminocrotonate was 96%; bp 92-95°C (8 mm Hg), mp 18°C. Published data [14]: 92-95°C (8 mm Hg) (the unlabeled compound).

Reaction of sym-Triazine with the Hydrochlorides of the Enaminones (IIIa-d). A mixture of 2 mmole of sym-triazine and 2 mmole of the hydrochloride of the enaminone (IIa-d) in 7 ml of absolute acetonitrile was boiled under a reflux condenser for 6 h. The precipitate (formamidine hydrochloride, mp 81-82°C) was separated, and the solution was evaporated. The residue was separated on a plate with aluminum oxide (Brockman neutral) in the 1:1 ethyl acetate—benzene system.

Ethyl 6-Methyl-2,4-diphenylpyrimidinecarboxylate (Xa). A mixture of 2 mmole of 2,4,6-triphenyl-3,5-diazapyrylium pentachlorostannate [17] and 2 mmole of ethyl β-aminocrotonate in 7 ml of absolute acetonitrile was boiled for 6 h. The precipitate was separated, and the solution was evaporated to dryness. The pyrimidine (Xa) was purified in a column of silica gel L100/250 μ in the 1:5 ethyl acetate—benzene system.

6-Methyl-2,4-diphenyl-5-acetylpyrimidine (Xb). Compound (Xb) was obtained similarly by the reaction of 2,4,6-triphenyl-3,5-azapyrylium pentachlorostannate with the enaminone (IIb).

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