SOME TRANSFORMATIONS OF PYRIMIDINE N,N'-DIOXIDES

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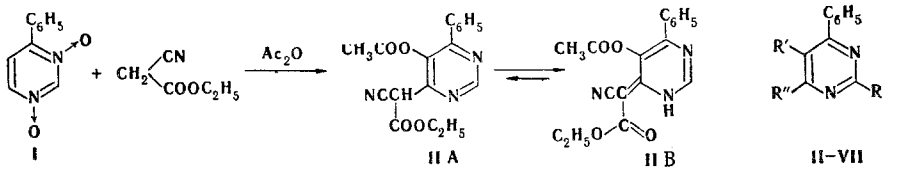
(5-Acetoxy-4-phenyl-6-pyrimidinylidene)cyanoacetic ester is formed in the reaction of 4-phenylpyrimidine N,N'-dioxide with cyanoacetic ester in acetic anhydride, whereas 5-hydroxy-6-phenylpyrimidine 1-oxide is formed in chloroform solution in the presence of acetic anhydride. The first compound is converted to a furo[3,2-d]pyrimidine derivative by treatment with alkali, while the second compound is methylated by diazomethane to give the 5-methoxy derivative.

We have previously reported the reaction of 4-phenylpyrimidine 1-oxide with cyanoacetic ester (CAE), which led to products of opening of the pyrimidine ring [1]. Continuing our research on pyrimidine N-oxides we studied the behavior in this reaction of new pyrimidine derivatives, viz., pyrimidine N-oxides [2], the chemical properties of which have not been described in the literature.

It is known that N-oxides of azines are alkylated by CH_2-active compounds in the presence of acylating agents and that the resulting α-C derivatives exist primarily in the form of methylidene derivatives [3, 4]. When we carried out the condensation of 4-phenylpyrimidine 1,3-dioxide (I) with CAE, we isolated a bright-yellow compound (with empirical formula $C_{17}H_{15}N_3O_4$) (II), which differs from the empirical formula of the expected condensation product ($C_{15}H_{13}N_3O_3$). Bands corresponding to the stretching vibrations of a conjugated nitrile group are observed in the IR spectrum of II, but the spectrum does not contain the absorption bands of an ordinary ester group [5]. However, the spectrum does contain an intense band at 1620 cm^{-1}, which is characteristic for the methylidene derivatives obtained from azines and CAE and is related to the absorption of an ester group that is tied up in an intramolecular hydrogen bond [4-6]. The long-wave absorption maximum (372 nm) in the UV spectrum of the compound obtained also indicates a pyrimidinylidene structure [6, 7]. The absence in the IR spectrum of the absorption band characteristic for the N → O group (1220-1280 cm^{-1}) and the presence of the absorption of a carbonyl group at 1790 cm^{-1} provided a basis for us to assume the presence of an acetoxy group in the molecule [5]. The spectral data presented are in agreement with possible structures II-V.



II R=H, R′=$OCOCH_3$, R″= CAE; III R=$OCOCH_3$, R′=H, R″= CAE, IV R= CAE, R′=H, R″=$OCOCH_3$; V R= CAE, R′=$OCOCH_3$, R″=H; VI R=H, R′=H, R″= CAE; VII R= CAE, R′=H, R″=H; (—CH(CN)$COOC_2H_5$= CAE)

A comparison of the long-wave absorption maxima of the compound [λ_{max} 372 nm (log ε 4.14)] and the similarly constructed pyrimidinylidene derivatives VI [λ_{max} 378 nm (log ε 4.15)] [7] and VII [λ_{max} 405 nm (log ε 3.53)] [8] made it possible to assume that the reaction of dioxide I with CAE takes place in the 6 position, as in the case of 4-phenylpyrimidine 1-oxide and [1] 1-methyl-4-phenylpyrimidinium iodide [9], and to assume that structures II and III are more hypothetical.

The final selection of the structure was made from data from the PMR spectra of the compound in $CDCl_3$ (Table 1). In addition to signals of the protons of ethoxy, acetoxy, and phenyl groups, the spectrum of II contains only one doublet at 8.27 ppm (J = 3Hz, 1H), which excludes structures III and IV, in the spectra of which the 5-H signal should be a singlet and

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TABLE 1. Chemical Shifts of the 2-H and 6-H Protons of II, VI, and VII

Compound	δ, ppm (J, Hz)	
	In $CDCl_3$	In CF_3COOH
II	8,27, d ($J=3$)	8,92, s
VI (2-H)	8,25, d ($J=3$)	8,98, s
VII (6-H)	8,20, dd ($J=7$, $J'=2$)	8,27 d ($J=7$)

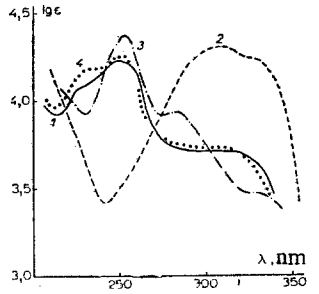
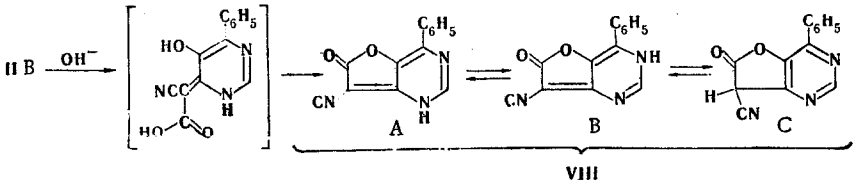


Fig. 1. UV absorption spectra: 1) 5-hydroxy-6-phenylpyrimidine 1-oxide (IX); 2) 4-phenyl-pyrimidine 1-oxide; 3) 6-phenylpyrimidine 1-oxide; 4) 5-methoxy-6-phenylpyrimidine 1-oxide (X).

should be found at stronger field. However, it was difficult to assign this signal to 2-H (for structure II) or to 6-H (for V) from the magnitude of the chemical shift. At the same time, the difference in the chemical shifts of the 2-H and 6-H protons in pyrimidine derivatives should be substantial in CF_3COOH, in which the equilibrium between forms A and B is shifted to favor form A as a result of protonation [4]. Thus the 2-H signal in VI is shifted 0.73 ppm to weak field, while the position of the 6-H signal (in VII) remains almost unchanged. The observed significant shift of the signal of the proton in the spectrum of II when the solvent is changed (Table 1) thus constitutes evidence for the presence of a 2-H proton in the molecule, and the (5-acetoxy-4-phenyl-1,6-dihydro-6-pyrimidinylidene)cyanoacetic ester structure (II) can consequently be assigned to the compound obtained.

Compound II contains a fragment similar to derivatives of o-hydroxyphenylacetic acids, which are readily deacylated and saponified under alkaline conditions with subsequent cyclization of the resulting o-hydroxyphenylacetic acids to 2-coumarones [10]. As expected, as a result of alkaline treatment of II we obtained a substance that was identified as 2-oxo-3-cyano-7-phenyl-2,4-dihydrofuro[3,2-d]pyrimidine (VIII) from analytical and spectral data.



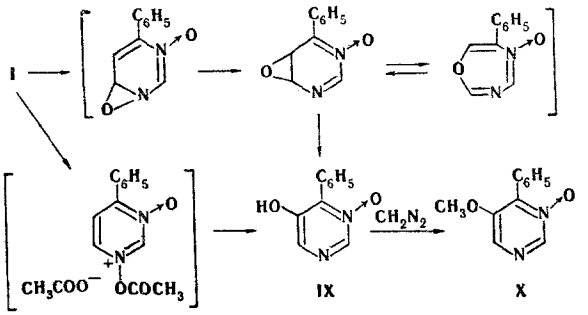
Its spectrum contains absorption bands at 2230 cm^{-1} (CN) and at 1780 and 1750 cm^{-1} (lactone CO [11]). Three signals at 8.60 (1H, 5-H), 8.17 ($2H_o$, aromatic), and 7.73 ppm (3H, aromatic) are observed in its PMR spectrum. The absence of a $>$ CHCN signal of tautomer VIIIc at $\delta <$ 7.5 ppm may be a consequence of the fact that this tautomer is not present in appreciable amounts in $CDCl_3$ solution and that the compound exists in form A or B or as an equilibrium mixture of these forms. The long-wave absorption maximum in the UV spectrum at 345 nm also indicates an increase in the conjugation chain as compared with that expected for an aromatized pyrimidine ring (the VIIIc form).

Thus both α alkylation and β acetoxylation occur in the reaction of dioxide I with CAE. It is known that α or γ acetoxylation is characteristic for the N-oxides of azines [12], whereas the β derivatives are isolated from the reaction mixtures usually in very small amounts [12].

The yield of condensation product II was low under the conditions indicated above. The reaction was complicated by side processes with considerable resinification. Since it may be assumed that the condensation of I with CAE proceeds via a scheme similar to that in [1] through additional activation of the pyrimidine by interaction of the N → O groups with acetic anhydride, the condensation under consideration was carried out in chloroform in the presence of only 2-3 moles of acetic anhydride in order to reduce the effect of the latter only to activation of the N-oxide group [1, 12]. However, in this case no products of reaction of I with CAE were isolated, but an isomer of the starting compound was obtained.

It is known that the N-oxides of azines can undergo a number of isomeric transformations to oxo azines, to five-membered carbonyl-containing compounds, etc. [13]. The absence of a carbonyl group in the compound is apparent from the IR spectrum, but at the same time, the intense absorption bands at 1580 and 1370 cm^{-1} indicated retention of the pyrimidine ring, and the band at 1240 cm^{-1} indicated the presence of an N → O group in this compound [1]. The broad absorption band at 2300-3100 cm^{-1} (in KBr) and the band at 3650 cm^{-1} (in CCl_4) indicated the presence of a hydroxy group with phenolic character in the molecule; this was confirmed by a positive qualitative reaction with $FeCl_3$. These data correspond to substituted 5-hydroxypyrimidines, which display the properties of phenols [14].

In addition to aromatic protons (7.40-7.80 ppm), the PMR spectrum of pyrimidine IX contains two singlets at 8.77 and 8.07 ppm (1H each), which can be assigned, respectively, to the signals of 2-H and 6-H protons. The absence of appreciable spin—spin coupling between these protons indicates that the N → O group is not attached to the nitrogen atom that separates these protons, since a characteristic splitting of 2 Hz exists for such compounds [15].



The similarity in the chromophore systems of IX and 6-phenylpyrimidine 1-oxide and their difference in IX and 4-phenylpyrimidine 1-oxide (Fig. 1) indicate the presence of an N → O group in IX attached to the nitrogen atom in the α position relative to the phenyl group.

On the basis of these data it may be assumed that the compound that we obtained is 5-hydroxy-6-phenylpyrimidine 1-oxide (IX).

It has been previously shown that 5-hydroxypyrimidines and their N-oxides are methylated by diazomethane [16]. Treatment of IX with diazomethane made it possible to obtain 5-methoxy-6-phenylpyrimidine 1-oxide (X), which differs from the previously described 5-methoxy-4-phenylpyrimidine 1-oxide (XI) [17], in good yield. As compared with the spectrum of the starting compound, the absorption band of an OH group vanishes in the IR spectrum of oxide X, a $\nu C\text{-}O\text{-}C$ band (1230 cm^{-1}) appears, and the $\nu_{N\to O}$ band (1255 cm^{-1}) is retained. The chromophore system of the 5-methoxy derivative is similar to the chromophore system of the starting 5-hydroxypyrimidine (Fig. 1). The PMR spectrum contains four signals at 9.06 (1H, s, 2-H), 8.57 (1H, s, 6-H), 7.76 (5H, aromatic), and 3.90 ppm (3H, s, CH_3O). Chromatographically identical compounds are formed in the deoxygenation of X and XI with triethyl phosphite.

It has been shown that IX is formed when oxide I is treated with Ac_2O or with a solution of the latter in chloroform, but its development was not noted when I was refluxed for a long time in chloroform or when an alcohol solution of I was irradiated with UV light.

The conversion of N-oxides of azines to β-hydroxy derivatives in the pyridine and quinoline series [13], as well as in the pyrimidine series [18], has been described. Bellamy and Streith [13] assume that the reaction may proceed through intermediate oxaziridines with

conversion of the latter by means of a 1,5-sigmatropic shift to oxazepines of β-hydroxy azines. In the case of dioxide I both a similar transformation through oxaziridines and a transformation through an N^{+}-acetoxy derivative may occur.

EXPERIMENTAL

The IR spectra of KBr pellets of solutions of the compounds in $CHCl_3$ or CCl_4 were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with a Varian 56/60A spectrometer with hexamethyldisiloxane as the internal standard. The individuality of the compounds was verified by means of thin-layer chromatography (TLC) on Silufol UV-254. Dioxide I was obtained by the method in [2]. The synthesis of VI and VII was described in [7] and [8], respectively.

(5-Acetoxy-4-phenyl-1,6-dihydro-6-pyrimidinylidene)cyanoacetic Ester (II). A 0.7-g (3.9 mmole) sample of dioxide I was dissolved by heating in 15 ml of acetic anhydride, 1.0 g (8.8 mmole) of CAE was added, and the mixture was allowed to stand for 4 h. The excess acetic anhydride was removed by vacuum distillation, and the residue was treated with water and allowed to stand for 24 h. The mixture was made alkaline with sodium bicarbonate solution and extracted with chloroform, and the extract was dried with magnesium sulfate. The chloroform was evaporated in vacuo, and the residue was treated with alcohol to give 0.3 g of II (23%) of II with mp 196-198°C (from alcohol). UV spectrum, λ_{max} (log ε): 208 (4.17), 298 (4.23), 372 nm (4.15). PMR spectrum (in $CDCl_3$): 14.3 (1H, NH), 8.27 (1H, d, J = 3 Hz, 2-H), 7.83 (2H, aromatic), 7.50 (3H, m, aromatic), 4.30 (2H, q, J = 7 Hz, CH_2CH_3). 2.25 (3H, s, $COCH_3$), and 1.30 ppm (3H, t, J = 7 Hz, CH_2CH_3), Found: C 62.8; H 4.71; N 12.9%; M 325 (by mass spectrometry). $C_{17}H_{15}N_3O_4$. Calculated: C 62.8; H 4.62; N 12.9%; M 325.

2-Oxo-3-cyano-7-phenyl-2,4-dihydrofuro[3,2-d]pyrimidine (VIII). A 0.15-g (0.4 mmole) sample of acetoxypyrimidine II was dissolved in 2 ml of alcohol containing 30 mg of NaOH, and the mixture was allowed to stand at room temperature for 3 days. The alcohol was then evaporated, and the residue was dissolved in water. The aqueous solution was acidified with acetic acid to precipitate 0.1 g (70%) of VIII with mp > 300°C (after reprecipitation from a solution in ammonium hydroxide by the addition of acetic acid). UV spectrum, λ_{max} (log ε): 212 (4.31), 234 (4.26), 265 (4.29), 345 nm (4.24). PMR spectrum (in d_6-DMSO): 8.60 (1H, s, 5-H); 8.17 and 7.73 ppm [m, (2H + 3H), aromatic]. Found: C 63.8; H 3.0; N 16.7%; M 237 (by mass spectrometry). $C_{13}H_7N_3O_2 \cdot H_2O$. Calculated: C 63.4; H 3.3; N 17.1%; M 237.

5-Hydroxy-6-phenylpyrimidine 1-Oxide (IX). A 0.5-ml sample of acetic anhydride was added to a solution of 0.4 g (2.2 mmole) of dioxide I in 45 ml of chloroform, and the mixture was refluxed for 10 h. The solvent was removed by vacuum distillation, water was added to the residue, and the mixture was allowed to stand for 24 h for decomposition of the anhydride residues. The water was decanted, and the residual oil was treated with alcohol to give 0.1 g (25%) of IX with mp 244-246°C (dec., from alcohol). The aqueous layer after extraction with chloroform was evaporated, and the residue was recrystallized from alcohol to give another 0.07 g of IX. The overall yield was 40%. UV spectrum, λ_{max} (log ε): 204 (4.00), 251 (4.23), 319 nm (3.72). PMR spectrum (in d_7-DMF): 8.77 (1H, s, 2-H), 8.07 (1H, s, 6-H), and 7.40-7.80 ppm (5H, m, aromatic). Found: C 63.5; H 4.3; N 14.8%; M 188 (by mass spectrometry). $C_{10}H_8N_2O_2$. Calculated: C 63.7; H 4.3; N 14.9%; N 188.

5-Methoxy-6-phenylpyrimidine 1-Oxide (X). An ether solution of diazomethane obtained from 1 g of nitrosomethylurea was added to a suspension of 0.15 g (0.8 mmole) of pyrimidine IX in 5 ml of chloroform, and the mixture was allowed to stand at room temperature for 5 h. The solvent was then removed in vacuo to give methoxypyrimidine X with mp 215-218°C (from methanol). UV spectrum, λ_{max} (log ε): 205 (4.05), 232 (4.18), 251 (4.25), 319 sh nm (3.71). PMR spectrum (in CD_3OD): 9.06 (1H, s, 2-H), 8.57 (1H, s, 6-H), 7.76 (5H, m, aromatic), and 3.90 ppm (3H, s, OCH_3). Found: C 64.7; H 5.0; N 13.5%. $C_{11}H_{10}N_2O_2$. Calculated: C 65.3; H 5.0; N 13.8%.

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SYNTHESIS OF SUBSTITUTED INDOLO[1,2-c]QUINAZOLINES

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It was established that N-acetylindoxyl arylhydrazones are converted to 12-acetamidoindolo[1,2-c]quinazolines in acetic acid in the presence of acetic anhydride, evidently through a step involving the formation of arylhydrazoindole derivatives. A new method for the synthesis of 12-acetamidoindolo[1,2-c]quinazolines from N,O-diacetylindoxyls and arylhydrazines is proposed.

We have shown that indolo[1,2-c]quinazolines are formed in the reduction of N-acetyl-3-arylazoindoles with zinc dust in acetic acid in the presence of acetic anhydride and sodium acetate [1]. We assumed that the indicated reaction proceeds through an intermediate step involving the formation of N-acetyl-3-arylhydrazoindoles, which in acidic media undergo a rearrangement of the o-benzidine type and are then converted to indolo[1,2-c]quinazolines [1]. In this connection, in the present research we carried out the synthesis and studied the behavior in acidic media of N-acetylindoxyl arylhydrazones, which in the tautomeric form can be regarded as N-acetyl-3-arylhydrazoindoles. The phenylhydrazone (Ia), p-chlorophenylhydrazone (Ib), and p-nitrophenylhydrazone (Ic) of N-acetylindoxyl were obtained from N-acetylindoxyl [2] and the corresponding arylhydrazines (Ia was previously described in [3]). The presence in the PMR spectra of these compounds of singlet signals at δ 4.75 ppm with an intensity of two proton units, which are due to the methylene protons of the indoxyl molecule, confirms the structure of Ia-c. When Ia-c are heated in acetic acid in the presence of acetic anhydride, they undergo a rearrangement similar to the o-benzidine rearrangement, probably through a step involving the formation of the tautomeric hydrazine form (A), after which, as a result of cyclocondensation of the rearrangement product (B), they form 12-aminoindolo[1,2-c]quinazolines (IIa-c), which are acetylated during the reaction and are converted to 12-acetamidoindolo[1,2-c]quinazolines (IIIa-c).

We also studied the reaction of N,O-diacetylindoxyls with a twofold excess of the arylhydrazines in alcohol and found that the reaction proceeds in different directions, depending on the character of the substituents in the phenyl ring of the arylhydrazine and the benzene ring of the indoxy molecule. Thus N-acetylindoxyl arylhydrazones Ib and Ic, which are iden-

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