ALKYLATION AND ACYLATION OF 2-AMINOPYRIMIDINE N-OXIDES

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Products of both O- and N-acylation are formed in the acylation of 2-aminopyrimidine N-oxides, whereas only O-alkylation products are formed by the action of alkylating agents. The reaction of 2-aminopyrimidine N-oxides with aldehydes gives only products of reaction at the amino group; the structures of the resulting compounds depend on the reactivity of the carbonyl component.

Aminopyrimidine N-oxides, which display interesting biological properties [1, 2], have not yet been adequately studied. Reports dealing with methods for the synthesis of these compounds and their chemical properties are limited, and the N-oxides of di- and triaminopyrimidines are still more accessible [1-4]. 2-Aminopyrimidine 1-oxide (I) [5], 2-amino-4,6-dimethylpyrimidine 1-oxide (II) [6], and substituted 2-amino-4-aryloxypyrimidine 1-oxides [7] have been synthesized from 2-monoamino derivatives. Continuing our study of pyrimidine N-oxides [8] we investigated the effect of the N→O group on the reactivity of the 2-amino group in alkylation and acylation reactions.

We selected N-oxides I and II and the previously undescribed 2-amino-4-phenylpyrimidine 1-oxide (III) as the starting compounds. The latter compound was obtained by the oxidation of 2-amino-4-phenylpyrimidine with hydrogen peroxide in the presence of catalytic amounts of sodium tungstate in analogy with the oxidation of 2-aminopyridines and pyrazines [9]. However, in contrast to pyridines, in addition to oxidation to an N-oxide, we observed significant destructive oxidative decomposition of phenylpyrimidine to benzoic acid, which led to the isolation of N-oxide III from the reaction mixture in the form of the benzoate. A decrease in the oxidation temperature from 70°C to 40°C slows down the formation of III markedly, but destructive oxidation still cannot be avoided.

Compounds I-III contain two reaction centers (the NH_2 and N→O groups) at which alkylation and acylation are possible.

The acylation of N-oxides II and III by the action of Ac_2O, AcCl, or PhCoCl proceeds significantly more rapidly than acylation of the corresponding pyrimidines. The action on N-oxide III of an equimolar amount of Ac_2O or PhCOCl in acetone, chloroform, or pyridine at room temperature gives monoacyl derivatives, in the IR spectra of which a band of stretching vibrations of an N→O group (ν 1180 cm^{-1}) is retained [10], and a band of a carbonyl group is found at 1700-1740 cm^{-1}. On the basis of these data and the PMR spectral data, which are examined below, it may be assumed that the derivatives obtained are 2-acetamido- and 2-benzamido-4-phenylpyrimidine 1-oxides (IV, VI). 2-Acetamido-4,6-dimethylpyrimidine 1-oxide (V) was similarly obtained from N-oxide II and Ac_2O in acetone. Compound V is identical to the N-oxide obtained by oxidation of 2-acetamido-4,6-dimethylpyrimidine by the method in [6].

The reaction of N-oxide III with acetyl chloride was faster than the reaction with acetic anhydride; however, if the reaction mixture was worked up a few minutes after the disapperarance of III [according to thin-layer chromatography (TLC)], primarily the starting pyrimidine and a very small amount of IV were isolated. These results, as well as chromatographic observation of the course of the acylation in various solvents, made it possible to assume that initial attack by the acyl cation takes place at the oxygen atom of the N→O group rather than at the nitrogen atom of the amino group. When this reaction was carried out in dry acetonitrile, it led to the formation of unstable chloride VII, which darkens in air and contains an absorption band of a carbonyl group in its IR spectrum at 1825 cm^{-1}, from which we obtained stable perchlorate VIII (νCO 1830 cm^{-1}, which is characteristic for N-acetoxyazinium deriv-

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TABLE 1. Spectral Characteristics of the Compounds Obtained

Compound	IR spectrum, ν, cm^{-1} (KBr)				PMR spectrum, δ, ppm (J, Hz)					
	N→O	C=O	NH_2 (deform.)	NH_2(NH) or OH	solvent	5-H	6-H	CH_3CO	R	H_{arom}
III	1175	—	1635	—	D_6-DMSO	7,30 d (7)	8,47 d (7)	—	—	8,07 m, 7,65 m
IV	1165	1740	—	3240	$CDCl_3$	7,45 d (7)	8,39 d (7)	2,47 s	9,98 (NH)	7,99 m, 7,35 m
V	—[a]	1695	—	—	$CDCl_3$	6,87 s	—	2,48 s	2,48 (6H, $2CH_3$)	—
					D_2O	7,17 s	—	2,37 s	2,47 (6H, $2CH_3$)	—
VI	—[a]	1725	—	3280 (KBr), 3300 (CCl_4)	$CDCl_3$	—[b]	8,40 d (7)	—	10,90 (NH)	8,05m, 7,41m
VIII	—	1830	1660	—	D_6-DMSO	—[b]	8,78 d (7)	1,92 s	—	8,15m, 7,54 m
IX	—	1795	1660	3380, 3500	DMSO	—[b]	8,73 d (7)	—	—	8,13m, 7,83 m, 7,73—7,35m
X	—	1850	1680	—	D_6-DMSO	6,83 s	—	1,80 s	2,38 s (3H, CH_3), 2,28 s (3H, CH_3)	—
XI	—	1715	—	—	D_6-DMSO		8,65 d (7)	1,94 s	—	8,21 m, 7,57 m
XII	—	1720	—	2600—3550	DMSO	—[b]	8,76 d (7)	—	—	8,30—7,40 m
XIV	1175	1715	—	—	—	—	—	—	—	—
XV	—	1780	—	—	—	—	—	—	—	—
XVI	1160	1715	—	—	—	—	—	—	—	—
XVII	—	—	1665	—	D_6-DMSO	—[b]	9,28 d (7)	—	4,21 s (3H, CH_3O), 3,42 s (3H, $CH_3SO_4^-$)	8,17m, 7,58 m
XVIII	—	—	1640	—	D_6-DMSO	—b	9,28 d (7)	—	4,21 s (3H, CH_3O)	8,16 m, 7,60 m
XIX (acetate)	1175	—	—	—	D_6-DMSO	— b	8,51 d (6)	1,90 (3H, CH_3COOH)	—	8,09 m, 7,47 m
XX	1150	—	—	—	D_6-DMSO	6,88 dd (13 and 10)	8,56 dd (13 and 3)	—	8,03 dd (1H, 4H) (10 and 3)	7,63—7,20 m
XXIII	—	—	—	3450 (CCl_4)	$CDCl_3$	6,85 d (5)	8,13 d (5)	—	4,66 (2H, CH_2), 6,07 (1H, NH)	8,06 m, 7,36 m
XXV	1170	—	—	3530 (OH, CCl_4)	DMSO	6,98 add (12 and 10)	8,60 dd (12 and 4)	—	7,98 dd (1H, 4H) (10 and 4) 6,00 (1H, >$CHCCl_3$)	—
XXVI	1160	—	—	3520 (OH, CCl_4)	DMSO	—[6]	8,63 d (7)	—	6,31 (1H, >$CHCCl_3$) 8,28 (1H, NH)	8,26—7,65 m

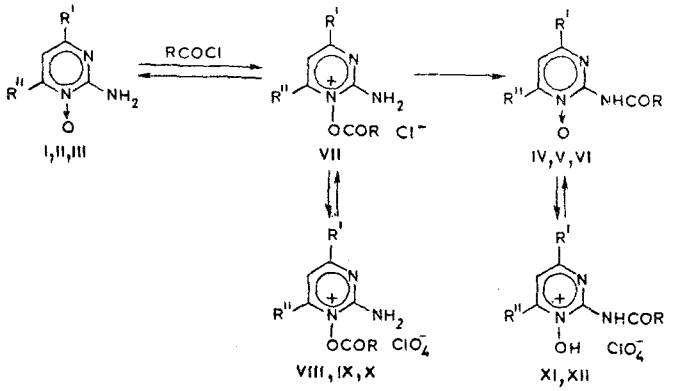
[a] The 1100-1300 cm^{-1} region contains several bands, the assignment of which is difficult.
[b] The 5-H signal coincides with the H_{arom} signal.

TABLE 2. Melting Points and Results of Elementary Analysis of the Synthesized Compounds

Compound	mp, °C	Found, %				Empirical formula	Calc., %			
		C	H	Cl	N		C	H	Cl	N
III	192—193[a]	63,8	4,8	—	22,3	$C_{10}H_9N_3O$	64,2	4,8	—	22,4
IV	178—178,5[b]	63,1	5,2	—	18,3	$C_{12}H_{11}N_3O_2$	62,8	4,8	—	18,3
V	148 (dec.)[c]	53,2	6,1	—	23,4	$C_8H_{11}N_3O_2$	53,0	6,1	—	23,1
VI	175—177[b]	70,3	4,3	—	14,6	$C_{17}H_{13}N_3O_2$	70,1	4,5	—	14,4
VIII	150—155[d]	43,6	3,8	11,6	13,3	$C_{12}H_{12}ClN_3O_6$	43,7	3,7	10,8	12,8
IX	165—170[d]	52,5	3,8	9,2	10,4	$C_{17}H_{14}ClN_3O_6$	52,1	3,6	9,05	10,7
X	117—125[d]	34,1	4,0	12,7	14,8	$C_8H_{12}ClN_3O_6$	34,1	4,3	12,6	14,9
XI	101—104[d]	44,0	4,1	—	13,0	$C_{12}H_{12}ClN_3O_6$	43,7	3,7	10,8	12,8
XII	118—121[d]	—	—	9,1	10,3	$C_{17}H_{14}ClN_3O_6$	—	—	9,05	10,7
XIV	188—190[b]	66,4	4,4	—	18,1	$C_{17}H_{14}N_4O_2$	66,6	4,6	—	18,3
XVI	185—187[e]	60,7	4,0	—	16,2	$C_{17}H_{13}ClN_4O_2$	59,6	3,8	10,4	16,4
XVII	148—151[b]	44,9	4,5	—	13,1	$C_{12}H_{15}N_3O_5S$	45,9	4,8	—	13,4
XVIII	182—183,5[f]	44,1	3,9	—	13,9	$C_{11}H_{12}ClN_3O_5$	43,8	4,0	—	13,9
XIX	253—256,5[f]	66,1	4,9	—	15,9	$C_{27}H_{22}N_6O_2 \cdot CH_3COOH$	66,1	5,0	—	16,1
XX	233—237[b]	58,2	4,6	—	27,1	$C_{15}H_{14}N_6O_2$	58,1	4,5	—	27,1
XXIII	126—128[a]	77,9	5,3	—	16,0	$C_{17}H_{15}N_3$	78,4	5,4	—	16,1
XXIV	174—175	73,9	5,2	—	19,6	$C_{27}H_{22}N_6 \cdot 0,5H_2O$	73,8	5,2	—	19,2
XXV	94—97[g]	28,2	2,4	39,4	16,1	$C_6H_6Cl_3N_3O_2$	27,9	2,3	41,1	16,3
XXVI	195—197[b]	43,4	3,1	31,9	12,6	$C_{12}H_{10}Cl_3N_3O_2$	43,1	3,0	31,8	12,6

[a]From aqueous alcohol. [b]From alcohol. [c]From benzene—alcohol. [d]The product was washed with absolute ether, and the melting point was obtained in a sealed capillary. [e]From $CHCl_3$-alcohol. [f]From alcohol—acetic acid. [g]From dioxane.

atives [11]). The data from the IR spectra and the results of elementary analysis provided a basis for the assumption that the compounds obtained are 1-acetoxy-2-amino-4-phenylpyrimidinium chloride and perchlorate. 1-Benzoxy-2-amino-4-phenyl- and 1-acetoxy-2-amino-4,6-dimethylpyrimidinium perchlorates (IX, X) were similarly obtained from III and II, respectively, by the action of benzoyl and acetyl chlorides.



I R′=R″=H; II R′=R″=CH_3, III R′=C_6H_5, R″=H; IV, VII, VIII, XI R=CH_3, R′=C_6H_5, R″=H; V, X R=R′=R″=CH_3; VI, IX, XII R=R′=C_6H_5, R″=H

A comparison of the spectral characteristics of 2-acylaminopyrimidine N-oxide perchlorates XI and XII with the spectral data for the perchlorates of 1-acyloxy derivatives VIII-X (Table 1) indicates their substantial difference. Thus in the case of perchlorates of 1-acyloxy derivatives the absorption band of the CO group is found at 1800-1850 cm^{-1}, whereas it is found at ∿1700 cm^{-1} in the case of perchlorates of 2-acylaminopyrimidines; in the latter case the band remains essentially unchanged as compared with the absorption band of the starting IV-VI, respectively. The bands of vibrations of the NH_2 group that are absent in the spectra of acylamino derivatives IV-VI, XI, and XII are retained in the IR spectra of VII-X. At the same time, a shift to weak field of the signal of the 6-H proton, which is in the α position relative to the nitrogen atom, as compared with N-oxides III, IV, and VI is observed in the PMR spectra of VIII, IX, XI, and XII, which have a quaternized nitrogen atom (Table 1).

The perchlorates of 1-acyloxy-2-aminopyrimidines are stable in solid form at room temperature for several weeks; however, in solution in, for example, acetone they are converted irreversibly to acetamido derivatives.

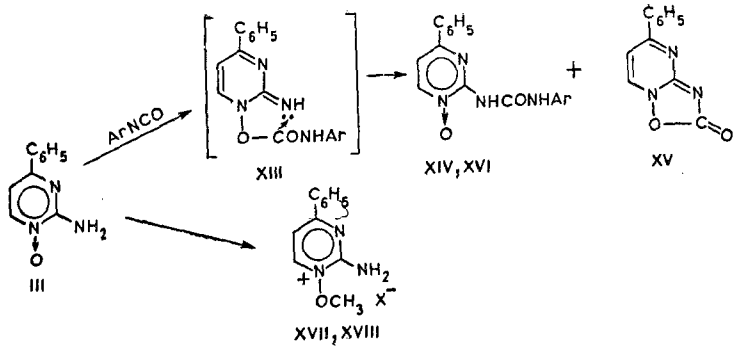
1-Acyloxypyrimidinium cations were previously only assumed as intermediates in some reaction of pyrimidine N-oxides [8]; for the first time we have isolated them in the form of perchlorates for derivatives that contain a donor amino group. 1-Acetoxy-4-phenylpyrimidinium perchlorate was not isolated under similar conditions. The presence of an amino group in the pyrimidine ring evidently stabilizes the structure of a cation of the pyrimidinium type (VII-X).

Consequently, the primary reaction of 2-aminopyrimidine N-oxides in the case of acylation with acid anhydrides and halides is attack by the acyl cation on the oxygen atom of the N→O group to give 1-acyloxy derivatives of pyrimidine, which readily undergo rearrangement to more stable 2-acylaminopyrimidine N-oxides, evidently via a scheme similar to that presented in [4].

From among other acylating agents, taking into account the interest in substituted 2-ureidopyrimidines [12], we examined the action of phenyl and p-chlorophenyl isocyanates. We isolated two substances from the reaction mixture after the reaction of pyrimidine III and phenyl isocyanate. According to the analytical and spectral data (Tables 1 and 2), one of them corresponded to the expected 2-phenylureido-4-phenylpyrimidine 1-oxide (XIV). The second compound, which was isolated in small amounts, gave an IR spectrum with a band at 1785 cm^{-1} (CO) and had the empirical composition $C_{11}H_7N_3O_2$; in analogy with [13], it evidently has the 2-oxo-7-phenyl-2H-1,2,4-oxadiazolo[2,3-a]pyrimidine (XV) structure. 2-(p-Chlorophenyl)ureido-4-phenylpyrimidine 1-oxide (XVI) was isolated when p-chlorophenyl isocyanate was used under similar conditions.

During a study of the alkylation of 2-aminopyrimidine N-oxides we examined both the action of ordinary alkylating agents, viz., dimethyl sulfate and methyl p-toluenesulfonate, and the reaction with aldehydes, which makes it possible to obtain alkylamino derivatives (benzyl, methylol, etc.) from pyridines and their N-oxides [14].

In the case of alkylation of III with dimethyl sulfate or methyl p-toluenesulfonate we obtained only O-methoxy derivatives, which were isolated in the form of salts, viz., 1-methoxy-2-amino-4-phenylpyrimidinium methylsulfate (XVII) and perchlorate (XVIII). A signal

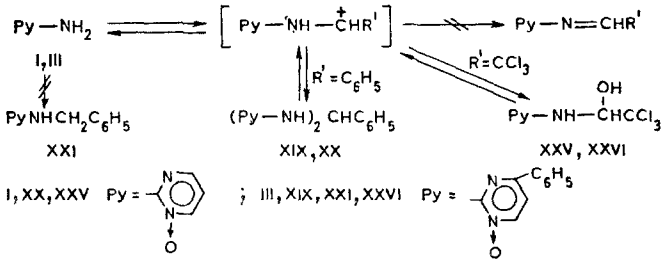


XIV Ar=C_6H_5, XVI Ar=p-C_6H_4Cl, XVII X^-=$CH_3SO_4^-$, XVIII X^-=ClO_4

of a methoxy group at 4.30 ppm appears in the PMR spectra of these compounds, while bands of and NH_2 group are retained in the IR spectra; an intense band at 1200-1300 cm^{-1} (C–O) is observed in the spectrum of XVII (an intense band of a perchlorate ion is found in this region in the spectrum of XVIII).

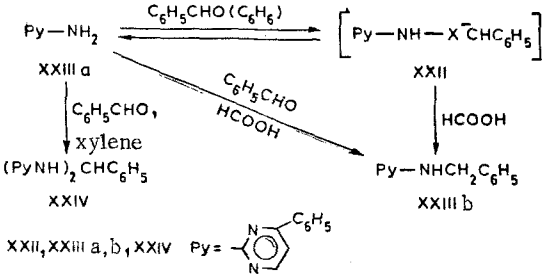
Literature data on the reaction of 2-aminopyrimidines with aldehydes are limited. It is known that 2-amino-4,6-dimethylpyrimidine reacts with chloral to give an N-methylol derivative [15], whereas 2-aminopyrimidine forms a bisproduct [16, 17]; a Schiff base was obtained from 2-aminopyrimidine only through the iminophosphorane [18]. The behavior of aminopyrimidine N-oxides in this reaction has not been studied.

We were able to achieve the condensation of III with benzaldehyde in refluxing xylene with the addition of catalytic amounts of phosphorus oxychloride. With respect to the analytical and spectral data, the compound obtained corresponds to the bis(1-oxy-4-phenyl-2-pyrimidinylamino)phenylmethane (XIX) structure (Tables 1 and 2). Bis(1-oxy-2-pyrimidinylamino)phenylmethane (XX) was similarly obtained from I.



Under milder conditions (in the absence of $POCl_3$ or in benzene) the reaction of N-oxides I and III with benzaldehyde does not take place, whereas 2-amino-4-phenylpyrimidine (XXIIIa) reacts with benzaldehyde when the components are refluxed in benzene with the addition of $POCl_3$. However, in this case the product is the unstable compound XXII, which, in analogy with [17], gives 2-benzylamino-4-phenylpyrimidine (XXIIIb) on treatment with formic acid. An increase in the temperature of condensation of 2-aminopyrimidine XXIIIa with benzaldehyde made it possible to obtain bisproduct XXIV.

In contrast to XXII, bisproducts XIX and XX upon treatment with formic acid do not form benzylamino derivatives XXI but undergo decomposition to the starting N-oxides. The reaction of 2-amino-4-phenylpyrimidine with benzaldehyde in formic acid leads to the formation of benzylamino derivative XXIIIb, whereas a similar reaction is not observed for aminopyrimidine N-oxides.



Products with structures other than that of benzaldehyde were isolated in the reaction of I and III with a more reactive carbonyl compound, viz., chloral in benzene. Unstable XXV, which decomposes on storing in air, was obtained from N-oxide I, while III gave relatively stable XXVI, to which, on the basis of analytical and spectral data, the 2-(α-hydroxy-β,β,β-trichloroethyl)amino-4R-pyrimidine 1-oxide structure (XXV, R = H; XXVI, R = Ph) was assigned. Bands of stretching vibrations of amino and oxo groups (3530-3540 cm^{-1} in CCl_4) are observed in the IR spectra of these compounds. As compared with the spectrum of the starting compound, signals at 6.00 and 6.31 ppm, which are related to the trichloroethyl group in XXV and XXVI, respectively, appear in the PMR spectra.

Thus products of both O- and N-acylation were isolated in the acylation of 2-aminopyrimidine N-oxides, whereas only products of reaction at the amino group were isolated in the reaction of these compounds with aldehydes; the structures of the compounds obtained depend on the reactivity of the carbonyl component.

EXPERIMENTAL

The IR spectra of KBr pellets (s 0.25%), solutions in CCl_4, and suspensions in perfluorinated oil were recorded with UR-20 and Specord spectrometers. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A56/60 spectrometer with hexamethyldisiloxane as the internal standard. The yields, melting points, and results of elementary analysis of the synthesized compounds are presented in Table 2.

2-Aminopyrimidine 1-oxide (I) was obtained by the method in [5] in 30% yield and had mp 185-187°C. 2-Amino-4,6-dimethylpyrimidine 1-oxide (II) was obtained by the method in [6] in 20% yield (mp 252°C), as well as by oxidation of 2-amino-4,6-dimethylpyrimidine with a mixture of 30% H_2O_2 and CH_3COOH by the method in [19] in 20% yield.

2-Amino-4-phenylpyrimidine 1-Oxide (III). A mixture of 10.9 g (64 mmole) of pyrimidine XXIIIa, 200 ml of 30% H_2O_2, and 2 g of $Na_2WO_4 \cdot 2H_2O$ was heated with stirring at 70°C for 3

h until the solid material dissolved completely. The mixture was then cooled, and the resulting precipitate was removed by filtration and washed with water to give 10 g (50%) of a product with mp 156-157°C (from aqueous alcohol). Found: N 13.5%. $C_{10}H_9N_3O \cdot C_6H_5COOH$. Calculated: N 13.6%.

A solution of 10 g of the benzoate in chloroform was washed with a 10% solution of potassium carbonate, and the organic layer was dried with magnesium sulfate and evaporated to give 5.2 g (44% based on the starting pyrimidine) of product. UV spectrum, λ_{max} (log ε): 220 (4.39), 275 (4.11), and 360 nm (4.21).

Perchlorate of III. This compound, with mp 170-172°C (in a sealed capillary), was obtained by the addition of a small excess of perchloric acid to a solution of III in acetic acid or acetonitrile. PMR spectrum (DMSO): 8.77 (1H, d, J = 7 Hz, 6-H), 8.13 (2H, m, aromatic protons), and 7.65 ppm (3H, m, aromatic + 5-H protons). Found: Cl 12.8; N 14.3%. $C_{10}H_9N_3O \cdot HClO_4$. Calculated: Cl 12.3; N 14.6%.

Perchlorate of II. This compound, with mp 197-200°C (in a sealed capillary), was similarly obtained (D_6-DMSO): 6.83 (1H, s, 5-H), 2.40 (3H, s, 6-CH_3), and 2.33 ppm (3H, s, 4-CH_3). Found: C 30.1; H 4.38; N 17.2$_5$. $C_6H_9N_3O \cdot HClO_4 \cdot H_2O$. Calculated: C 29.9; H 4.97; N 17.4%.

2-Acetamido-4-phenylpyrimidine 1-Oxide (IV). A solution of 1 g (5 mmole) of pyrimidine in 10 ml of acetone and 0.56 ml (6 mmole) of Ac_2O was stirred at room temperature for 3.5 h, and the resulting precipitate was removed by filtration and washed with acetone to give 0.8 g (72%) of product. UV spectrum, λ_{max} (log ε): 232 (4.34), 296 (4.09), and 347 nm (4.23).

2-Acetamido-4,6-dimethylpyrimidine 1-Oxide (V). A mixture of 0.7 g (5 mmole) of pyrimidine II in 30 ml of acetone and 0.56 g (6 mmole) of Ac_2O was stirred at 40°C for 3.5 h, after which the solvent was evaporated, and the residue was treated with a solution of sodium bicarbonate. After 2 h, the mixture was evaporated to dryness, and the residue was separated with a column filled with silica gel [elution with CH_2Cl_2–alcohol (3:1)] to give 0.6 g (69%) of a product with mp 148°C (mp 148°C [6]).

2-Benzamido-4-phenylpyrimidine 1-Oxide (VI). A mixture of 2 g (10 mmole) of N-oxide III in 50 ml of pyridine and 1.2 ml (10 mmole) of benzoyl chloride was stirred at 20°C for 5 h, after which it was poured into water, and the aqueous mixture was acidified with 2% HCl solution. The precipitate was removed by filtration to give 2.5 g of pyrimidine VI. UV spectrum, λ_{max} (log ε): 264 (4.42), 312 (4.16), and 349 nm (4.26).

Perchlorates XI and XII were obtained in the same way as the perchlorates of II and III.

1-Acetoxy-2-amino-4-phenylpyrimidinium Chloride (VII). A mixture of 0.7 g (4 mmole) of oxide III in 5 ml of dry acetonitrile and 0.3 ml of acetyl chloride was stirred for 10 min, after which the precipitate was removed by filtration and washed with ether to give 0.7 g (70%) of product. IR spectrum: 1825 (CO) and 1665 cm^{-1} [$\delta(NH_2)$]. The product was unstable in air.

1-Acetoxy-2-amino-4-phenylpyrimidine Perchlorate (VIII). A 0.3-ml sample of 70% $HClO_4$ was added to a suspension of chloride VII in acetonitrile, absolute ether was added to the resulting solution, and the precipitate was removed by filtration and washed with absolute ether to give perchlorate VIII. UV spectrum (in H_2O), λ_{max} (log ε): 225 (4.23), 280 (4.12), and 340 nm (3.96).

A solution of 0.2 g of perchlorate VIII in 10 ml of acetone was allowed to stand at 20°C for 10 days, after which the mixture was treated with sodium carbonate solution and extracted with chloroform. The chloroform was evaporated to give oxide IV.

Perchlorates IX and X were similarly obtained from pyrimidines II and III by the action of AcCl or PhCOCl.

2-Phenylureido-4-phenylpyrimidine 1-Oxide (XIV). A mixture of 0.5 g (2.7 mmole) of pyrimidine III and 0.5 ml of phenyl isocyanate in 35 ml of absolute xylene was refluxed for 10 h until the starting compound vanished. The precipitate was removed by filtration to give 0.4 g (48% based on the alcohol) of product. Compound XV (40 mg), with mp 231-233°C, precipitated from the alcohol filtrate on standing. M^+ 213.0552 (high-resolution mass spectrum). $C_{11}H_7N_3O_2$. Calculated: M 213.0538.

Compound XVI was similarly obtained from pyrimidine III and p-chlorophenyl isocyanate.

1-Methoxy-2-amino-4-phenylpyrimidinium Methylsulfate (XVII). A 1-g (5 mmole) sample of III was heated in 15 ml of chloroform and 0.5 ml (5 mmole) of dimethyl sulfate at 40°C for 3.5 h, after which another 0.5 ml of dimethyl sulfate was added, and the mixture was heated for another 30 min. It was then cooled, and the resulting precipitate was removed by filtration to give 1 g (60%) of N-methoxy derivative XVII. The perchlorate obtained from XVII was identical to perchlorate XVIII.

1-Methoxy-2-amino-4-phenylpyrimidinium Perchlorate (XVIII). A mixture of 1 g (5 mmole) of III and 1.9 g (5 mmole) of methyl p-toluenesulfonate was heated at 100°C for 12 h, after which it was dissolved in 5 ml of alcohol, and 2 ml of $HClO_4$ was added. The resulting precipitate was removed by filtration and washed with ether to give 0.8 g (47%) of product. UV spectrum (in H_2O), λ_{max} (log ε): 224 (4.23) and 294 nm (4.24).

Bis(1-oxy-4-phenyl-2-pyrimidinylamino)phenylmethane (XIX). Two drops of $POCl_3$ were added to 2.7 g (14 mmole) of III and 1.4 ml (14 mmole) of benzaldehyde in 25 ml of absolute xylene, and the reaction mixture was refluxed with a Dean–Stark adapter for 17 h. The mixture was then cooled, and the precipitate was removed by filtration to give 2.3 g of product. Recrystallization from alcohol–acetic acid gave the acetate of XIX (13%). UV spectrum, λ_{max} (log ε): 222 (4.60), 248 (4.29), 278 sh (4.36), and 360 nm (4.37).

Bisproduct XX was similarly obtained in 32% yield from oxide I after refluxing for 4 h, while bisproduct XXIV was obtained in 15% yield from pyrimidine XXIIIa.

2-Benzylamino-4-phenylpyrimidine (XXIIIb). A 3-g (17 mmole) sample of pyrimidine XXIIIa was refluxed in 50 ml of absolute benzene and 1.8 ml (17 mmole) of benzaldehyde containing three drops of $POCl_3$ for 8 h in an apparatus equipped with a Dean–Stark adapter. The precipitate was removed by filtration to give 44.3 g of XXII with mp 168-175°C. The odor of benzaldehyde developed when alcohol was added. A 1-g sample of XXII was heated with 10 ml of formic acid for 4 h, after which the mixture was cooled and poured into water. The aqueous mixture was neutralized with sodium bicarbonate solution, and the resulting precipitate was removed by filtration to give 0.3 g of pyrimidine XXIIIb. UV spectrum, λ_{max} (log ε): 250 (4.39) and 331 nm (3.68).

Compound XXIIIb was also obtained by refluxing equimolar amounts of aminopyrimidine XXIIIa and benzaldehyde in formic acid for 13 h with subsequent workup as described above.

2-(α-Hydroxy-β,β,β-trichloroethylamino)pyrimidine-1-oxide (XXV). A solution of 0.86 ml (10 mmole) of chloral in 10 ml of benzene was added dropwise to a suspension of 1 g (9 mmole) of pyrimidine I in 10 ml of absolute benzene, and the reaction mixture was stirred at 40°C for 4 h. It was then cooled, and the resulting precipitate was removed by filtration to give 1.1 g of product. The precipitate was separated by filtration to give 1.1 g of product. The precipitate was separated with a column filled with silica gel [elution with $CHCl_3$–alcohol (10:1)]. The yield was 0.6 g. The product should be stored *in vacuo*. UV spectrum, λ_{max} (log ε): 229 (4.31), 255 (3.78), and 348 nm (3.78).

2-(α-Hydroxy-β,β,β-trichloroethylamino)-4-phenylpyrimidine-1-oxide (XXVI). This compound was similarly obtained in 70% yield as described above from pyrimidine III and chloral. UV spectrum, λ_{max} (log ε): 225 (4.38), 278 (4.12), and 357 nm (4.23).

LITERATURE CITED

1. G. Rey-Bellet, R. Reiner, and D. E. Schwartz, German Offen., No. 2026997; Chem. Abstr., 74, 76443 (1971).
2. J. C. Muller and H. Ramuz, German Offen. No. 2804518; Chem. Abstr., 89, 197595 (1978).
3. T. J. Delia and D. L. Venton, J. Heterocycl. Chem., 9, 73 (1972).
4. J. M. McCall, R. E. Ten Brink, M. E. Royer, and H. Ko, Heterocycl. Chem., 15, 4184 (1978).
5. L. W. Deady, Synth. Commun., No. 7, 509 (1977).
6. B. Bobranskii, M. Mordavski, A. Relczarska, and J. Pomorski, Arch. Immunol. Ther. Exp., 16, 804 (1968).
7. U.S. Patent No. 3464987; Ref. Zh. Khim., 19N, 375 (1970).
8. V. F. Sedova, A. S. Lisitsyn, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 10, 1237 (1972).
9. R. M. Titkova, A. S. Elina, and N. P. Kostyuchenko, Khim. Geterotsikl. Soedin., No. 10, 1237 (1972).

10. R. A. Jones and A. R. Katritzky, J. Chem. Soc., No. 7, 2937 (1960).
11. V. J. Traynelis and P. L. Pacini, J. Am. Chem. Soc., 86, 4917 (1964).
12. French Patent No. 2036922; Chem. Abstr., 75, 118335 (1971).
13. A. R. Katritzky, J. Chem. Soc., No. 7, 2063 (1956).
14. R. A. Abramovitch (editor), "Pyridine and its derivatives," in: The Chemistry of Heterocyclic Compounds, Vol. 14, Supplement, Part 3, Interscience Publ., New York–London (1974), p. 65.
15. V. S. Reznik, N. G. Pashkurov, R. R. Shagidullin, and R. A. Bulgakova, Khim. Geterotsikl. Soedin., No. 1, 384 (1967).
16. L. Butula, Pharmazie, 33, 428 (1978).
17. I. A. Kaye and I. C. Kogon, Rec. Trav. Chim., 71, 309 (1952).
18. J. Bödeker and K. Courault, J. Prakt. Chem., 322, 336 (1980).
19. R. H. Wiley and S. C. Slaymaker, J. Am. Chem. Soc., 79, 4917 (1957).

SYNTHESIS AND STRUCTURE OF 2'-SUBSTITUTED 1-(1,3-DIOXAN-5-YL)URACILS. POSITIVE ROLE OF THE $Eu(fod)_3$ NMR SHIFT REAGENT

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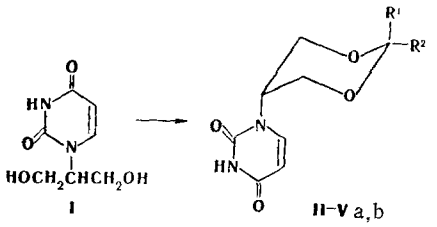
The configuration of 1-(2-R-1,3-dioxan-5-yl)uracils and the conformation of the dioxane ring in these compounds were investigated by ^1H NMR spectroscopy with the aid of the $Eu(fod)_3$ shift reagent. It is shown that the dioxane ring exists in the preferred chair conformation with an axial orientation of the pyrimidine ring; this is confirmed by the resonance of the 5'-H_a proton in the form of a broad singlet with $\nu_{1/2} \sim 8.5$ Hz. An analysis of the spectral peculiarities of the synthesized compounds made it possible to establish the orientation of the substituents attached to the second C_2 steric center. The three-dimensional structure of 1-(2,2-dimethyl-1,3-dioxan-5-yl)uracil was determined by an x-ray diffraction study, and the axial orientation of the pyrimidine ring was confirmed. It is shown that significant flattening of the carbon part of the ring (ψ = 46.6°) is observed in this molecule. An intramolecular ($C_6 \ldots O_{1'}$ = 3.05 Å) hydrogen bond was observed in the molecule of this compound.

By means of the reaction of 1-(1,3-dihydroxy-2-propyl)-uracil [1] with acetone, isobutyraldehyde, and orthoformic and orthoacetic esters with Dowex-50 ion-exchange resin in the H^+ form [2] as the catalyst we synthesized cyclic acetals and ketals, viz., 2'-substituted 1-(1,3-dioxan-5-yl)-uracils (II-V):



I II-V a,b

II $R^1=R^2=Me$; III $R^1=H$, $R^2=i$-Pr; IV a $R^1=OEt$, $R^2=H$; IV b $R^1=H$, $R^2=OEt$; Va $R^1=OEt$, $R^2=Me$; Vb $R^1=Me$, $R^2=OEt$

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