PYRIMIDINES

XLVII.* NEW METHOD FOR THE SYNTHESIS OF 2-AMINOPYRIMIDINES

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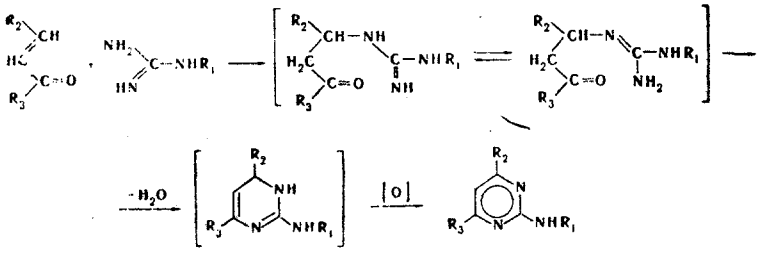
A method for the preparation of 2-amino(acetamido)pyrimidines by condensation of α,β-unsaturated carbonyl compounds with guanidine (acetylguanidine) was developed.

The extensive use of 2-aminopyrimidines in the synthesis of highly effective medicinal preparations [2-4] and other pyrimidine derivatives has stimulated the development of methods for their preparation; however, most of these methods either involve many steps or start from compounds that are difficult to obtain in [5, 6]. Condensation of α,β-unsaturated carbonyl compounds with amidines (guanidine) might have been one of the simplest methods for the synthesis of 2-substituted pyrimidines. However, attempts to use benzalacetone, m-nitrobenzalacetone, dibenzalacetone, benzalacetone dibromide, ethyl styryl ketone, isopropyl styryl ketone, cinnamaldehyde, α-bromocinnamaldehyde, and acrolein in the condensation with benzamidine were unsuccessful [7]. Only 2,4,6-trisubstituted pyrimidines could be obtained by condensation of benzamidine with chalcones in the presence of alcoholic alkali [7]. In addition, it has been shown that the condensation of mesityl oxide with benzamidine and guanidine gives 2-phenyl- and 2-amino-4,4,6-trimethyl-4,5-dihydropyrimidines, which, however, cannot be dehydrogenated to the corresponding pyrimidines because of the presence of two methyl groups bonded to the 4 carbon atom [8, 9].

We proposed to synthesize 2-aminopyrimidines from various α,β-unsaturated carbonyl compounds by using molecular sieves (zeolites), which are catalysts for reactions of amines with carbonyl compounds and are also good dehydrating agents [10], to facilitate the formation of the pyrimidine ring. The dihydropyrimidine that is probably formed during the reaction can be dehydrogenated by various methods.

In fact, 2-acetamido-4,6-diphenylpyrimidine was obtained when benzalacetophenone was condensed with acetylguanidine in the presence of molecular sieves in dimethyl sulfoxide (DMSO), which has oxidative properties [11], when dry air was bubbled into the reaction mixture (see Table 1). The synthesized pyrimidine was identical to a sample obtained by acetylation of 2-amino-4,6-diphenylpyrimidine.



The reaction evidently begins with nucleophilic attack by guanidine at the activated double bond of the α,β-unsaturated carbonyl compound (Michael addition) with subsequent ring closing, dehydration, and oxidation of the resulting dihydropyrimidine.

We investigated the behavior of a number of other α,β-unsaturated carbonyl compounds (particularly aldehydes) in analogous condensations. It was found that cinnamaldehyde reacts with acetylguanidine to

*See [1] for communication XLVI.

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TABLE 1. 2-Amino(acetamido)pyrimidine

Compound	R_1	R_2	R_3	mp, °C	Empirical formula	Found, %			Calculated, %			λ_{max}, nm (lg ε)	Yield, %
						C	H	N	C	H	N		
I	$COCH_3$	C_6H_5	C_6H_5	226—227	$C_{18}H_{15}N_3O$	74,60	5,31	14,36	74,72	5,23	14,53	205 (4,49); 223 (4,46) 254 (4,54); 314 (4,42)	43
II	$COCH_3$	C_6H_5	CH_3	145—146[a]									41
III	$COCH_3$	C_6H_5	H	220—221	$C_{12}H_{11}N_3O$	67,58	5,21	19,74	67,50	5,20	19,72	208 (4,13) sh, 221 (4,24) 246 (4,34); 281 (4,00)	67
IV	$COCH_3$	p-$(CH_3)_2NC_6H_4$	H	255—256	$C_{14}H_{16}N_4O$	65,38	6,21	22,01	65,60	6,29	21,86	208 (4,26) sh, 232 (4,39) 356 (4,49)	34
V	$COCH_3$	p-$NO_2C_6H_4$	H	273—275	$C_{12}H_{10}N_4O_3$	55,92	3,88	21,86	55,81	3,90	21,70	209 (4,31); 246 (4,30) 272 (4,20); 303 (4,15)	37
VI	$COCH_3$	CH_3	H	153—154[b]									16
VII	$COCH_3$	H	H	146—147[c]									6
VIII	H	C_6H_5	C_6H_5	135—137[d]									40
IX	H	C_6H_5	CH_3	174—175[e]									43
X	H	C_6H_5	H	165[f]									39
													29

[a]According to [12], this compound has mp 146°. [b]According to [14], this compound has mp 152-154°. [c]According to [15], this compound has mp 145-146°. [d]According to [16], this compound has mp 135-137°. [e]According to [12], this compound has mp 173°. [f]According to [13], this compound has mp 165°.

give 2-acetamido-4-phenylpyrimidine (III), the hydrolysis of which with sulfuric acid gives 2-amino-4-phenylpyrimidine (X) in quantitative yield. It is interesting to note that the presence of dimethylamino and nitro groups in the para position of the benzene ring of cinnamaldehyde leads to a decrease in the yields of the corresponding pyrimidines (IV, V) by a factor of approximately two.

2-Acetamido-4-methyl-6-phenyl- (II), 2-acetamido-4-methyl- (VI), and 2-acetamidopyrimidine (VII), respectively, were obtained by condensation of benzalacetone, crotonaldehyde, and acrolein with acetylguanidine.

Thus it was shown for the first time that it is possible to obtain 2-aminopyrimidines from α,β-unsaturated aldehydes.

α,β-Unsaturated carbonyl compounds also undergo condensation with free guanidine and its salts. 2-Amino-4,6-diphenyl (VIII) and 2-amino-4-phenylpyrimidine (X), respectively, are formed in the reaction of benzalacetophenone and cinnamaldehyde with guanidine carbonate. Similar results were also obtained with guanidine acetate. 2-Amino-4-methyl-6-phenyl (IX) and 2-amino-4-phenylpyrimidine (X), respectively, were obtained by condensation of benzalacetone and cinnamaldehyde with free guanidine. 2-Aminopyrimidines were obtained in a number of cases when guanidine was used, but it is preferable to use acetylguanidine because it gives higher yields of the desired products.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds (c 0.25%) were recorded with UR-10 and UR-20 spectrometers. The UV spectra of ethanol solutions of the compounds ($2.5\text{-}5 \cdot 10^{-3}$ M) were recorded with a Specord UV-Vis spectrophotometer. The course of the reactions and the individuality of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in an ether–methanol (8 : 1) system. The molecular weights were determined with an MS-3301 spectrometer. The melting points, results of elementary analysis, and the UV spectral data for the compounds obtained in this study are presented in Table 1.

The compounds obtained in this study that were also previously described in the literature were identified by means of authentic samples from their IR and UV spectra, chromatographic behavior, and mixed melting-point determinations.

General Method for the Preparation of 2-Acetamido(amino)pyrimidines. A solution of 0.010 mole of the α,β-unsaturated carbonyl compound in 5 ml of DMSO and 4 g of freshly calcined molecular sieves* were added slowly with shaking to a solution of 0.011 mole of acetylguanidine (guanidine or its salts) in 10 ml of DMSO, after which the mixture was heated at the appropriate temperature for 8-9 h in a stream of dry air. The resulting brown solution was decanted from the sieves and allowed to stand for 3-4 days. Subsequent workup of the reaction mixture and isolation of the 2-acetamido(amino)pyrimidines were accomplished by various methods depending on their properties.

2-Acetamido-4,6-diphenylpyrimidine (I). A) This compound was obtained from acetylguanidine and benzalacetophenone at a bath temperature of 130-140°. The precipitate was removed by filtration. An additional amount of product was isolated by vacuum evaporation of the filtrate and treatment of the residue with a small amount of cold acetone. The substance was recrystallized twice from ethanol prior to analysis.

B) A mixture of 1.24 g (0.005 mole) of 2-amino-4,6-diphenylpyrimidine and 4-5 ml of acetic anhydride was heated on an oil bath at 120° for 2 h, after which it was cooled, and the precipitated crystals were removed by filtration to give 1 g (69%) of product.

2-Acetamido-4-methyl-6-phenylpyrimidine (II). This compound was obtained from acetylguanidine and benzalacetone at a bath temperature of 135°. Half of the solvent was removed by vacuum evaporation, and the residue was poured into 250 ml of water. The aqueous solution was extracted with five 50-ml portions of chloroform, the extract was dried over magnesium sulfate, and the chloroform was evaporated. Acetone (4-5 ml) was added to the residue, the mixture was allowed to stand for a long time in a refrigerator, and the resulting precipitate was removed by filtration to give 0.93 g of the product, which was recrystallized from ethanol.

*Grade 4A and 5A molecular sieves in the forms of granules activated by heating at 350° for 6-7 h were used in this study.

2-Acetamido-4-phenylpyrimidine (III). A) This compound was obtained from acetylguanidine and cinnamaldehyde at a bath temperature of 130-140°. The product was isolated as in the preparation of I and was recrystallized twice from ethanol prior to analysis.

B) A mixture of 0.87 g (0.005 mole) of 2-amino-4-phenylpyrimidine and 3 ml of acetic anhydride was heated on an oil bath at 120° for 2 h. The precipitated needles of III were removed by filtration to give 0.89 g (75%) of product.

2-Acetamido-4-(p-dimethylaminophenyl)pyrimidine (IV). This compound was obtained from acetylguanidine and p-dimethylaminocinnamaldehyde at a bath temperature of 135° and was isolated by the method used to isolate I. The product was recrystallized three times from ethanol prior to analysis.

2-Acetamido-4-(p-nitrophenyl)pyrimidine (V). This compound was obtained from acetylguanidine and p-nitrocinnamaldehyde at a bath temperature of 135° and was isolated by the method used to isolate I. The product was sublimed at a bath temperature of 200-230° and 1 mm (mercury standard) and recrystallized twice from ethanol prior to analysis.

2-Acetamido-4-methylpyrimidine (VI). This compound was obtained from acetylguanidine and crotonaldehyde at a bath temperature of 120-130°. A sample was selected from the reaction mixture and analyzed for its VI content by GLC.* The reaction mixture was poured into 300 ml of water, and the aqueous solution was extracted with five 50-ml portions of chloroform. The extract was dried over magnesium sulfate, the chloroform was evaporated, and the residue was crystallized by storing in a vacuum desiccator. It was then recrystallized from benzene.

2-Acetamidopyrimidine (VII). This compound was obtained from acetylguanidine and freshly distilled acrolein at a bath temperature of 110°. The yield was determined by GLC. The product was isolated by the method used to isolate VI and recrystallized from ethyl acetate.

2-Amino-4,6-diphenylpyrimidine (VIII). This compound was obtained from guanidine carbonate and benzalacetophenone at a bath temperature of 130°. The reaction mixture was poured into 300 ml of water, and the aqueous mixture was extracted with five 60-ml portions of chloroform. The extract was dried over magnesium sulfate, the chloroform was evaporated, and the residue was chromatographed with a column filled with silica gel and elution by ether.

2-Amino-4-methyl-6-phenylpyrimidine (IX). This compound was obtained from guanidine (from 1.05 g of guanidine hydrochloride and an equivalent amount of sodium ethoxide in alcohol with subsequent evaporation of the alcohol) and benzalacetone at a bath temperature of 110°. The reaction time was 4 h. The product was isolated by the method used to isolate VIII and was recrystallized from benzene.

2-Amino-4-phenylpyrimidine (X). A) This compound was obtained from guanidine and cinnamaldehyde at a bath temperature of 130-140°. The bulk of the DMSO was vacuum evaporated, and the residue was dissolved in 15% HCl. The resulting solution was treated with four 40-ml portions of ether to remove impurities, made alkaline to pH 9 with 5% NaOH solution, and extracted with chloroform. The yield was 0.67 g.

B) Guanidine carbonate was condensed with cinnamaldehyde via the method described above to give 0.48 g of X.

C) A 2.13-g (0.010 mole) sample of III was hydrolyzed by refluxing in 50 ml of 15% HCl, after which the solution was cooled, made alkaline to pH 9 with dilute NaOH solution, and extracted with four 50-ml portions of chloroform. Removal of the chloroform by distillation gave 1.70 g (≈100%) of X.

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*Gas–liquid chromatography was carried out with an LKhM-7A chromatograph with a 4-m long column filled with 15% QF-1 on Chromosorb W; the carrier gas was helium, and the flow rate was 60 ml/min at 100-250°.

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PEPTIDES OF AMINONUCLEIC ACIDS

POLYPEPTIDES OF β-(1-PYRIMIDYL)-α-AMINO ACIDS

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Polyamino acids with degrees of polymerization on the order of 9-10 were obtained by polymerization of p-nitrophenyl esters of β-(1-pyrimidyl)-α-alanines. Their hybridization with RNA is demonstrated.

In order to create polymeric physiologically active substances capable of forming associates with nucleic acids we developed methods for the synthesis of polypeptides of β-(1-pyrimidyl)-α-amino acids and studied their properties.

To synthesize the poly[β-(1-uracilyl)-α-alanines] we chose polymerization of their p-nitrophenyl esters. It is well known that the method of activated esters, which makes it possible to obtain polypeptides of regular structure, has found broad application in recent years in peptide chemistry [1]. We have previously described the preparation of N-carbobenzoxy-DL-Willardiine [β-(1-uracilyl)-α-alanine] p-nitrophenyl ester [2]. A similar method was used to obtain N-carbobenzoxy-β-(1-thyminyl)-α-alanine p-nitrophenyl ester. The carbobenzoxy group of the compounds is split out with 33% HBr in glacial acetic acid. The hydrobromides of the p-nitrophenyl esters of (1-uracilyl)amino acids are extremely hygroscopic compounds, and they are therefore used in the polymerization reaction immediately after their preparation. Small amounts of acetic acid impurity do not interfere with the polymerization and catalyze the aminolysis of the p-nitrophenyl esters. The polymerization was carried out in 5 days at room temperature in dimethylformamide (DMF) solution (with the addition of a definite amount of triethylamine) by the methods in [3, 4]. The polypeptides were precipitated from solution by the addition of methylene chloride. In an investigation of the effect of different amounts of triethylamine on the polymerization and on the molecular weight of the polymer obtained it was established that it is not possible to change the degree of polymerization substantially in this way.

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