EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of thin layers or mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CCl_4 were recorded with a Tesla BS-487 spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

Bis(5-methyl-2-furyl)phenylmethane (I). A 0.1-ml sample of 58% $HClO_4$ was added to a refluxing solution of 10 ml (0.1 mole) of benzaldehyde in 80 ml of benzene, 25 ml (0.27 mole) of 2-methylfuran was then added dropwise, and the mixture was refluxed until 1.8 ml of water had been removed by distillation. It was then cooled, washed with 5% sodium carbonate solution, and dried with Na_2SO_4. The solvent was removed, and the residue was fractionated in vacuo with collection of the fraction with bp 163-165°C (4 mm). The yield was 22.9 g (91%). Compounds II-XVIII were similarly obtained. In the synthesis of VI the furan component was added all at once. In the isolation of VII, VIII, XI, XII, and XVIII the residue obtained after removal of the solvent was purified by recrystallization from hexane.

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ACYLATION OF 2-AMINO-5-PHENYL-4-OXAZOLINONE AND 2-AMINO-4-IMIDAZOLINONES

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The acylation of 2-amino-5-phenyl-4-oxazolinone and 2-amino-1-methyl-4-imidazolinone with acetyl chloride in benzene in the presence of triethylamine leads to the formation of 2-acetamido-5-phenyl-4-oxazolinone and 2-acetamido-1-methyl-4-imidazolinone. The acylation of 2-amino-4-imidazolinone under the indicated conditions, as well as with acetic anhydride, gives 1-acetylimidazolidine-2,4-dione. 3-Acetyl-6-methyl-2H-pyran-2,4(3H)-dione (dehydroacetic acid) is formed as a side product in the acylation of 2-amino-4-azolinones with acetyl chloride in benzene in the presence of triethylamine. The IR and PMR spectra of the compounds obtained are presented.

It is known that 2-amino-4-thiazolinone [pseudothiohydantoin (I, X = S, R = H)] reacts readily with acetic anhydride to give a 2-acetyl derivative [1]; however, it is not acylated with acetyl chloride in benzene in the presence of triethylamine [2]. One might have assumed that the lack of a reaction in the latter case is explained by the peculiar acid-base properties of pseudothiohydantoin, which is an amphoteric compound with very weak acid (pK_a 11.7) and base (pK_a 2.1) functions [3]. The low basicity constitutes evidence that this compound is a very weak nucleophile, while the low acidity hinders its activation in acylation via a general-base-catalysis scheme; moreover, the pseudothiohydantoin anion has anomalously low nucleophilicity [2].

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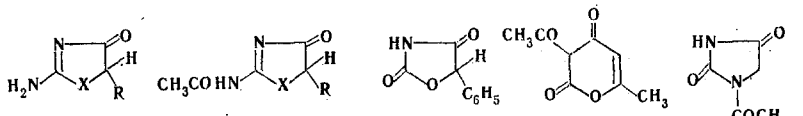

Ia-c IIa, b III IV V

I, II a X = O, R = C_6H_5; b X = NCH_3, R = H; Ic X = NH, R = H

We have established that 2-amino-5-phenyl-4-oxazolinone (pemoline) (Ia) and 2-amino-1-methyl-4-imidazolinone (creatinine) (Ib) react with acetyl chloride in benzene in the presence of triethylamine, as well as with acetic anhydride [4, 5], to give products of acetylation at the exocyclic nitrogen atom (IIa and IIb, respectively). This fact, although it has not been rigorously confirmed by the corresponding quantitative characteristics of the reactivities of the compounds under discussion, does not fit into the framework of the customary concepts. One should expect that the aza and oxa analogs of pseudothiohydantoin would have even lower acidities than pseudothiohydantoin itself [6]. This is evidently (the pK_a values are not presented in the literature) actually the case [7, 8], although, like pseudothiohydantoin [9], pemoline (Ia) is capable of forming a sodium salt [7]. Thus activation of Ia,b by generation of anions in benzene in the presence of triethylamine is even less likely than for pseudothiohydantoin. In addition, the basic properties of pemoline Ia are even more weakly expressed than in the case of pseudothiohydantoin (pK_a 0.90 [10]). Considering the significant difference in the basicities of creatinine (Ib) and 2-amino-4-imidazolinone (glycocyamidine) (Ic) (pK_a 4.84 and 4.80, respectively) and their isosteric analogs pseudothiohydantoin and pemoline (Ia), it may be assumed that the pK_a values presented for Ib,c pertain to protonation at the ring $N_{(1)}$ atom. However, it is known that the pK_a values for the basic ionization of pseudothiohydantoin and pemoline (Ia) pertain to protonation of the $N_{(3)}$ atom of the preponderant tautomeric amino form [3, 11] in which these compounds are also depicted in this paper. The amino form also dominates in the case of creatinine (Ib) and glycocyamidine (Ic) [12], and one should expect that the constants of the protonation of these compounds at the $N_{(3)}$ atom should be of the same order of magnitude as the constant of pseudothiohydantoin or lower. Consequently, if the nucleophilicities of Ia, b, c are judged from the constants of protonation at the ring $N_{(3)}$ atom, the possibility that these compounds should not be stronger nucleophiles than pseudothiohydantoin can be excluded.

Without conducting kinetic investigations there is no doubt that one can draw categorical conclusions in favor of one or another reaction mechanism. However, considering the impossibility of any significant ionization of the examined compounds in benzene in the presence of triethylamine we assume that the reaction under discussion proceeds primarily via a nucleophilic-catalysis mechanism. The observed disparity between the basicities and nucleophilicities of Ia, b on the one hand and pseudothiohydantoin on the other constitutes evidence for the unreliability of the prediction of the reactivities of potentially tautomeric systems on the basis of any characteristic of the preponderant tautomeric form. First, the reactive particle may be a molecule of the other tautomeric form, for which this characteristic (in this case the ionization constant of the neutral molecule) may change in a series of heteroanalogs in a direction opposite to that for the preponderant form. Second, even if the preponderant tautomeric form reacts, "migration of the reaction center," in this case from the ring $N_{(3)}$ nitrogen atom, which is protonated, to the exocyclic nitrogen atom, which is acylated, is always possible. We know nothing about the change in the basicity of the latter in series of I heteroanalogs (X = S, NH, NCH_3, O).

5-Phenyloxazolidine-2,4-dione (III) is obtained in the hydrolysis of the 2-acetyl derivative (IIa) of pemoline. According to data from thin-layer chromatography (TLC), IIa undergoes partial hydrolytic cleavage even upon standing in air. Attempts to transaminate this compound by the method in [4] by heating with diethylamine without a solvent or with aniline in absolute benzene were unsuccessful. According to TLC data, new compounds are not formed in the reaction mixture, and unchanged starting acetyl derivative IIa was isolated from it. 2-Amino-5-phenyl-4-oxazolinone (Ia) and acetanilide were isolated from the reaction mixture when IIa was heated briefly in aniline. Acyl transfer was probably due to the high activity of the acetyl carbonyl group in the IIa molecule as a consequence of the —I and —M effects of the heterocyclic ring [13]. 3-Acetyl-6-methyl-2H-pyran-2,4(3H)-dione (dehydroacetic acid) (IV) is formed as a side product in the acylation of Ia, b under the indicated conditions [14].

Acetyl derivatives of 2-amino-4-imidazolinone (glycocyamidine) (Ic) have not been described. We made an attempt to obtain an acetyl derivative of glycocyamidine Ic by acylation with acetic anhydride and acetyl chloride in benzene in the presence of triethylamine. One should have expected that glycocyamidine Ic would be acylated primarily at the more basic ring $N_{(1)}$ atom. In both cases workup of the reaction mixture gave 1-acetylimidazolidine-2,4-dione (1-acetylhydantoin) (V)[15], which may be obtained as a result of solvolysis of the intermediately formed unstable 1-acetylglycocyamidine, the exocyclic imino group of which is activated by the adjacent acetamido grouping. Compound IV was also obtained in the case of acylation with acetyl chloride.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with Tesla BS-487C (80 MHz) and Tesla BS-497C (100 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with IKS-29 and UR-10 spectrometers. The UV spectra of solutions in ethanol were recorded with an SF-16 spectrophotometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in an ethanol—chloroform system (1:10) with development in UV light (IIa, b, III, and IV) and in iodine vapors (V). The mass spectra of IIa and IV were recorded with an MKh-1303 spectrometer with a system for direct introduction of the samples; the inlet system temperatures were 130 and 70°C, and the ionizing voltage was 70 eV.

2-Acetamido-5-phenyl-4-oxazolinone (IIa). A 10.3-g (0.13 mole) sample of acetyl chloride was added dropwise with vigorous stirring to a mixture of 21.3 g (0.12 mole) of 2-amino-5-phenyl-4-oxazolinone (Ia) and 13.1 g (0.13 mole) of triethylamine in 200 ml of absolute benzene while maintaining the temperature of the reaction mixture at 0-5°C. The mixture was then stirred for 4-5 h with gradual raising of the temperature of the reaction mixture to the boiling point. The next day, the triethylamine hydrochloride and unchanged Ia were removed by filtration, the solvent was removed from the filtrate by distillation, and the oily residue was separated by adsorption column chromatography with a column (with a volume of 100 cm^3) packed with silica gel (Silpearl 100/250μ, Czechoslovakian SSR) by elution with chloroform. The residue was applied to the column in the form of a solution in chloroform mixed with the adsorbent. The fractions were detected by means of TLC. The corresponding eluates were evaporated. The last fractions yielded 1.5 g (5%) of IIa with mp 194-196°C (mp 194°C [4]). IR spectrum: 3210, 3080, 3045, 2955, 2900 sh, 2835, 1760, 1700, 1600, and 1485 cm^{-1}. The UV spectrum changed with time. PMR spectrum (in d_6-DMSO): 12.14 (1H, s, NH), 7.50 (5H, m, C_6H_5), 6.14 [1H, s, $C_{(5)}H$], and 2.40 ppm (3H, s, CH_3). Found: C 60.9; H 4.8; N 13.1%; M 217, $C_{11}H_{10}N_2O_3$. Calculated: C 60.6; H 4.6; N 12.8%; M 218.02. No melting-point depression was observed for a mixture of a sample of this product with a sample of IIa obtained by the method in [4].

2-Acetamido-1-methyl-4-imidazolinone (IIb). This compound, with mp 123-124°C (mp 124-125°C [5]), was similarly obtained in 25% yield from 2-amino-1-methyl-4-imidazolinone (Ib). IR spectrum: 3200, 2950, 2910, 1785, 1755, 1625, and 1595 cm^{-1}. UV spectrum, λ_{max} (log ε): 223 (3.44) and 255 nm (3.60). PMR spectrum (in d_6-DMSO): 3.98 [2H, s, $C_{(5)}H_2$], 2.94 [3H, s, $N_{(1)}$—CH_3], and 1.96 ppm (3H, s, CH_3CO). Found: C 46.4; H 5.8; N 27.2%. $C_6H_9N_3O_2$. Calculated: C 46.4; H 5.8; N 27.1%. No melting-point depression was observed for a sample of this compound with a sample of IIb obtained by the method in [5].

1-Acetylimidazolidine-2,4-dione (V). A) A 5.0-g (0.05 mole) sample of 2-amino-4-imidazolinone (Ic) was heated at 65-70°C in 10 ml of acetic anhydride for 2 h, and the resulting reaction mass was poured into 150 ml of ether. The ether mixture was maintained at 0°C for 2 h, and the resulting precipitate was crystallized from ethanol to give 1.45 g (20%) of a product with mp 141-143°C (mp 143-144°C [15]). IR spectrum: 3240, 3125, 1825, 1795, 1750, and 1675 cm^{-1}. No absorption maxima were present in the UV spectrum below 220 nm. PMR spectrum (in d_6-DMSO): 4.20 [2H, s, $C_{(5)}H_2$] and 2.38 ppm (3H, s, CH_3). Found: C 42.7; H 4.6; N 19.5%. $C_5H_6N_2O_3$. Calculated: C 42.3; H 4.3; N 19.7%.

B) Compound V, with mp 140-142°C (from benzene), was obtained in 9% yield by the method used to prepare IIa, b. Found: C 42.5; H 4.2; N 20.2%. $C_5H_6N_2O_3$. Calculated: C 42.3; H 4.3; N 19.7%. The spectral characteristics were similar to those for the sample obtained by method A. No melting-point depression was observed for a mixture of samples obtained by methods A and B.

3-Acetyl-6-methyl-2H-pyran-2,4(3H)-dione (Dehydroacetic Acid) (IV). This compound was isolated from the first fractions of the eluate in the preparation of IIa, b and V by acylation of the corresponding 2-amino-4-azolinones (Ia-c) with acetyl chloride in benzene in the presence of triethylamine. The product was obtained in 10% yield (with respect to acetyl chloride) and had mp 110-111°C (mp 108.5-109°C [14] and 104-110°C [16, 17]). IR spectrum: 3090, 2930, 2810, 1720, 1710, 1645, 1620 sh, 1570 sh, 1550, and 1450 cm^{-1}. UV spectrum, λ_{max} (log ε): 224 (4.06) and 308 nm (4.10) [18]. PMR spectrum (in CCl_4): 5.76 [1H, s, $C_{(3)}H$], 5.38 (OH), 2.55 (3H, s, CH_3), and 2.20 ppm (3H, s, CH_3). PMR spectrum (in d_6-DMSO, 80 MHz): 6.22 [1H, s, $C_{(3)}H$], 2.44 (3H, s, CH_3), and 2.20 ppm (3H, s, CH_3). Found: C 57.3; H 4.2; N 8.0%. $C_8H_8O_4$. Calculated: C 57.1; H 4.8%; M 168.15.

5-Phenyloxazolidine-2,4-dione (III). A 0.22-g (1 mmole) sample of IIa was refluxed in water for 1 h, after which the mixture was cooled, and the precipitated III was crystallized from water to give 0.09 g (50%) of a product with mp 111°C (mp 111-112°C [19]). IR spectrum: 3300 and 1830 cm^{-1}. No absorption maxima were present in the UV spectrum below 215 nm. PMR spectrum (in d_6-DMSO): 12.32 (1H, s, NH), 7.64 (5H, m, C_6H_5), and 6.24 ppm [1H, s, $C_{(5)}H$]. Found: C 61.3; H 4.2; N 8.0%. $C_9H_7NO_3$. Calculated: C 61.0; H 4.0; N 7.9%.

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