1-Benzyl-4-methyl-5-cyano-6-(di-n-butylamino)-7-azaindole (If) was synthesized as described in the preceding experiment. The residue after evaporation of xylene was placed on a column (30 mm diameter, 20 cm high) with 90 g of 40/100 μ silica gel. The column was washed with 100 ml of hexane and 300 ml of 9:1 hexane–benzene, and 1.6 g of If was eluted.

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SYNTHESIS AND SOME REACTIONS OF 4-NITRO DERIVATIVES OF IMIDAZO[4,5-c]PYRIDIN-2-ONES

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Imidazo[4,5-c]pyridine and its N-methyl derivatives do not undergo nitration, but the 2-oxo derivatives of these compounds are easily nitrated when heated. Some properties of the resulting 4-nitroimidazo[4,5-c]pyridin-2-ones have been studied.

The introduction of a nitro group into the imidazo[4,5-c]pyridine molecule has not been previously studied. However, work in this direction is of considerable importance in developing the chemistry of this heterocycle.

We have shown that imidazo[4,5-c]pyridine (I) and its 1- and 3-methyl substituted derivatives (II, III) are inert to nitrating mixtures. These compounds do not change when treated with nitric acid or potassium nitrate in concentrated sulfuric acid and high-strength oleum at temperatures up to 200°. The same result was obtained after heating the dinitrate of base I with gaseous sulfur trioxide at 100°. For this reason it was of interest to carry out the nitration of 2-oxo derivatives of compounds I-III, especially because with the analogous substituted imidazo[4,5-b]pyridines the strong activating effect of the oxo group appears in this reaction [1].

Nitration of 1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVa) with nitrating mixture proceeds at about 100° to form the mononitro derivative in almost quantitative yield. For example, the PMR spectrum of the product in CF_3COOH solution (Table 1) has two doublets of aromatic protons (8.03 and 8.63 ppm), the spin–spin coupling constants (SSCC) of which, at 6.5 Hz, unambiguously demonstrate their vicinal location; this is possible only in 4-nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Va). In the spectrum of 7-nitroimidazo[4,5-c]-pyridin-2-one (VI) the pyridine ring protons do not show spin–spin coupling.

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TABLE 1. PMR Spectra of Newly Synthesized Compounds

Compound	Solvent	Chmeical shift, δ, ppm				SSCC, Hz
		$C_{(4)}$	$C_{(6)}$	$C_{(7)}$	N- and O-alkyl groups	
Va	CF_3COOH	—	8,63 (d, 1H)	8,03 (d, 1H)		$J_{67}=6,5$
	DMSO-D_6	—	8,47 (d, 1H)	7,87 (d, 1H)		$J_{67}=5,0$
Vb	CF_3COOH	—	8,73 (d, 1H)	7,97 (d, 1H)	3,82 (s, 3H, $N_{(1)}$—CH_3)	$J_{67}=5,4$
	DMPA-D_7	—	8,19 (d, 1H)	7,56 (d, 1H)	3,43 s, 3H, $N_{(1)}$—CH_3)	$J_{67}=5,2$
Vc	CF_3COOH	—	8,68 (d, 1H)	8,15 (d, 1H)	4,02 (s, 3H, $N_{(3)}$—CH_3)	$J_{67}=5,0$
	DMSO-D_6	—	8,08 (d, 1H)	7,38 (d, 1H)	3,33 (s, 3H, $N_{(3)}$—CH_3)	$J_{67}=5,2$
Vd	CF_3COOH	—	8,63 (d, 1H)	7,87 (d, 1H)	3,95 (s, 3H, $N_{(3)}$—CH_3); 3,77 (s, 3H, $N_{(1)}$—CH_3)	$J_{67}=6,3$
	DMSO-D_6	—	8,20 (d, 1H)	7,63 (d, 1H)	3,42 (s, 3H, $N_{(1)}$—CH_3); 3,38 s, 3H, $N_{(3)}$—CH_3)	$J_{67}=5,2$
VI [5]	CF_3COOH	9,40 (, 1H)	9,00 (s, 1H)	—		$J_{45}=0$
VII a	CF_3COOH	—	7,86 d, 1H)	7,09 d, 1H)		$J_{67}=6,9$
VII b	CF_3COOH	—	7,74 d, 1H)	6,94 (d, 1H)	3,60 (s, 3H, $N_{(1)}$—CH_3)	$J_{67}=7,0$
VII c	CF_3COOH	—	7,76 (d, 1H)	7,04 (d, 1H)	3,87 (s, 3H, $N_{(3)}$—CH_3)	$J_{67}=6,9$
VII d	CF_3COOH	—	7,78 (d, 1H)	7,03 (d, 1H)	3,89 (s, 3H, $N_{(3)}$—CH_3); 3,63 (s, 3H, $N_{(1)}$—CH_3)	$J_{67}=6,9$
VIII b	CF_3COOH	—	8,02 (d, 1H)	7,34 (d, 1H)	3,80 (s, 3H, $N_{(3)}$—CH_3); 3,65 (s, 3H, $N_{(1)}$—CH_3); 4,49 (s, 3H, O—CH_3)	$J_{67}=7,0$
VIII c	CF_3COOH	—	7,98 (d, 1H)	7,31 (d, 1H)	3,82 (s, 3H, $N_{(3)}$—CH_3); 3,66 (s, 3H, $N_{(1)}$—CH_3); 4,76 (q, 2H, O—CH_2—); 1,70 (t 3H, C—CH_3)	$J_{67}=7,1$ $J_{\alpha\beta}=6,8$
VIII d	CF_3COOH	—	7,98 (d, 1H)	7,31 (d, 1H)	3,85 (s, 3H, $N_{(3)}$—CH_3); 3,66 s, 3H, $N_{(1)}$—CH_3); 4,63 (t, 2H, O—CH_2—); 2,06 (m, 2H, C—CH_2—C); 1,17 (t, 3H, C—CH_3)	$J_{67}=6,6$ $J_{\alpha\beta}=6,4$ $J_{\beta\gamma}=7,4$
VIII e	CF_3COOH	—	8,01 (d, 1H)	7,31 (d, 1H)	3,77 s, 3H); $N_{(3)}$—CH_3); 3,60 (s, 3H, $N_{(1)}$—CH_3); 4,67 (t, 2H, O—CH_2—); 2,13—1,40 (m, 4H, C—CH_2—CH_2—C); 1,01 (t, 3H, C—CH_3)	$J_{67}=6,8$ $J_{\alpha\beta}=5,6$ $J_{\gamma\delta}=6,0$

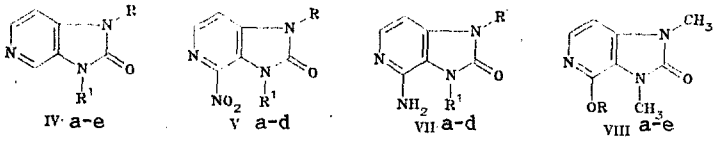
Analogously to the formation of Vb, the 1-methyl derivative of base Iva also nitrates (IVb) [2]. But the introduction of a nitro group into 3-methylimidazopyridin-2-one (IVc) requires more severe conditions; the reaction goes at 125-130° to give 4-nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Vc) in good yield. The PMR spectra of Vb, c resemble that of Va, and are distinguished from it by the N-methyl signals (Table 1). It is important to note that aside from the substances mentioned, no nitro derivatives of other structure could be detected in the nitration products of bases IVa-c. All this indicates that the reaction under consideration is highly selective. Of the two free α-positions in the pyridine ring of IVa-c, only $C_{(4)}$ undergoes attack by a nitrating agent. Even in the case of IVc, where the $N_{(3)}$-methyl group shields the reaction center, the 4-nitro derivative forms. Further increase in the shielding effect of the $N_{(3)}$ substituent, e.g., in 3-ethylimidazo[4,5-c]-pyridin-2-one (IVe), stops the reaction at position 4 completely, but it does not promote the entrance of the nitro group at the other unoccupied α-position of the pyridine ring, viz., at $C_{(6)}$.

TABLE 2. 4-Substituted Imidazo[4,5-c]pyridin-2-ones

Compound	mp*, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Va	400	39,8	2,5	31,0	$C_6H_4N_4O_3$	40,0	2,2	31,1	98 (A), 99 (B)
Vb	309—310	43,6	3,3	29,1	$C_7H_6N_4O_3$	43,3	3,1	28,9	93 (A), 96 (B)
Vc	274—275	43,1	2,9	28,7	$C_7H_6N_4O_3$	43,3	3,1	28,9	77 (B)
Vd	225	46,1	4,0	27,1	$C_8H_8N_4O_3$	46,2	3,9	26,9	90 (A), 96 ( )
VIIa	309—310	47,8	3,9	37,2	$C_6H_6N_4O$	48,0	4,0	37,3	99,9 (B)
VIIb	360	50,9	5,2	33,8	$C_7H_8N_4O$	51,2	4,9	34,1	99,9
VIIc	242—243	51,0	5,3	33,7	$C_7H_8N_4O$	51,2	4,9	34,1	96
VIId	240	53,8	5,8	31,1	$C_8H_{10}N_4O$	53,9	5,7	31,4	92 (A), 82 ( )
VIIIa	310—311	53,9	5,2	23,3	$C_8H_9N_3O_2$	53,6	5,1	23,5	80
VIIIb	144—145	55,9	5,8	21,7	$C_9H_{11}N_3O_2$	55,9	5,7	21,8	99,9
VIIIc	78—79	58,1	6,4	20,2	$C_{10}H_{13}N_3O_2$	58,0	6,3	20,3	95
VIIId	75—76	59,8	6,8	18,9	$C_{11}H_{15}N_3O_2$	59,7	6,8	19,0	94
VIIIe	50—51	61,2	7,2	18,0	$C_{12}H_{17}N_3O_2$	61,3	7,3	17,9	85

*Compounds VIIa,c recrystallized from water, Va from DMPA, Vb from water or ethanol, Vc from nitromethane, Vd, VIId from ethanol, VIIIa from water or nitromethane, VIIIb-e from hexane, VIIb was reprecipitated from weak acid solution by ammonia.

The nitro compounds Va-c (Table 2) are high melting and insoluble in many solvents. Since they are weak acids, however, they dissolve readily in aqueous alkali to give yellow solutions. When such solutions are treated with dimethyl sulfate at room temperature, a compound forms with mp 224-225° in high yield that is insoluble in alkali but soluble in alcohol; its PMR spectrum contains methyl signals (3.78 and 3.96 ppm in CF_3COOH). This material is also obtained with bases Vb, c are methylated with diazomethane in nitromethane medium. We therefore assign this compound the structure of 4-nitro-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Vd).



IV a-e V a-d VII a-d VIII a-e

IV, V, VII a, b e R=H, b, d R=CH_3; a, b R^1=H, c, d R^1=CH_3, e R^1=C_2H_5;
VIII aR=H, b R=CH_3, c R=C_2H_5, dR=n-C_3H_7, e R=n-C_4H_9

All the nitro compounds V are easily converted to the respective amines VIIa-d by such reducing agents as iron, sodium sulfide, hydrazine, and hydroiodic acid. The two latter reagents give especially good results. Moreover when Va-d are reduced by hydrazine hydrate no catalyst is needed and the amine yields approach quantitative [3].

4-Nitro-1,3-dimethylimidazo[4,5-c]pyridin-2-one, Vd, can replace the nitro group by a hydroxy or alkoxy group, similar to what occurs with 2- and 4-nitropyridines [4]. Such a conversion is easily carried out by heating Vd with water or the appropriate alcohol in the presence of alkali. The properties of the resulting 4-hydroxy- and 4-alkoxy-1,3,-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-ones (VII) are shown in Table 2. In the PMR spectra of bases VIIIb-e, besides the coublets of the aromatic protons at positions 6 and 7 and the N-methyl singlets, the signals of the O-alkyl hydrogens also appear (Table 1).

EXPERIMENTAL

PMR standards were obtained on Tesla BS-467 (60 MHz) and Varian XL-100/15 (100 MHz) instruments; internal standard, TMS.

The properties of V, VII, and VIII are shown in Table 2.

Reaction of Nitrating Mixture with Imidazo[4,5-c]pyridine (I) [6] and Its 1- and 3-Methyl Derivatives (II, III) [7]. A. A mixture of 0.36 g (3 mmole) of compound I, 2.1 g of H_2SO_4 (d 1.86) and 0.6 g (9.5 mmole) of HNO_3 (d 1.50) was heated in a sealed glass tube at 170-180° for 5 h. The contents of the tube were poured on ice and neutralized with po-

tassium hydroxide to pH 6-7. The colorless precipitate was filtered off, dried, and recyrstallized from dioxane. There was isolated 0.3 g (85%) of the starting compound, mp 167-168°.

B. A mixture of 2.38 g (20 mmole) of base I and 2.2 ml of HNO_3 (d 1.35) was evaporated on a boiling water bath, and the residue was recrystallized from 2 N HNO_3. There was obtained 4.4 g (90%) of the dinitrate of I (prisms), mp 220-221° (with decomposition). Found: C 29.3; H 3.0; N 28.6%. $C_6H_5N_3 \cdot 2HNO_3$. Calculated: C 29.4; H 2.9; N 28.6%.

A mixture of 2.5 g (10 mmole) of I dinitrate and 6 g of 60% oleum, prepared at 2-5°, was heated in a sealed tube at 100° for 2 h. After cooling the contents of the tube were poured on ice and neutralized to pH 6 with sodium carbonate solution. The precipitate was filtered off, dried, and recrystallized from dioxane to give 0.8 g (67%) of imidazopyridine I, mp 167-168°. The mother-salt solution was evaporated almost to dryness and washed with boiling alcohol (3 × 20 ml). The aqueous alcohol solution was evaporated to dryness, the residue was washed twice with hot alcohol, and the extract was evaporated. Recrystallization from dioxane gave an additional 0.30 g (25%) of I, mp 165-167°.

C. Into the inner tube of a straight Liebig condenser held horizontal was placed 1 g (4 mmole) of imidazo[4,5-c]pyridinium dinitrate, and gaseous sulfur trioxide was introduced while water vapor at 100° was passed through the jacket. After 2 h heating the tube contents were dissolved in 5 ml of water, and the solution was neutralized to pH 6 and evaporated to dryness. The solid residue was washed with alcohol (3 × 5 ml), the solution was evaporated to dryness, and the residue was recrystallized from dioxane. There was obtained 0.44 g (94%) of compound I, mp 168-169° (according to [6], mp 169-170°).

In all the experiments the isolated base samples did not depress the mp in a mixture with an authentic sample of I.

The ability of 7-nitroimidazo[4,5-c]pyridine (IX) [8] and similar nitro compounds to give an intense yellow color in alkaline medium was used for the qualitative detection of small amounts of nitration products of compound I. In no test did alkalization of reaction mixture, mother liquors, or unpurified unreacted I give a yellow color, or give reason to speak of the presence of nitro compounds.

D. A mixture of 0.27 g (2 mmole) of base II, 1.80 ml of H_2SO_4 (d 1.86), and 0.33 ml of HNO_3 (d 1.50) was heated in a sealed tube at 200° for 4 h. After cooling the mixture was poured on ice and made strongly alkaline with 40% sodium hydroxide solution. The oil that separated crystallized when cooled. The precipitate was filtered off and dried. Recrystallization from 1:1 benzene–hexane gave 0.22 g (81%) of starting compound II, mp 111-112° (according to [7], mp 111.5-112.5°).

Nitration of 3-methylimidazopyridine III was attempted under similar conditions. After the mixture was heated, 88% of the starting compound was separated, mp 101-102° (from benzene) (according to [7], mp 101-101.5°).

4-Nitro-3,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Va). A. To a solution of 2.0 g (14.8 mmole) of base IVa [5] in 8 ml of concentrated H_2SO_4 was added 1.50 g (14.8 mmole) of potassium nitrate in 8 ml of concentrated H_2SO_4 with cooling in ice, and the mixture was heated for 3 h at 100°. The mixture was cooled, poured on ice, and neutralized with aqueous ammonia. The precipitate was filtered off, washed with water and dried. Yield, 2.6 g.

B. To a solution of 60.0 g (440 mmole) of base IVa in 220 ml of concentrated H_2SO_4 was added a mixture of 52 ml of HNO_3 (d 1.50) and 52 ml of concentrated H_2SO_4 dropwise at 4-5°. After being held at room temperature for 0.5 h the reaction mixture was heated for 2 h in a boiling water bath. The cooled mixture was poured on 1 kg of ice and neutralized with dry ammonium carbonate, and finally with ammonia to pH 5. The precipitate was filtered off, washed with cold water, and dried. Yield, 79.2 g.

4-Nitro-1-methyl- and 4-nitro-3-methyl-1,3,-dihydro-2H-imidazopyridines (Vb and Vc) were obtained similarly, but in [5] compound IV was nitrated at 125-130°.

4-Nitro-1,3,-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Vd). A. To a mixture of 1.0 g (5.5 mmole) of compound Va and 0.8 g (14.3 mmole) of potassium hydroxide in 13.5 ml of water was added 1.3 ml (13.4 mmole) of dimethyl sulfate dropwise with vigorous stirring, at such a rate that the temperature of the reaction mixture did not exceed 30-32°. After 10-15 min a precipitate formed. The mixture was stirred another 0.5 h at room temperature, 1 ml of 8% KOH solution and 0.6 ml (6.2 mmole) of dimethyl sulfate were added, and

the mixture was kept for 1 h. Then another 1 ml of 8% KOH was added, and the mixture was left overnight. The precipitate was filtered off, washed with water, and dried. Yield, 1.04 g.

B. To a suspension of 0.32 g (1.65 mmole) of compound Vb in a solution of 0.16 g (4.0 mmole) of NaOH in 30 ml of water was added 0.40 ml (4 mmole) of dimethyl sulfate dropwise with stirring. After holding for 0.5 h, a solution of 0.2 g of sodium hydroxide in 2 ml of water, and 0.40 ml of dimethyl sulfate were added and the mixture was left overnight. The bright yellow precipitate was filtered off, washed with water, and dried. Yield, 0.17 g (50%).

C. Into a suspension of 0.20 g (1 mmole) of compound Vb in 1.5 ml of nitromethane was poured 1.2 ml of a 4% ether solution of diazomethane and the mixture was held for 1 day at 10-15°. After the ether was distilled off the residue was recrystallized from alcohol. Yield, 0.16 g (76%).

D. A suspension of 0.20 g (1 mmole) of nitro compound Vc in 1 ml of nitromethane was methylated with 1.3 ml of 4% ether solution of diazomethane as described in method C. Yield, 0.18 g (84%).

E. To a solution of 0.40 g (2 mmole) of compound Vc in 4.2 ml of 6% NaOH solution was added 0.65 ml (6.9 mmole) of dimethyl sulfate dropwise with stirring. After holding for 1 h at room temperature, 1 ml of 8% NaOH was added and the mixture was stirred another 3 h. The precipitate was filtered off, washed with 5% NaOH, and dried. Yield, 0.41 g. The material did not depress the melting points of the methylation products obtained by the methods described above.

4-Amino-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (VIIa). A. A solution of 0.50 g (2.8 mmole) of compound Va in a mixture of 4 ml of alcohol, 2 ml of water, and 5 drops of concentrated HCl was heated to boiling; 1.0 g (18 mmole) of pulverized carbonyl iron was added in portions with vigorous stirring, and the mixture was boiled for 6 h. The precipitate was filtered off and washed with hot water (3 × 2 ml), and the filtrate was evaporated to half its volume and alkalized with 20% NaOH solution. The precipitate was filtered off, washed with water, and dried. Yield, 0.25 g (60%).

B. A mixture of 1.0 g (5.5 mmole) of Va, 10 ml of hydroiodic acid (d 1.7), and 1.0 g (32 mmole) of red phosphorus was boiled for 4 h. The phosphorus was filtered off, and the filtrate was evaporated to 1/3 its starting volume and alkalized with aqueous ammonia to pH 8. The precipitate was filtered off, washed with a minimal amount of cold water, and dried. Yield, 0.75 g (91%).

C. A mixture of 1.80 g of Va and 10 ml (200 mmole) of hydrazine hydrate was heated at the boiling point for 2 h. The solution was evaporated to dryness and the residue was recrystallized from water. Yield, 1.50 g. This amine did not depress the melting point of samples obtained by methods A and B.

4-Amino-1-methyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (VIIIB) was obtained by method C from 1.95 g (10 mmole) of Vb and 15 ml (300 ml) of hydrazine hydrate. Yield, 1.64 g.

4-Amino-3-methyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (VIIc) was obtained by boiling a mixture of 1.95 g (10 mmole) of Vc and 20 ml of hydrazine hydrate. Yield, 1.58 g.

4-Amino-1,3-dimethyl-1,3-dihydro-2H-imidazo 4,5-c pyridin-2-one (VIId). A. It was obtained similarly to amine VIIa by method C from 2.08 g (10 mmole) of Vd and 15 ml of hydrazine hydrate. Yield, 1.64 g.

B. A mixture of 1.0 g (4.8 mole) of Vd, 20 ml of 45% hydroiodic acid, and 1.0 g (32 mmole) of red phosphorus was boiled for 4 h. The phosphorus was filtered off, and the filtrate was evaporated to 1/3 its original volume and alkalized with 20% NaOH solution. The reaction product was extracted with chloroform (3 × 5 ml). Yield, 0.71 g.

4-Hydroxy-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (VIIIa). A mixture of 2.1 g (10 mmole) of Vd and 70 ml of 5% NaOH solution was heated at the boiling point for 4 h. After cooling the solution was neutralized with concentrated HCl and evaporated to dryness. The reaction product was extracted from the residue by methanol (3 × 8 ml) and the solvent was evaporated. Yield, 1.54 g.

4-Alkoxy-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-ones (VIIIb-e). To the solution obtained by heating 0.15 mole of NaOH (or KOH) in 1.8-2.0 mole of the appropriate alcohol was added 0.1 mole of Vd, and the mixture was boiled for 2-4 h. The sodium (or potassium) nitrate precipitate was filtered off, excess alcohol was distilled from the filtrate the reaction product was extracted with hot chloroform (50-60 ml) and the solvent was evaporated.

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SYNTHESIS OF N_6-SUBSTITUTED ADENINYL-9-β-D-GLUCOFURANURONOSIDES

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N_6-substituted adeninyl-9-β-D-glucofuranuronosides have been obtained by the condensation of trimethylsilylated 6-aminopurines with 1,2,5-tri-O-acetyl-β-D-glucofurano-6,3-lactone. The structure of the glucuronides was demonstrated by the UV, IR, and PMR spectra.

For the synthesis of nucleosidic derivatives of kinetine (6-furfurylaminopurine) and other 6-substituted adenines, mainly the amination of 6-chloro- and 6-methylmercaptopurine nucleosides has been used [1-4]; only in individual cases [5] has glycosylation of a 6-substituted adenine with a carbohydrate fragment been used.

The purpose of the present work was to synthesize potential cytokinines in the 6-substituted adenine glucuronide series. Attempts to use 1-(6-chloro- or 6-methylmercaptopurinyl-9)-β-D-glucofuranosides that we had previously synthesized [6] to obtain these compounds were unsuccessful, due to the instability of the glycoside bond and the lactone ring under the reaction conditions. We therefore synthesized the compounds by condensation of the trimethylsilyl derivatives of 6-methylamino- (IIa), 6-butylamino- (IIb), 6-cyclohexylamino- (IIc), 6-benzylamino- (IId), 6-morpholino- (IIe), and 6-furfurylaminopurine (IIf) with 1,2,5-tri-O-acetyl-β-D-glucofurano-6,3-lactone (III) [7] in 1,2-dichloroethane in the presence of the condensing agent trimethylsilyltrifluoromethanesulfonic acid (TMS-TF), which is more reactive than $SnCl_4$ which we used previously [6, 8].

When the reaction was carried out at 80° for 12 h (II:III:TMS-TF 1.1:1.0:1.2 moles), the principal product was the N_9-β-D-glucofuranoside of N_6-substituted purines (IVa-f). The TLC data bear witness that other nucleosidic products are formed in the reaction (not more than

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