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INTRAMOLECULAR CYCLIZATION OF 5-AMINO-4-BIS(β-CHLOROETHYL)AMINO-PYRIMIDINES

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4-R-5,6,7,8,9,10-Hexahydroimidazo[1,2,3-i,j]pteridinium chlorides and 4-R-7-(β-chloroethyl)-7,8-dihydroimidazo[1,2-c]pyrimidinium chlorides were obtained in the reaction of 6-R-5-amino-4-bis(β-hydroxyethyl)aminopyrimidines (R = H, Cl) with $SOCl_2$ or $POCl_3$. The pteridinium chlorides are formed through cyclization of the intermediately formed 4-R-8-(β-chloroethyl)-5,6,7,8-tetrahydropteridines, which, for R = Cl, were obtained independently by reduction of 4-chloro-6-bis-(β-chloroethyl)amino-5-nitropyrimidine. The conditions for the cyclization of imidazopyrimidinium chlorides to give imidazopteridinium chlorides were investigated.

It has been shown that the cyclization of N,N-bis(β-chloroethyl)-o-phenylenediamine leads to benzo[b]-1,4-diazabicyclo[2.2.2]octene [1], whereas N-haloalkyltetrahydroquinoxalines are converted under similar conditions either to benzodiazabicycloalkenes [2, 3] or to tetrahydropyridoquinoxalines through intramolecular C alkylation [3]; the formation of condensed heterocyclic systems that contain five-membered rings was not observed. In this connection, it seemed of interest to investigate the possibility and direction of the intramolecular cyclization of 5-amino-4-bis(β-chloroethyl)aminopyrimidines that contain a heteroatom adjacent to a chloroethylamino group. The literature contains a rather large amount of data on the chemical properties of 4(6)-haloalkylaminopyrimidines, and the case of cyclization at the pyrimidine nitrogen atom to give dihydroimidazo[1,2-c]- [4-14] and tetrahydropyrimido[1,2-c]pyrimidine [12-14] systems is particularly noted. However, in individual cases [15] in the cyclization of compounds that contain two nucleophilic centers for attack by the chloroethylamino group, viz., ring (pyrimidine) and exocyclic (5-amino group) nitrogen atoms, the formation of a 5,6,7,8-tetrahydropteridine system occurs exclusively due to the presence of a bulky substituent in this group.

We realized the synthesis of the starting diaminopyrimidines for the preparation of previously undescribed 4-bis(β-chloroethyl)aminopyrimidines with an amino group in the 5 position via the scheme presented above.

The amination of 4,6-dichloro-5-nitropyrimidine (I) [16, 17] with a stoichiometric amount of diethanolamine proceeds smoothly to give 4-chloro-6-bis(β-hydroxyethyl)amino-5-nitropyrimidine (II), the reduction of which on Raney nickel leads to 4-chloro-5-amino-6-

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TABLE 1. PMR and UV Spectra of II-XII

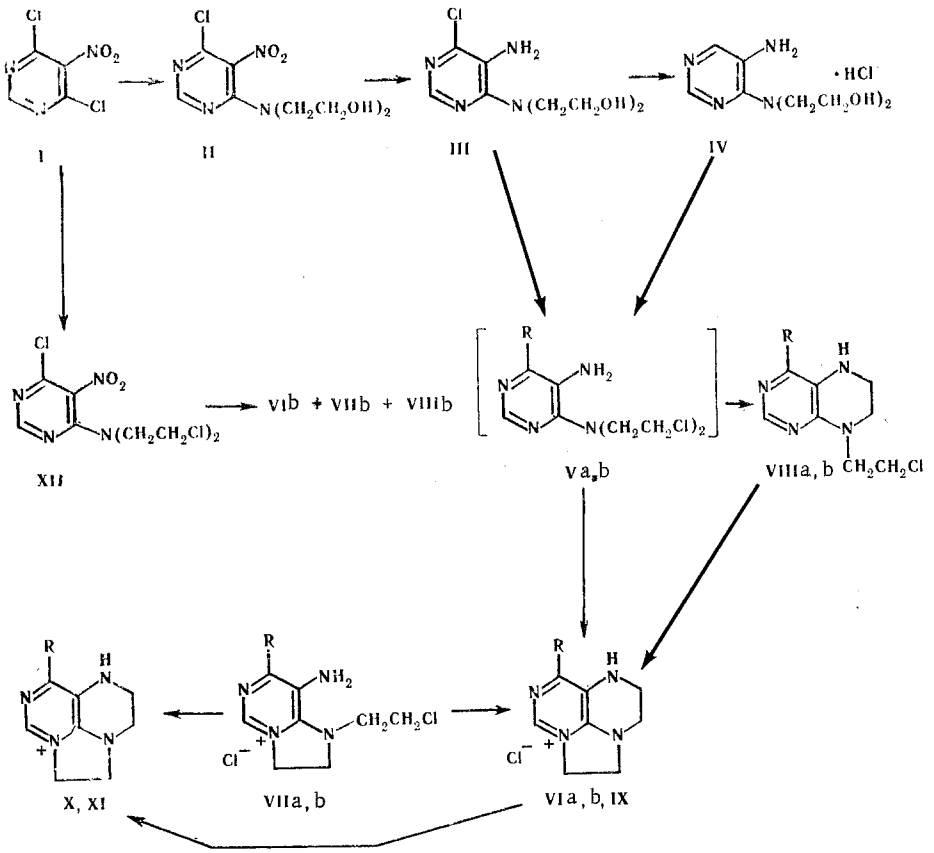
Compound	PMR spectrum, δ, ppm: solvent	signals of methylene protons [multiplicity, J (Hz)]	pyrimidine protons: 2-H	pyrimidine protons: 4-H	signals of other protons	intensity ratios	UV spectrum, λ_{max}, nm (log ε)[a]
II	$CDCl_3$	3,44—3,90 (m)	8,34	—	—[b]	10 : 1	206 (4,21), 255 (4,13)
III	The same	3,42—3,92 (m)	7,83	—	4,85—5,21[c]	8 : 1 : 4	214 (4,14), 275 (3,80), 316 (4,00)
IV	D_2O	3,83—4,26 (m)	7,82[d], 8,54[d]		—	8 : 1 : 1	214 (4,01), 323 (3,92)
VIa	d_6-DMSO	3,46, 3,57 (t, 4,8); 4,08, 4,73 (t, 9,5)	7,58,	8,30	7,33[e]	2 : 2 : 2 : 2 : 1 : 1 : 1	211 (4,08), 286 (3,76), 343 (3,78)
VIb	The same	3,49, 3,53 (t, 3,5); 4,08, 4,67 (t, 9,5)	8,26	—	7,21[e]	2 : 2 : 2 : 2 : 1 : 1	206 (4,26), 289 (3,91), 345 (3,95)
VIIa	„ „	3,98, 4,22 (t, 6,5); 4,13, 4,69 (t, 10)	8,03,	8,49	5,78[f]	2 : 2 : 2 : 2 : 1 : 1 : 2	208 (4,19), 274 (3,93), 342 (3,91)
VIIb	„ „	3,98, 4,30 (t, 6,5); 4,20, 4,68 (t, 10)	8,33	—	5,94[f]	2 : 2 : 2 : 2 : 1 : 2	213 (4,21), 280 (3,92), 342 (3,99)
VIIIb	$CDCl_3$	3,18—3,50 (m); 3,56—3,90 (m)	7,88	--	4,09[e]	2 : 6 : 1 : 1	216 (4,38), 289 (3,94), 316 (4,03)
IX	CD_3OD	3,32 (s); 3,88, 4,50 (t, 8)	8,08	—	3,25[g]	4 : 2 : 2 : 1 : 6	227 (4,06), 258 (4,32), 332 (4,01)
X	D_2O	3,60—3,77 (m); 4,28, 4,86 (t, 9)	8,05	—	—	4 : 2 : 2 : 1	208 (4,24), 284 (3,89), 345 (3,92)
XI	The same	3,66, 3,85 (t, 4); 4,39, 4,99 (t, 9)	7,60,	8,71	—	2 : 2 : 2 : 2 : 1 : 1	208 (4,22), 283 (3,87), 345 (3,90)
XII	$(CD_3)_2CO$	3,77—4,14 (m)	8,49	—	—	8 : 1	208 (4,11), 253 (4,07), 348 (3,85)

[a]Compound IX was investigated in the form of the hydrochloride. [b]The signals of the NH_2 and OH protons are superimposed on the signals of the methylene protons. [c]The NH_2 and OH protons. [d]Doublets, J_{4-6} = 1.5 Hz. [e]The NH protons. [f]The NH_2 protons. [g]Dimethylamino group.

TABLE 2. Amino- and Imidazopyrimidines (II-IV, VIIa, XII) and Chloroethyl- and Imidazopteridines (VIa, b, VIIIb, IX-XI)

Compound	mp, °C	R_f (system)	Found, %: C	H	Cl	N	Empirical formula	Calc., %: C	H	Cl	N	Yield, %
II	88—93[b]	0,47 (A)	36,5	4,2	13,7	21,3	$C_8H_{11}ClN_4O_4$	36,6	4,2	13,5	21,3	92
III	89—91[c]	0,35 (A)	41,1	5,4	—	24,0	$C_8H_{13}ClN_4O_2$	41,3	4,2	—	24,3	78
IV	154—156[d]	0,47 (B)	40,9	6,4	15,2	24,3	$C_8H_{15}ClN_4O_2$	40,9	6,4	15,1	23,9	95
VIa	227—230[d, e]	0,20 (B)	40,9	4,9	29,5	—	$C_8H_{11}ClN_4 \cdot HCl$	40,9	5,1	30,2	—	30[f]
VIb	>250[d, e]	0,25 (B)	41,0	5,2	29,6	23,9	$C_8H_{12}Cl_2N_4$	40,9	5,1	30,2	23,8	50[f]
VIIa	180—200[d, e]	0,35 (B)	40,9	4,5	30,4	24,1	$C_8H_{10}Cl_2N_4$	41,2	4,3	30,4	24,0	58[f]
VIIIb	106—107[g]	0,76 (A)	41,4	4,5	30,5	23,4	$C_8H_{10}Cl_2N_4$	41,2	4,3	30,4	24,0	39
IX	190—195[d]	0,35 (B)	43,0	6,1	25,4	25,0	$C_{10}H_{16}ClN_5 \cdot HCl$	43,2	6,2	25,5	25,2	29[f]
X	216—218[d]	0,19 (B)	28,8	4,0	—	16,4	$C_8H_{12}Br_2N_4O$	28,3	3,6	—	16,5	59[h]
XI	222—223,5[d, e]	0,19 (B)	29,7	3,9	—	16,7	$C_8H_{12}Br_2N_4$	29,7	3,7	--	17,3	58
XII	74—76[g]	0,89 (A)	32,3	2,7	--	--	$C_8H_9Cl_3N_4O_2$	32,1	2,7	--	—	68

[a]Compounds VIa and IX were investigated in the form of their hydrochlorides. [b]From chloroform. [c]Twice from acetone. [d]Twice from absolute ethanol. [e]With decomposition. [f]From III and IV in $SOCl_2$. [g]Determined by the method in [18]. [h]From VIIb.



V—VIII a R=H; b R=Cl; IX R=N(CH$_3$)$_2$; X R=OH; XI R=H

bis(β-hydroxyethyl)aminopyrimidine (III). The catalytic dechlorination of pyrimidine III on Pd/C gives 5-amino-4-bis(β-hydroxyethyl)aminopyrimidine hydrochloride (IV) in high yield. It should be noted that attempts to obtain diaminopyrimidine IV by reduction of nitropyrimidine II with hydrogen on Pd/C were unsuccessful — complex multicomponent mixtures were always obtained.

Thionyl chloride and phosphorus oxychloride were used for exchange of the OH group for chlorine in III and IV. A two-component mixture, which was separated by column chromatography, was obtained in the reaction of diaminopyrimidine IV with $SOCl_2$ at room temperature. The compound with a lower chromatographic mobility (system B) contained only ionic chlorine, which contradicted the expected 5-amino-4-bis(β-chloroethyl)aminopyrimidine structure (Va) and made it possible to assume that this compound is the product of its cyclization (VIa). In the PMR spectrum of the compound obtained (see Table 1) the signals of methylene protons show up in the form of four coupled (in pairs) triplets. With respect to their chemical shifts and spin-spin coupling constant (SSCC), the two weak-field triplets corresponding to four protons with an SSCC of 9.5 Hz are similar to the signals of the CH_2CH_2 fragment in dihydroimidazo[1,2-c]pyrimidinium chlorides [13, 14]; the weakest-field signal is related to the CH_2 group bonded to the pyrimidine nitrogen atom. The other two triplets at 3.5 ppm with a lower SSCC are unsymmetrical. Symmetrization of these signals is observed when an additional rf field is superimposed in the region of the broad singlet at 7.33 ppm, which corresponds to one proton. On the basis of these data, it may be concluded that the latter signal is related to the NH group that is bonded to the ethylene bridge and undergoes spin-spin coupling with the protons of the α-CH_2 group. Thus the 5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium chloride structure (VIa), which is in good agreement with the results of elementary analysis for its hydrochloride (see Table 2), can be assigned to the isolated compound. According to the results of elementary analysis, the second compound, which has a higher R_f value and predominates in the mixture, contains two chlorine atoms (one ionic and one covalent) in a ratio of 1:1, and this also contradicts pyrimidine structure Va. In the PMR spectrum of this compound the two triplets are similar with respect to their chemical shifts and SSCC to the signals of the CH_2CH_2 bridge of the dihydroimidazole ring of VIa, which makes it possible to assign the 5-amino-7-(β-chloroethyl)-8,9-dihydro-

imidazo[1,2-c]pyrimidinium chloride structure (VIIa) to the isolated compound. The other two triplets at 4-4.2 ppm with a lower SSCC are related to a β-chloroethyl group. The results of elementary analysis confirm the structure of VIIa.

Mixtures of two products were obtained in both cases when chloropyrimidine III was subjected to reaction with $SOCl_2$ or $POCl_3$ at room temperature. With respect to the spectral data (PMR and IR spectroscopy) the isolated compound with the lower R_f value was very similar to imidazopteridine VIa. Taking into account the results of elementary analysis one can assign the 4-chloro-5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium chloride structure (VIb) to it. Additional evidence for the structure of VIb is the fact that imidazopteridine hydrochloride VIa was obtained in high yield when VIb was dechlorinated on Pd/C. On the basis of the differential spectrum of the mixture obtained and VIb we assigned the 4-chloro-5-amino-7-(β-chloroethyl)-8,9-dihydroimidazo[1,2-c]pyrimidinium chloride structure (VIIb) to the second compound, which we were unable to purify to remove the admixed imidazopteridine VIb. It should be noted that the yield of VIIb is higher in $POCl_3$ than in $SOCl_2$ (66 and 25% yields, respectively).

It seemed of interest to ascertain the pathway via which imidazopteridines VIa and VIb are formed — from imidazopyrimidines VIIa and VIIb or from the intermediately formed β-chloroethyltetrahydropteridines VIII. If the reaction is realized via the first pathway (from VIIa and VIIb), the VIa:VIIa and VIb:VIIb ratios in the reaction mixtures should increase with time. In the second case, after consumption of starting IV and III, the VIa:VIIa and VIb:VIIb ratios should remain constant. We demonstrated by special kinetic experiments by means of PMR spectroscopy with maintenance of pyrimidine III in $SOCl_2$* that the compositions of the reaction mixtures after disappearance of starting III are virtually independent of the reaction time and that the percentages of VIb and VIIb are 60 and 40%, respectively. Thus VIIb evidently does not undergo cyclization to imidazopteridine VIb under these conditions. This is also confirmed by the stability of VIIb in solution in $SOCl_2$. These results constitute evidence that the intermediately formed bis(chloroethyl)amine Vb, under conditions of exchange of the OH groups for chlorine atoms, undergo cyclization via two pathways, viz., at the pyrimidine nitrogen atom to give imidazopyrimidine VIIb and at the 5-amino group with the intermediate formation of chloroethylpteridine VIIIb and subsequent rapid secondary cyclization to give imidazopteridine VIb.

To determine the possibility of cyclization of VIIb to give imidazopteridine VIb and to estimate the rate of this reaction we studied the behavior of VIIb in various solvents. According to PMR data, this cyclization proceeds slowly in D_2O; the half-conversion time at room temperature is 30 days. When an aqueous solution of imidazopyrimidine VIIb is refluxed, the reaction is complete in 1 h; however, in addition to VI, we isolated a certain amount of unidentified polymeric products, the formation of which was also noted when VIIb was stored. Virtually no cyclization takes place when VIIb is refluxed in alcohol. When imidazopyrimidine VIIb is heated in DMF, it forms VIb, the reaction of which with dimethylamine gives 4-dimethylamino-5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium chloride (IX). The structure of the latter was proved on the basis of the PMR spectrum and the results of elementary analysis for its hydrochloride. The same product was obtained under similar conditions from imidazopyteridine VIb. An additional confirmation of its structure is the preparation of triamine IX from VIIb by reaction with dimethylamine under mild conditions. Imidazopteridine VIb also was not obtained when VIIb was refluxed in HBr. The isolated reaction product was 4-hydroxy-5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium bromide (X) hydrobromide, the structure of which was proved by means of PMR and IR spectroscopy and the results of elementary analysis. The same product was obtained under similar conditions from VIb; this is in agreement with the literature data on the hydrolysis of chloroimidazopyrimidinium halides [5, 8, 9, 13, 14].

Compound VIIa undergoes smooth cyclization to imidazopteridine VIa when it is heated in DMF and HBr; dibromide XI is isolated in the latter case.

We attempted the use of a different approach for the synthesis of bis(chloroethyl)amine Vb. The reaction of dichloropyrimidine I with bis(β-chloroethyl)amine gave 4-chloro-6-bis-(β-chloroethyl)amino-5-nitropyrimidine (XII), the structure of which was proved on the basis of the PMR spectrum and the results of elementary analysis. A mixture of three low-polarity

*In view of the low solubilities of IV, VIa, and VIIa in $SOCl_2$ the kinetic studies were made with their 4-chloro derivatives.

products (TLC in system A) was obtained in the reduction of XII on Raney nickel at 0°C after hydrogenation was complete; the compound with the highest R_f value gives a color reaction with dimethylaminobenzaldehyde, which is probably associated with the presence of Vb in the reaction mixture. However, further careful treatment leads to a significant change in the composition of the mixture, and only one low-polarity compound with R_f 0.76 was isolated in individual form, along with a mixture of VIb and VIIb in a ratio of 1:1 (PMR data) in an overall yield of ~60%. The PMR spectrum of the compound with R_f 0.76 and the results of elementary analysis make it possible to assign to it the 4-chloro-8-(β-chloroethyl)-5,6,7,8-tetrahydropteridine structure (VIIIb), the formation of which we assumed in the reaction of pyrimidine III with $SOCl_2$. In solution in alcohols and $CHCl_3$ VIIIb gradually cyclizes to give imidazopteridine VIb, whereas this reaction proceeds quantitatively in a few minutes in the case of refluxing in ethanol. Thus bis(chloroethyl)amine Vb, which we detected chromatographically, is an extremely unstable product that is inclined to undergo intramolecular cyclization reactions even under mild conditions, and this made it impossible to isolate it from the reaction mixture. Taking into account the fact that the cyclization of imidazopyrimidine VIIb to imidazopteridine VIb under mild conditions proceeds slowly, one might expect that not only VIIIb but also all of the VIb was formed due to initial attack by the chloroethylamino group at the 5-NH_2 group (the overall yield of VIb and VIIIb was 58%), whereas VIIb was formed through a competitive reaction at the pyrimidine nitrogen atom (the yield of VIIb was 38%). This is in good agreement with the results obtained in a study of the behavior of pyrimidine III in $SOCl_2$ and differs somewhat from the results obtained in the reaction of pyrimidine IV with $SOCl_2$ (the yields of VIa and VIIa were 30 and 60%, respectively). This difference is probably associated with the effect of the substituent (chloro) in the pyrimidine ring on the ratio of the rates of competitive intramolecular N-alkylation by the bis(chloroethyl)amino group of the two nucleophilic centers of the 5-aminopyrimidine fragment and constitutes evidence for the possibility of regulating the direction of primary attack by the bis(chloroethyl)amino group by means of the introduction of substituents in the pyrimidine ring. The relative percentages of the cyclization products in the reaction mixtures indicate the relative close reactivities of the endocyclic and exocyclic nitrogen atoms of 5-amino-4-bis(chloroethyl)aminopyrimidines in intramolecular cyclization reactions.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with Varian A56/60A and Bruker WP-200sy spectrometers with hexamethyldisiloxane as the internal standard [tert-butyl alcohol (1.27 ppm away from tetramethylsilane) was used for aqueous solutions]. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in chloroform–ethanol (10:1) (A) and tert-butyl alcohol–methyl ethyl ketone–formic acid–water (40:30:15:15) (B) systems. Column chromatography was carried out with KSK silica gel and activity II Al_2O_3. The identical character of the compounds obtained by different methods was proved by means of TLC (in system B) and the PMR and IR spectra.

4-Chloro-6-bis(β-hydroxyethyl)amino-5-nitropyrimidine (II). A solution of 8.67 g (82.5 mmole) of distilled diethanolamine in 40 ml of methanol was added dropwise with stirring and ice cooling in the course of 30 min to a solution of 8 g (41 mmole) of dichloropyrimidine I in 150 ml of methanol, and the mixture was maintained under these conditions for another hour, after which the methanol was removed by vacuum distillation. The residual oil was transferred to a column (3 × 25 cm) packed with silica gel and eluted with system A. The yellow fraction was collected and evaporated, and the residue was triturated with absolute ether to give 9.97 g of amber-yellow product II. The characteristics of the synthesized compounds are presented in Table 2.

4-Chloro-5-amino-6-bis(β-hydroxyethyl)aminopyrimidine (III). A solution of 10 g (0.38 mole) of nitropyrimidine II in 200 ml of absolute ethanol was hydrogenated with periodic cooling of the mixture with cold water in the presence of ~12 g of Raney nickel until the theoretically calculated amount of hydrogen had been absorbed (4 h), after which the solution was filtered, the precipitate was washed with methanol (five 15-ml portions), and the filtrate was evaporated. The residual oil was separated with a column (5 × 35 cm) packed with silica gel in system A, and the fractions containing a product with R_f 0.35 were combined and evaporated. The resulting oil was triturated with 30 ml of absolute ether and

allowed to stand at −4°C for 2 h. The precipitate was separated to give 6.91 g of colorless III. When the amount of starting II was increased to 20-30 g, the yield of aminopyrimidine III decreased to 45-50%.

5-Amino-4-bis(β-hydroxyethyl)aminopyrimidine Hydrochloride (IV). A solution of 1 g (4.3 mmole) of III in 25 ml of absolute ethanol was hydrogenated with hydrogen in the presence of 0.5 g of 10% Pd/C at 50-55°C until the theoretical amount of hydrogen had been absorbed (9 h), after which the solution was filtered, and the precipitate was washed with hot methanol (five 5-ml portions). The filtrate was evaporated, and the resulting oil was allowed to stand overnight in a vacuum desiccator (here and subsequently, P_2O_5 and NaOH, which were poured into separate dishes in the same desiccator, were used as the drying agents). The yield of crystalline IV was 963 mg.

Reaction of 5-Amino-4-bis(β-hydroxyethyl)aminopyrimidine (IV) with $SOCl_2$. A suspension of 0.4 g (1.7 mmole) of IV in 6 ml [9.95 g (84 mmole)] of freshly distilled $SOCl_2$ was allowed to stand at 20°C for 24 h, after which the mixture was evaporated, the residue was treated (with ice cooling) with 5 ml of absolute methanol, and the mixture was evaporated. The product was separated with a column (2 × 25 ml) packed with silica gel by successive elution with methanol (∿200 ml) and methanol—formic acid (10:1). A few drops of a methanol solution of HCl were added to the fractions containing compounds with R_f 0.35 and 0.2 (in system B), and the mixture were evaporated. The first fraction yielded 231 mg of VIIa, and the second fraction yielded 119 mg of the hydrochloride of VIa. Imidazopteridine VI was obtained by elution of the hydrochloride with methanol through a column (2 × 15 cm) packed with Al_2O_3. Found for VIa: Cl (ionic) 17.3%. $C_8H_{11}ClN_4$. Calculated: Cl 17.9%.

Reaction of 4-Chloro-5-amino-6-bis(β-hydroxyethyl)aminopyrimidine (III) with $SOCl_2$. A 1-g (4.3 mmole) sample of pyrimidine III was added in small portions to 15 ml [24.5 g (0.21 mole)] of freshly distilled $SOCl_2$; and the mixture was allowed to stand at 20°C for 24 h. The excess $SOCl_2$ was removed by vacuum distillation, and the residue was treated (with ice cooling) with 5-10 ml of absolute methanol. Acetone (30 ml) was added, and the mixture was concentrated to half its original volumne (during which the acetone—methanol azeotrope was removed by distillation). The resulting solution was allowed to stand at −4°C for 24 h, and the precipitate was separated to give 407 mg of slightly colored VIb. The acetone mother liquor was evaporated, the residue was dissolved in 3-5 ml of absolute methanol, and the solution was added dropwise with stirring to 300 ml of absolute ether. The liberated oil was shaken for several hours with 30 ml of acetone, and the precipitate was separated to give another 93 mg of VIb for an overall yield of 503 mg. The mother liquor was diluted (with stirring) with 250 ml of absolute ether, and the liberated oil began to crystallize after prolonged trituration with absolute ether. The yield of VIIb was 0.29 g; the product contained 5-10% VIb (according to PMR data).

For kinetic studies, 40 mg of III or VIIb was dissolved in 0.6 ml of $SOCl_2$, and the solution was maintained at 20°C for 1, 2, and 4 days, after which the $SOCl_2$ was removed by vacuum distillation, and the residue was dissolved in 0.3 ml of CD_3OD. The relative percentages of VIIb and VIb in the mixtures obtained were determined on the basis of the relative integral intensities of the signals of the pyrimidine protons in the PMR spectra (8.23 and 8.04 ppm, respectively).

Reaction of 4-Chloro-5-amino-6-bis(β-hydroxyethyl)aminopyrimidine (III) with $POCl_3$. A mixture of 1 g (4.3 mmole) of III and 25 ml [41.8 g (0.27 mole)] of freshly distilled $POCl_3$ was allowed to stand at 20°C for 4 days (the starting compound dissolved in a few hours), after which the excess $POCl_3$ was removed by vacuum distillation, and the residue was treated with 10 ml of absolute methanol while cooling with ice (1 h). Acetone (30 ml) was added, and the acetone—methanol azeotrope was removed by distillation three times as described for VIb. The resulting solution was added dropwise with stirring to 250 ml of absolute ether, and the precipitate was separated and washed with acetone to give 248 mg (25%) of VIb. The mother liquor was worked up as described above in the reaction of III with $SOCl_2$ to give 762 mg of VIIb. For purification it was refluxed with stirring with 25 ml of acetone for 6 h, and the precipitate was separated and dried in a vacuum desiccator. The purified product contained 7-10% imidazopteridine VIb (according to PMR data).

5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium Chloride Hydrochloride (VIa·HCl). A) A solution of 1 g (4.3 mmole) of VIb in 25 ml of absolute ethanol was hydrogenated in the presence of 0.5 g of 10% Pd/C at 50-55°C until the theoretical amount of hydrogen had been

absorbed (4.5 h). The precipitate was separated and washed with methanol (five 5-ml portions), the filtrate was evaporated, and the resulting oil was applied to a column (1.5 × 20 cm) packed with silica gel and eluted with 150 ml of methanol. A few drops of a methanol solution of HCl were added to the resulting solution, the mixture was evaporated, and the residue was triturated with acetone to give 873 g (87%) of the hydrochloride of VIa.

B) A mixture of 0.2 g (0.85 mmole) of VIIa and 20 ml of absolute DMF was heated at 145-150°C for 1.5 h, after which the DMF was distilled *in vacuo*, and the brown residue was treated with 3 ml of a saturated solution of Na_2CO_3. The resulting solution was evaporated, and the residue was dried in a vacuum desiccator. The product was washed with absolute alcohol (five 5-ml portions), the filtrate was evaporated, the residue was dissolved in 5 ml of absolute alcohol, and the solution was filtered. The solution was evaporated again, and the residue was chromatographed with a column (1.5 × 10 cm) packed with silica gel by successive elution with 20 ml of absolute alcohol (this fraction was discarded) and 30 ml of absolute methanol. The methanol solution was acidified with HCl, the mixture was evaporated, and the residue was triturated with acetone to give 126 mg (63%) of the hydrochloride of VIa.

4-Chloro-5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium Chloride (VIb). A mixture of 0.2 g (0.74 mmole) of VIIb and 20 ml of water was refluxed for 1 h, after which it was evaporated *in vacuo*, and the residue was washed with methanol (three 3-ml portions) to give 0.25 g of a colorless polymeric product. The filtrate was evaporated *in vacuo* to give 145 mg (84%) of VIb.

Dimethylamino-5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium Chloride (IX). A) A mixture of 0.2 g (0.74 mmole) of VIIb and 20 ml of absolute DMF was heated at 145-150°C for 5 h, after which the MDF was removed by vacuum distillation, and the brown residue was treated with 2.5 ml of a saturated solution of Na_2CO_3. The water was removed *in vacuo*, and the residue was dried in a vacuum desiccator. The product was washed with absolute alcohol (five 3-ml portions), the filtrate was evaporated, and the residue was dissolved in 2 ml of absolute methanol. Acetone (25 ml) was added to the solution, and the methanol–acetone azeotrope was removed by distillation three times as described in the reaction of III with $SOCl_2$. The solution was allowed to stand at −4°C for 18 h, after which it was filtered, and the filtrate was heated to the boiling point and treated with 1 ml of a saturated solution of HCl in ethanol. The mixture was maintained at −4°C for 24 h, and the precipitate was separated and dried in a vacuum desiccator to give 70 mg of the hydrochloride of IX. Compound IX was obtained by elution of its hydrochloride with methanol through a column (1.5 × 20 cm) packed with Al_2O_3.

B) A mixture of 0.4 g (1.72 mmole) of imidazopteridine VIb and 40 ml of absolute DMF was heated with stirring at 140-150°C for 7 h, after which it was worked up as in method A. The yield of the hydrochloride of IX was 356 mg (74%). The characteristics of the isolated compound were similar to those of the sample obtained by method A.

C) A solution of 0.2 g (4.45 mmole) of dimethylamine in 4 ml of absolute methanol was added with stirring and ice cooling in the course of 15 min to a solution of 0.25 g (1.06 mmole) of imidazopteridine VIb in 8 ml of absolute methanol, after which the mixture was maintained with cooling for another 45 min. It was then evaporated *in vacuo* and worked up as in method A, except that the alcohol solution of HCl was not added. The acetone solution was evaporated, and the residue was triturated with absolute ether to give 237 mg (91%) of IX in the form of a colorless and very hygroscopic and unstable product.

4-Hydroxy-5,6,7,8,9,10-hexahydroimidazo[1,2,3-i,j]pteridinium Bromide (X) Hydrobromide. A) A mixture of 0.2 g of imidazopyrimidine VIIb and 20 ml of distilled HBr was refluxed for 3 h, after which it was evaporated *in vacuo*, and the residue was dried in a vacuum desiccator and dissolved in 7-10 ml of absolute methanol. Acetone (25 ml) was added to the solution, and the acetone–methanol azeotrope was removed by distillation three times as described above. The yellow precipitate was separated and washed with acetone. The yield was 148 mg.

B) Compound X was obtained as described above from 0.4 g (1.72 mmole) of imidazopteridine VIa and 40 ml of HBr. The reaction product was washed additionally with alcohol (three 3-ml portions). The yield was 491 mg (84%). The characteristics of X were similar to those of the sample obtained by method A.

5,6,7,8,9,10-Hexahydroimidazo[1,2,3-i,j]pteridinium Bromide (XI) Hydrobromide. A mixture of 0.2 g (0.85 mmole) of imidazopyrimidine VIIa and 20 ml of freshly distilled HBr was refluxed for 3 h, after which it was evaporated *in vacuo*, and the residue was dried in a vacuum desiccator and washed with absolute methanol (three 5-ml portions) to give 94 mg of colorless XI. The mother liquor was evaporated, and the residue was refluxed with 5 ml of absolute alcohol. The precipitate was separated without cooling and washed with absolute alcohol (two 2-ml portions) to give another 65 mg of XI for an overall yield of 159 mg.

4-Chloro-6-bis(β-chloroethyl)amino-5-nitropyrimidine (XII). A solution of 3 ml [2.17 g (21.5 mmole)] of distilled triethylamine in 10 ml of absolute methanol was added dropwise with stirring and ice cooling in the course of 15 min to a solution of 2 g (10.3 mmole) of nitropyrimidine I and 1.84 g (10.3 mmole) of bis(β-chloroethyl)amine hydrochloride in 30 ml of absolute methanol, and the mixture was maintained at this temperature for another 15 min. The methanol was removed *in vacuo* without heating, and the residual oil was shaken with 150 ml of absolute ether for 10 min. The precipitate was separated and washed with absolute ether. The mother liquor was evaporated, the residue was shaken again with 150 ml of absolute ether, and the mixture was allowed to stand at −4°C for 1 h. The precipitate was separated, and the solution was evaporated in vacuo to give 2.74 g (89%) of crude product. Washing with absolute alcohol (three 4-ml portions) gave 2.1 g of XII. To obtain a sample for analysis, a 0.5-g sample of this product was dissolved in 20 ml of absolute ether, the solution was concentrated to a small volume, 8-10 ml of absolute alcohol was added, and the mixture was maintained at −4°C. The precipitate was separated and dried with a vacuum desiccator. Bis(chloroethyl)amine XII was unstable in solutions in alcohol, ether, and $CHCl_3$ but could be stored in solid form for several weeks in a refrigerator.

Hydrogenation of 4-Chloro-6-bis(β-chloroethyl)amino-5-nitropyrimidine (XII). A solution of 0.5 g (1.67 mmole) of pyrimidine XII in 10 ml of absolute ethanol was hydrogenated at 0°C in the presence of 1.5 g of Raney nickel until the calculated amount of hydrogen had been absorbed (2 h). The precipitate was removed by filtration and washed with absolute methanol. The mother liquor was evaporated *in vacuo* without heating, and the resulting colorless oil was allowed to stand at room temperature for 15 min and triturated with 30 ml of absolute ether. The precipitate was separated and washed with absolute ether. Evaporation of the mother liquor gave 141 mg of colorless VIIIb. The precipitate was removed by filtration and washed with absolute methanol (five 3-ml portions). The filtrate was evaporated, and the residue was dried in a vacuum desiccator to give 0.25 g of a mixture of VIb and VIIb. According to data from the PMR spectrum of this mixture in CD_3OD, the yield of VIb was 19%.

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