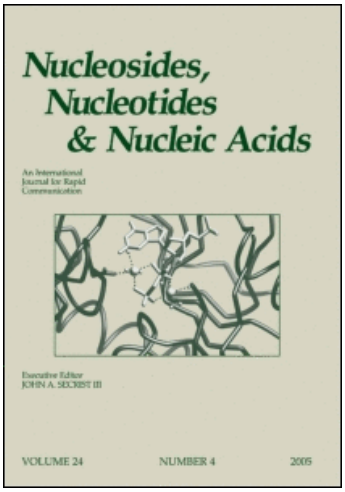

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Synthesis of 7-Deazatriacanthine and Restricted Rotation of Amino Groups in Pyrrolo[2,3-d]Pyrimidines

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SYNTHESIS OF 7-DEAZATRIACANTHINE AND RESTRICTED ROTATION OF AMINO GROUPS IN PYRROLO[2,3-d]PYRIMIDINES

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ABSTRACT - Isopentenylation of 7-deazaadenine results in the formation of 7-deazatriacanthine (2a) and its corresponding isomer 5a. Chromatographic separation was difficult, but after Dimroth rearrangement of 5a into the exocyclic compound 3a, 7-deazatricanthine could be isolated. Similiar to its parent purine compound, 3a cyclizes in the presence of strong acid to give the tricyclic system 4. NMR data reveal that 7-deazatriacanthine exists as the amino tautomer 2a. Protonation of N-1 alkylated 7-deazaadenine occurs at N-7 to give compound 6 which exhibits restricted rotation of the amino group. The rotational barrier was determined from temperature dependent proton NMR spectra and found to be about 70 $kJmol^{-1}$.

Several 3-alkylated adenines exhibit remarkable properties. They can be generated from nucleic acids [1] as alkylation at that positiondestabilizes the N-glycosylic bond [2] of the nucleotide leading to the excission of the nucleobase. On the other hand isopentenylation or introduction of an amino acid residue leads to biologically active molecules. Examples are discadenine [3], a spore germination inhibitor and the plant hormone triacanthine (1b) [4], which induces flowering in Pharbitis nil [5].

As is known from cytokinines, the replacement of the purine base by a pyrrolo[2,3-d]pyrimidine heterocycle renders them anticytokinines [6]. This prompted us to synthesize the 7-deaza analogue of triacanthine (2a) and to investigate the properties of N-1 alkylated 4-amino-7H-pyrrolo-[2,3-d]pyrimidines.

In an earlier publication we have reported on the methylation of 4-amino-7H-pyrrolo[2,3-d]pyrimidine [7]. In contrast to the methylation of adenine where formation of the N-3 methyl isomer 1a was predominant [8], no regioselective reaction was observed with 7-deazaadenine, and the N-3 and N-1 methylated compounds (5b and 6b) were formed in almost

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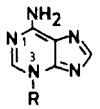
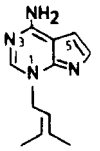
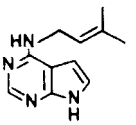


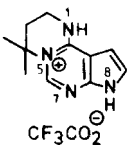
1a : R = Me
b : R = Ip



2a
b : Me instead of Ip



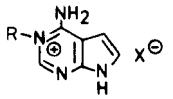
3a
b : Me instead of Ip



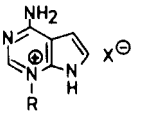
4

Me = CH_3

Ip =



5a : R = Ip ; X = $Br^{\ominus}$
b : R = Me, X = $Cl^{\ominus}$
c : R = Ip ; X = $AcO^{\ominus}$



6a : R = Ip ; X = $Br^{\ominus}$
b : R = Me ; X = $Cl^{\ominus}$
c : R = Ip ; X = $AcO^{\ominus}$

identical amounts. Applying the reaction conditions used for the synthesis of triacanthine [9] on the isopentenylation of 7-deazaadenine and employing an excess of 1-bromo-3-methyl-2-butene no reaction product was formed even at elevated temperature. However, when hexamethylphosphoric acid triamide (HMPA) was used as the reaction medium a smooth conversion took place. The ^1H NMR spectrum of the crude reaction mixture indicated the presence of two reaction products - tentatively assigned structures 5a and 6a - in 70 % yield and about 30 % of starting material. The latter was not observed immediately after the alkylation procedure when TLC exhibited only a single spot (solvent system B, R_f 0.36). This implied that back formation of the starting material occured due to the workup procedure. A similiar dealkylation of N-3-(Δ^2-isopentenyl)adenine has been reported by Reese [10] and it was proposed that this was due to an acid-catalyzed process.

Ion exchange chromatography of the crude reaction mixture separated the products 5c and 6c from starting material, but did not resolve the isomers which were present in a ratio of 2:3 (^1H NMR). As we have shown for 4-amino-3-methyl-3H-pyrrolo[2,3-d]pyrimidine. HCl , N-3 isomers are readily rearranged to the corresponding N-4 isomers (3b) [7] which exhibit

different mobility on TLC. Therefore, compound 5a was converted into the exocyclic isomer 3a by Dimroth rearrangement. The resulting product mixture of 3a and 6a was then separated by liquid extraction with ethyl acetate. The organic phase contained 3a and the aqueous phase 6a. By consecutive chromatography compound 3a was obtained crystalline and its structure was verified by comparison with an authentic sample prepared by nucleophilic displacement of the halide in 4-chloro-7H-pyrrolo[2,3-d]pyrimidine with Δ^2-isopentenylamine [11].

When 3a was heated with trifluoroacetic acid ring closure occured to give the tricyclic compound 4. This was isolated crystalline as the trifluoro acetate in 62 % yield. The pK_a value of 4 was determined spectrophotometrically and found to be 11.1 similiar to that of 4-amino-3-methyl-3H-pyrrolo[2,3-d]pyrimidine (5b) (pK_a = 10.8) [7]. The proton NMR spectrum displayed signals of two methylene groups at 2.14 and 3.57 ppm instead of the olefinic proton at 5.4 ppm in 3a thus confirming the proposed structure. The two exchangable protons of 4 are linked to N-8 and most likely to N-1. The first is demonstrated by the coupling of 8-NH to 9-H and 10-H, the second is deduced from the coupling of the 2-methylene protons to the proton bound to N-1.

7-Deazatriacanthine was isolated from the aqueous extraction layer by chromatography in 36 % yield as the crystalline hydrobromide 6a. The free base 2a could be obtained by passing this through a bed of anion-exchange resin. The UV spectrum of 7-deazatriacanthine is very similiar to that of 4-amino-1-methyl-1H-pyrrolo[2,3-d]pyrimidine (2b) and further more shows the same pH dependence. The pK_a value was found to be 8.9, identical to that of 2b [7].

Further indication of the structure came from the ^{13}C NMR data (TABLE). Close agreement was found for the signals in the aromatic region of the spectrum for 6a and 6b. Moreover, the side chain signals of 6b are close to that taken from natural triacanthine (1b). Comparison of the data for the N-4 and N-1 Δ^2-isopentenyl compounds 3a and 2a, respectively, shows that the N-1 substituent affects C-2, C-6 and C-7a to the greatest extent. The altered positioning of the side chain can also be deduced from the strong downfield shift of the NCH_2 signal.

Direct proof of the structure came from the $^{13}C/^{1}H$ coupling data in ^{13}C NMR. Here, C-2 is easily identified by its one-bond coupling ^1J of 211 Hz with 2-H. This doublet is split further into triplets with a long-range coupling ^3J of 4.2 Hz which shows that the Δ^2-isopentenyl

TABLE. ^{13}C and ^{1}H NMR Data of 4-Amino-7H-pyrrolo[2,3-d]pyrimidines and Triacanthine (1b) [a].

compd.	C-2	C-4	C-4a	C-5	C-6	C-7a	NCH_2	C=	CH=	CH_3(E)	CH_3(Z)
3a	151.5	155.9	102.6	98.7	122.6	150.1	37.9	133.1	120.5	25.4	17.7
6a	145.9	158.1	102.6	102.0	123.2	140.0	48.0	137.8	116.1	25.0	17.9
2a	141.6	156.3	104.4	99.2	136.8	146.1	45.9	137.1	119.1	25.2	17.9
6b	147.2	158.4	102.4	102.3	123.3	139.0	37.1 [b]				
1b [c]	147.8	153.2	110.3		144.4	147.5	47.5	139.6	117.2	25.3	18.0

compd.	2-H	5-H	6-H	NH_2	NCH_2(3)	CH=	CH_3
2a	8.20	6.56 (d,2.4)	7.20 (d,2.4)	7.49	4.95 (d,7.2)	5.43 (t,7.2)	1.83, 1.70
6a	8.47	6.86 (d,3.6)	7.38 (d,3.6)	8.70, 8.88	4.39 (d,7)	5.43 (t,7)	1.77, 1.73
1b [d]	8.42		7.84	7.84	4.94 (d,7)	5.51 (t,7)	1.88, 1.77
2b	8.25	6.60 (d,3)	7.18 (d,3)	7.73	3.88		
6b	8.62	6.97 (d,3.6)	7.44 (d,3.6)	8.77, 9.03	4.03		

[a] All spectra were recorded in Me_2SO-d_6, chemical shifts are given as δ values relative to TMS as internal standard; coupling constants in parentheses are given in hertz. [b] NCH_3. [c] The pyrrolo[2,3-d]-pyrimidine numbering has been used. [d] 6-H = 8-H (purine numbering).

moiety is attached to either N-1 or N-3. Since the signal of C-4 is only a doublet due to its coupling to 2-H with ^3J = 12.1 Hz, the residue must be linked to N-1. The complex signal observed for C-7a supports this finding.

PROTONATION SITES OF N-1-ALKYLATED 7-DEAZAADENINES AND RESTRICTED ROTATION OF THEIR AMINO GROUPS

To determine the protonation sites in 7-deazapurines it is helpful to examine their proton NMR spectra. For both protonated compound 6a and 6b two signals are observed for the exchangable amino protons at room temperature, that coalesce at higher temperature (FIG. 1). This indicates hindered rotation around the C-NH_2 bond a fact that has not been reported for pyrrolo[2,3-d]pyrimidines, but has already been observed with 3-alkyl adenines [12].

From two series of temperature dependent ^1H NMR spectra the coalescence temperatures were found to be 62°C for 6a and 52°C for 6b. No such coalescence is expected for the protons of tautomer 7 and this structure is therefore excluded. The N-1-alkylated 7-deazaadenines are best represented by structures 6/9 where the rotational barrier manifests the relatively high contribution of the paraquinoide form 9.

For the 7-deazatriacanthine base 2a as well as for the N-1 methyl-derivative 2b two tautomeric forms have to be considered: namely structures 2/10 and 8. Since both compounds exhibit only one signal of two exchangable protons in the ^1H NMR (TABLE) structure 8 can be excluded and the free bases exist as the amino tautomers 2. Moreover, the equivalence of the amino protons shows that the zwitter ionic structure 10 is of minor importance here.

The π system of the N-3 alkylated 7-deazaadenines is reorganized on protonation, which must be represented by the transition 2 to 6/9. This is supported by the finding that strong changes occur in the chemical shifts of signals C-6 and C-7a due to the protonation at N-7 (TABLE).

The coalescence phenomena of the N-1 alkylated compounds needed further investigation, because contrary to expectation, the lower coalescence temperature T_c was found for compound 6b which exhibited the greater shift difference Δν of 54 Hz (FIG. 1). The rate of rotation of the amino group and thus the rate constant k increase with higher tem-

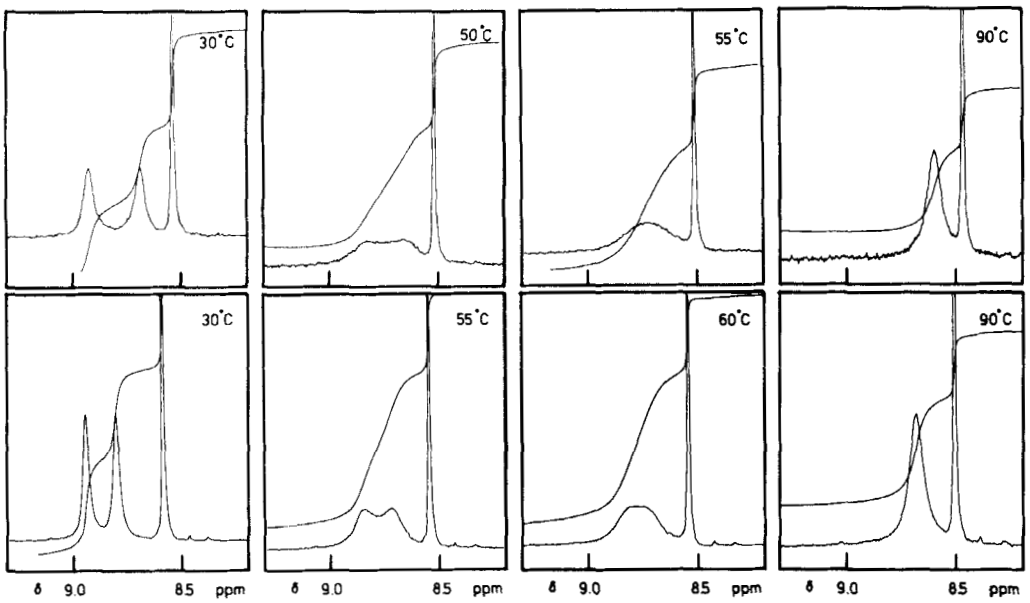
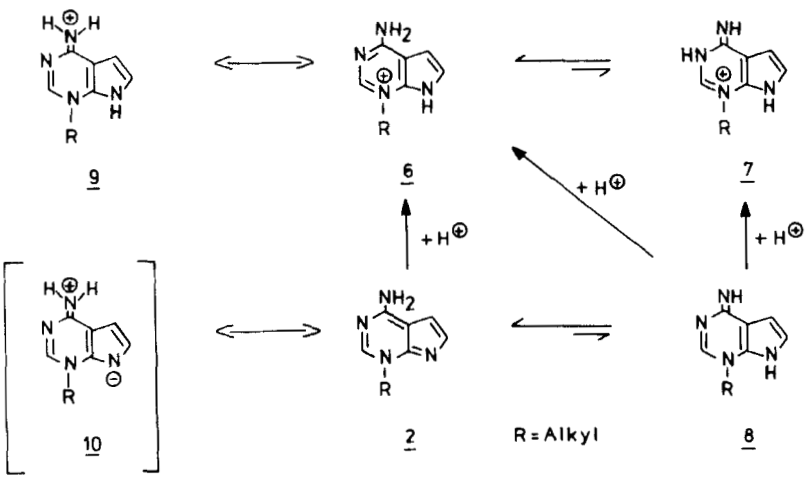


FIG. 1. Temperature-dependent ^1H NMR spectra of 6a (lower line) and 6b (upper line) in Me_2SO-d_6, TMS as internal standard. The downfield part of the spectrum is shown with the signals of the amino group and of the 2-H (about 8.5 ppm). Note the differences in the coalescence temperature T_c and in $\Delta\nu$ for the two amino protons.



peratures, simultanously k_c is directly proportional $\Delta\nu$, and the condition for coalescence $k = k_c$ is therefore met at higher temperatures.

The alterations in $\Delta\nu$ are due to the different anions which act as effective shift reagents [13]. The chloride anion in 6b causes a stronger anisotropy of the amino protons than the bromide anion in 6a, but the rate of rotations is not affected. The elevation of the coalescence temperature of the Δ^2-isopentenyl compound 6a must therefore be due to a slower rotation of its amino group.

Accordingly we performed a quantitative line shape analysis on both series to obtain the lifetimes τ and therefrom the rate constants k [14]. The resulting values were depicted as Eyring plots ($\ln(k/T)$ vs $1/T$) (FIG. 2).

Obviously the rotation is faster in the methyl derivative 6b (upper line) than in compound 6a (lower line) at a given temperature. From the slopes of the plots $\Delta H^{\neq}$ values were determined to be 68.6 $\pm$ 3.7 $kJmol^{-1}$ for 6a and 65.6 $\pm$ 3.9 $kJmol^{-1}$ for 6b. The intercepts gave $\Delta S^{\neq}$ values of - 12 $Jmol^{-1}K^{-1}$ for both compounds. Although the errors are pretty high it seems justified to claim that the difference in the rotational rate is due to energy barriers of different height and not to entropy effects. The free energy $\Delta G_c^{\neq}$ at the coalescence point is calculated to be 73 $\pm$ 4 $kJmol^{-1}$ for 6a and 70 $\pm$ 4 $kJmol^{-1}$ for 6b, which is slightly less than the $\Delta G_c^{\neq}$ of 77 $\pm$ 5 $kJmol^{-1}$ that can be estimated from the values of T_c and $\Delta\nu$ for 3-benzyl adenine hydrochloride [12].

Strong differences are found for the protonation between 7-deazatriacanthine and triacanthine. The former exhibits a higher pK_a value (2a: 8.9) than the natural compound 1b (pK_a = 5.4)[5]. Moreover, triacanthine (1b) is protonated at position 7 of the purine system, whereas the protonation site of the 7-deaza analogue 2a is the pyrrole nitrogen.

NOTE: The terms N-1, N-3, and N-7 always correspond to the pyrrolo-[2,3-d]pyrimidine numbering.

EXPERIMENTAL

Melting points were determined on a Berl apparatus (Wagner & Munz, Munich, FRG) and are not corrected. Elemental analyses were performed by Mikroanalytisches Labor Beller (Göttingen, FRG). Mass spectra were

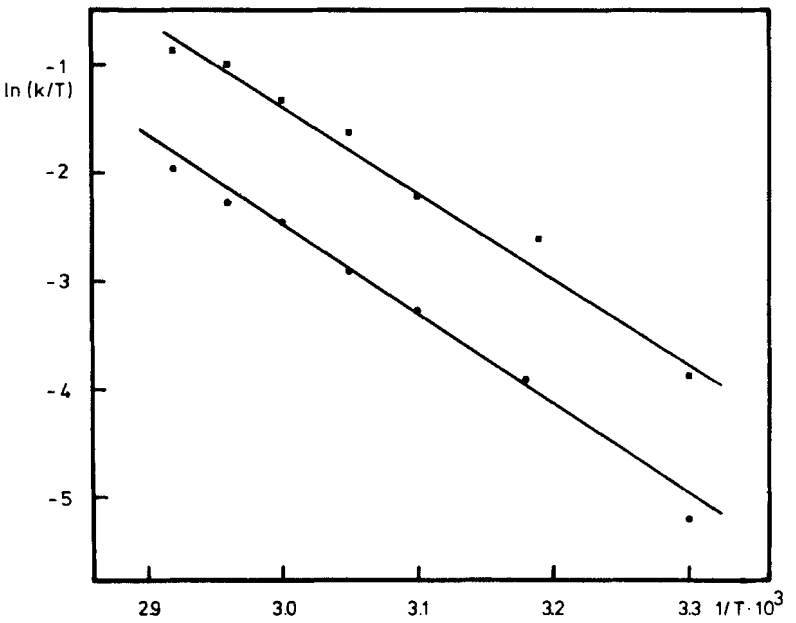


FIG. 2. Eyring plot for the restricted rotation of the amino group of the N-1 alkylated 7-deazaadenines 6a (● - ●) and 6b (■ - ■) as determined by proton NMR spectroscopy.

obtained with a Varian MAT 311A mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian EM-390, Bruker WM-250 and WP 200-SY spectrometers. Chemical shifts are given as δ values relative to tetramethylsilane as internal standard. UV spectra were measured on a Uvicon 810 spectrophotometer (Kontron, Switzerland) and pK_a values were obtained from pH dependent UV spectra in Teorell/Stenhagen [15] buffer. Thin-layer chromatography (TLC) was carried out on silica gel Sil-G-25-UV_{254} plates (Macherey & Nagel, Düren, FRG). Column chromatography was performed on silica gel 60 (Merck, Darmstadt, FRG). A Uvicon II UV detector connected with a Colora recorder was used to detect UV absorbing zones that were collected with an Ultrorac 7000 fractionscollector (LKB, Bromma, Sweden). Solvent systems used: A, $CHCl_3$ - MeOH (9:1); B, $CHCl_3$ - MeOH (4:1); C, CH_2Cl_2 - MeOH (95:5).

Temperature-dependent NMR spectra were recorded with a Bruker WP-200 SY spectrometer equipped with a B-VT 1000 temperature control unit. To obtain the k values the methods outlined in Ref. 14 were used. From the width at half-height of the amino group of 2a ($\Delta\nu_{1/2}$ = 5 Hz) T_2 (0.064 sec) was determined. The chemical shift difference of the an-

isotropic NH protons was measured from the spectra at about 40°C (6a: $\Delta\nu$ = 31 Hz, 6b: $\Delta\nu$ = 54 Hz) at 200 MHz.

Isopentenylation of 4-Amino-7H-pyrrolo[2,3-d]pyrimidine to 5a and 6a.

To a suspension of 4-amino-7H-pyrrolo[2,3-d]pyrimidine [16] (1.0 g, 7.5 mmol) in HMPA was added 1-bromo-3-methyl-2-butene [17] (4.0 mL, 5.13 g, 34.4 mmol) and the mixture was stirred at room temperature. When the starting material was completely dissolved TLC showed the formation of a new slower migrating zone (B, R_f 0.34). After 4 h the reaction was complete and the HMPA was evaporated in vacuo (0.2 mmHg) to almost dryness. The brownish residue was dissolved in water (50 mL) and neutralized with dilute aqueous ammonia. This was then applied to a column (10 x 2 cm) of a cation exchange resin (Lewatit CP 3050, H^+-form). After washing with water elution was performed with water/0.5 N acetic acid (linear gradient, 1000 mL each). Two zones were obtained: the first containing starting material (TLC, B, R_f 0.50), the second which gave a single spot(TLC, B, R_f 0.37) containing the reaction products. This zone left an amorphous solid on evaporation of the solvent. ^{1}H NMR (D_2O) δ 1.83 (6H, 2 CH_3), 4.98 (2H, d,7.5Hz, CH_2), 5.43 (1H, t, 7.5Hz,CH), 6.74 (1H, d, 3.6Hz, 5-H), 7.34 (1H, d, 3.6Hz, 6-H), 8.31 (1H, s,2-H), main signals attributed to compound 2c; and δ 1.83 (6H, 2 CH_3), 4.9 (2H, d,7.5Hz, CH_2), 5.35 (1H, t, 7.5Hz, CH=), 6.69 (1H, d 3.6Hz, 5-H), 7.29 (1H, d, 3.6Hz, 6-H), 8.25 (1H, 2-H) minor signals assigned compound 5c.

Dimroth Rearrangement of 5a/6a to 3a/6a.

The crude reaction mixture dissolved in water (50 mL) was adjusted to pH 6.0 with aqueous ammonia and a small amount of an offwhite precipitate was filtered off and discarded. The pH of the filtrate was then raised to 13.5 with 2 N sodium hydroxide (20 mL) and a precipitate that formed was dissolved by addition of methanol (25 mL). The solution was heated under reflux for 6 h when TLC exhibited a new spot (A, 0.49) attributed to the formation of compound 3a. After cooling and neutralization with 2 N acetic acid the solvent was evaporated and the residue was distributed between water (25 mL) and ethyl acetate (3 x 25 mL).

4-Amino-1-(3-methyl-2-butenyl)-1H-pyrrolo[2,3-d]pyrimidine hydrobromide (6a).

The aqueous layer of the extraction was evaporated to dryness in vacuo and the residue was dissolved in methanol (50 mL). Silica gel was

added and the mixture was evaporated in vacuo. The dry residue was taken up with CH_2Cl_2 - MeOH (95:5, 10 mL) and the resultant was applied to the top of a silica gel column (25 x 2 cm). Elution with solvent system C and evaporation of the main zone afforded 6a as an amorphous solid (760 mg, 36 %) which yielded a crystalline hydrobromide from water, mp. 193-195°C (dec., effervescence); TLC (B) R_f 0.19; UV (methanol) λ_{max} 289, 271 nm (ε 9400, 8700), λ_{min} 248 nm (ε 3900). Anal. calcd. for $C_{11}H_{15}BrN_4$: C, 46.65; H, 5.33; Br, 28.21; N, 19.78. Found: C, 46.67; H, 5.34; Br, 27.95.

4-Amino-1-(3-methyl-2-butenyl)-1H-pyrrolo[2,3-d]pyrimidine (7-Deaza-triacanthine, 2a).

The hydrobromide 6a (100 mg, 0.35 mmol) was dissolved in water (5 mL) and applied to the top of an ion-exchange column (Dowex 1 X 2, OH^--form, 20 x 1 cm). Elution with water afforded a main zone which contained the free base 2a. After evaporation of the water an amorphous solid (54 mg, 76 %) was obtained. This was crystallized from ethanol/water to afford 2a as colorless needles, mp. 133-135°C. Anal. calcd. for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.30; H, 6.85; N, 27.55.

4-(3-Methyl-2-butenylamino)-7H-pyrrolo[2,3-d]pyrimidine (3a) from Dimroth Rearrangement.

The combined organic layers were dried over sodium sulfate, filtrated and evaporated to give an amorphous residue that was dissolved in dichloromethane and applied to the top of a silica gel column (25 x 2 cm). Elution with solvent system C gave one main zone from which 3a was obtained as a glass (310 mg, 20 %) which could be crystallized from methanol/water affording white needles mp. 200°C, TLC (A) R_f 0.49; identical to 3a obtained by halide displacement.

4-(3-Methyl-2-butenylamino)-7H-pyrrolo[2,3-d]pyrimidine (3a) by Halide Displacement.

A solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine [18] (2.0 g, 13.0 mmol) and 3-methyl-2-butenylamine hydrochloride [19] (2.6 g, 16.4 mmol) in 1-butanol (50 mL) and triethylamine (20 mL) was heated under reflux for 24 h. The mixture was cooled. Crystallized triethylammonium chloride was filtered off and washed with 1-butanol. The combined

filtrates were concentrated in vacuo. The residue was taken up with ethanol (25 mL) treated with charcoal, filtered and evaporated. The product was crystallized (ethanol/water) to afford 3a (2.1 g, 80 %) as colorless needles mp. 200-202°C (lit.[11] 202-3°C); TLC(A) R_f 0.49; UV (methanol) λ_{max} 277, 218 nm (ε 18000, 17000); ^{1}H NMR (Me_2SO-d_6) δ 1.65 (6H, s, 2 CH_3), 4.12 (2H, d of d, J = 6 and 4Hz, CH_2NH), 5.40 (1H, t, J = 6Hz, CH=), 6.63 (1H, d, J = 3Hz, 5-H), 7.10 (1H, d, J = 3Hz, 6-H), 8.19 (1H, s, 2-H), 7.44 (1H, t, J = 4Hz, NH), 9.5 (1H, br s, ring NH). MS: m/e 202 (M), 159 (base peak); Anal. calcd. for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.22; H, 7.01; N, 27.57.

1,2,3,4-Tetrahydro-4,4-dimethyl-1H-pyrimido[1,2-c]pyrrolo[3,2-e]-pyrimidine trifluoroacetate (4).

A solution of 3a (0.4 g, 2.0 mmol) in trifluoroacetic acid (20 mL) was stirred at 55°C for 12 h. The solvent was evaporated in vacuo and through repeated evaporation with methanol and water the product was crystallized to give offwhite crystals. These were recrystallized from ethanol/water to yield colorless crystals (390 mg, 62 %), mp. 213°C (dec., effervescence); TLC (A) R_f 0.07; UV (methanol) λ_{max} 276, 228 nm (ε 13300, 17300); MS: m/e 203 (base peak, MH^+); ^{1}H NMR (Me_2SO-d_6) δ 1.72 (2H, s, 2 CH_3), 2.14 (2H, pt, J = 6Hz, 3-H), 3.57 (2H, m, 2-H), 6.90 (1H, d of d, J = 3.6 and 1.8Hz, 10-H), 7.43 (1H, d of d, J = 3.6 and 2.4Hz, 9-H), 8.70 (1H, s, slightly broadened, 6-H), 10.3 (1H, s, br, NH), 12.8 (1H, s, br, NH), ^{13}C NMR (Me_2SO-d_6) δ 27.8 (2 CH_3), 32.3 (C-3), 35.1 (C-2), 58.9 (C-4), 101.5 (C-10a), 101.6 (C-10), 124.9 (C-9), 141.4 (C-6), 145.3, 148.3 (C-7a, C-10b). Anal. calcd. for $C_{13}H_{15}F_3N_4O_2$: C, 49.36; H, 4.78; F, 18.02; N, 17.71. Found: C, 49.30; H, 4.93; F, 17.70; N, 17.40.

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