

7,9-DIALKYLADENINIUM SALTS. AN ALTERNATIVE SYNTHESIS, RING
OPENING, AND REARRANGEMENT TO N⁶,7-DIALKYLADENINES

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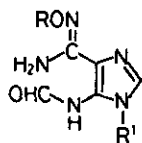
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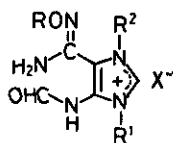
Abstract — Alkylation of N'-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamide (type I or II) (in the absence of any base) followed by hydrogenolysis of the N'-alkoxy group and cyclization (or *vice versa*) yielded the corresponding 7,9-dialkyladeninium salts (type VII), which readily rearranged to N⁶,7-dialkyladenines (type X) in boiling 1 N NaOH. Under milder basic conditions, VII underwent hydrolysis to produce 4-alkylamino-6-amino-5-formamidopyrimidines (VIII). The NaBH₄ reduction of 7,9-dimethyladeninium iodide (VIIa, X = I) gave the 7,8-dihydro derivative (XI).

The isolation of agelasine,¹ a marine product presumed to be a 7-substituted 9-methyladenine, from the sponge *Agelas dispar* has directed increasing attention to the chemistry of 7,9-dialkyladeninium salts (type VII). Efforts to extend our first synthesis² of 7,9-dimethyladeninium perchlorate (VIIa, X = ClO₄) to other alkyl analogues have led to the establishment of a general synthetic route to VII from N⁶-alkoxy-9-alkyladenines.³ This communication describes an alternative synthesis of the salts VII as well as their unique chemical behavior observed.

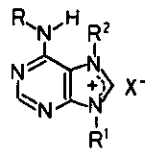
Alkylations of the formamidoimidazoles Ia^{4a} and II^{4a} the readily isolable intermediates⁴ in the Dimroth rearrangement of 1-methoxy-9-methyladenine and 1-ethoxy-9-ethyladenine, with MeI, EtI, and PhCH₂Br (Ia only) in HCONMe₂ at 30–50°C afforded the corresponding 3-substituted imidazolium salts [IIIa,b (X = I), IIIc (X = Br), IVd,e (X = I)] as crude products. On heating in boiling EtOH for 5 h, the imidazolium salts cyclized to give the N⁶-alkoxy-7,9-dialkyladeninium salts Va,b (X = I)⁵ and Vc (X = Br),⁵ identical with authentic samples,³ and VID,e (X = I)⁵ in 41–61% overall yields. Hydrogenolyses of Va,b (X = I) and Vc (X = Br) with H₂ and Raney Ni have already been shown³ to furnish the corresponding 7,9-dialkyladeninium



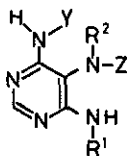
I, R = Me
II, R = Et



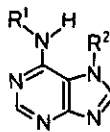
III, R = Me
IV, R = Et



V, R = MeO
VI, R = EtO
VII, R = H



VIII, Y = H; Z = CHO
IX, Y = CHO; Z = H



X

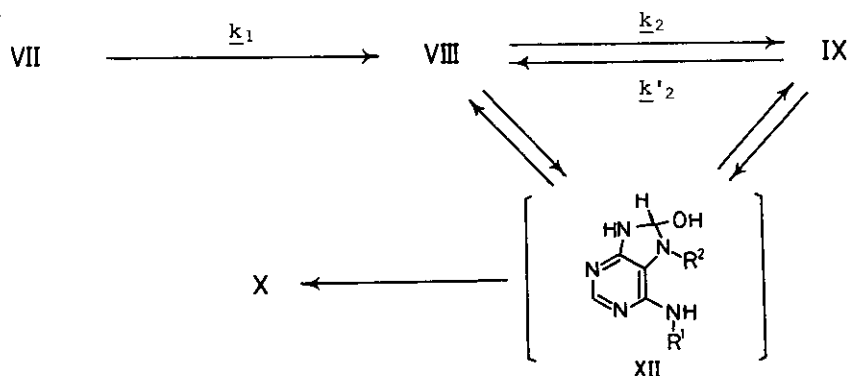


XI

a, R¹ = R² = Me b, R¹ = Me; R² = Et c, R¹ = Me; R² = PhCH₂ d, R¹ = Et; R² = Me
e, R¹ = R² = Et f, R¹ = Et; R² = PhCH₂ g, R¹ = PhCH₂; R² = Et

salts [VIIa,b (X = I), VIIc (X = Br)] in acceptable yields. The N⁶-ethoxy derivatives VIId,e (X = I) were likewise hydrogenolyzed to VIIId,e (X = I) in 63–82% yields. Alternatively, similar hydrogenolyses of the N¹-alkoxy group of IIIa,b (X = I), IIIc (X = Br), and IVd (X = I) and spontaneous cyclization directly produced the desired 7,9-dialkyladeninium salts [VIIa,b (X = I), VIIc (X = Br), VIId (X = I)] in 19–45% overall yields (from Ia or Id). Preferential 3-substitution⁶ on the imidazole ring of Ia and Id presents a contrast to the previous finding⁷ that the formamidoimidazoles (type I) are alkylated almost exclusively on the 5-formamido nitrogen atom when treated with alkyl halide in the presence of K₂CO₃.

The imidazolium structure of VII suggests that the center of low electron density is at C(8).⁸ The adeninium salts VIIa,b,d,e (X = I), VIIc (X = Br), and VIIf (X = ClO₄)³ were indeed unstable under basic conditions. Treatment of their aqueous solutions with Na₂CO₃ (0.5 N, 30–90 min) or Amberlite CG-400 (OH⁻) at room temperature gave the corresponding ring-opened derivatives (VIII) in 56–83% yields: VIIId,⁹ mp 247–248°C (dec.) [uv λ_{max} (95% EtOH) 223 nm (ε 44800), 257 (5600); λ_{max} (H₂O) (pH 1) 223 (29500), 268 (12900); λ_{max} (H₂O) (pH 7) 221 (41200), 258 (6100); λ_{max} (H₂O) (pH 13) 221 (41200), 257 (6050)]; VIIIf, mp 206–208°C (dec.); VIIIf, mp 191–192°C (dec.); VIIId, mp 205–207°C (dec.); VIIIf, mp 161.5–162.5°C (dec.); VIIIf, mp 155–155.5°C (dec.). Characterization of all as the 5-formamidopyrimidines was readily achieved by deter-



Scheme 1

mination of their nmr spectra in $\text{Me}_2\text{SO}-d_6$ [e. g., VIIIb: δ 0.99 (3H, t, $J = 7.3$ Hz, CH_2CH_3), 2.75 (3H, d, $J = 4.6$ Hz, NHCH_3), 3.2–3.65 (2H, m, NCH_2CH_3), 6.18 (2H, s, NH_2), 6.47 (1H, q, $J = 4.6$ Hz, NHCH_3), 7.77 (1H, s, C(2)-H or CHO), 7.89 (1H, s, CHO or C(2)-H)]. On treatment with boiling 1 $\underline{\text{N}}$ aqueous NaOH for 60 min, the adeninium salts VIIa,b,d,e (X = I), VIIc (X = Br), and VIIf (X = ClO_4) isomerized to the corresponding N⁶,7-dialkyladenines (X): Xa (87% yield), mp 309–310°C (lit.¹⁰ mp 311°C); Xb (86%), mp 254–255°C; Xc (91%), mp 181–182°C; Xd (55%), mp 184.5–185.5°C; Xe (50%), mp 160–162°C; Xf (73%), mp 129–130.5°C. The assignment of the N⁶,7-disubstituted structures was based on their uv spectra [e. g., Xb: λ_{max} (95% EtOH) 272.5 nm (shoulder) (ϵ 13700), 277 (14000); λ_{max} (H_2O) (pH 1) 279 (16900); λ_{max} (H_2O) (pH 7 or 13) 276 (14900)], similar to those reported¹⁰ for N⁶,7-dimethyladenine, and identity of Xb with a sample synthesized from 6-chloro-7-ethylpurine¹¹ and MeNH_2 . Cyclization of VIIa in 1 $\underline{\text{N}}$ aqueous NaOH (reflux, 60 min) or in AcNMe_2 with NaH (room temp., 40 min) also furnished Xa in 72% or 84% yield. In general agreement with the results of the NaBH_4 reduction of 7,9-disubstituted purines,¹² treatment of VIIa (X = I) with NaBH_4 (MeOH, room temp., 20 min) produced the 7,8-dihydro derivative XI [84% yield; mp 148–153°C (dec.); uv λ_{max} (95% EtOH) 293 nm (ϵ 5900); nmr ($\text{Me}_2\text{SO}-d_6$) δ 2.64 and 2.73 (3H each, s, NCH_3 's), 4.33 (2H, s, CH_2), 5.70 (2H, broad s, NH_2), 7.67 (1H, s, C(2)-H)], which slowly decomposed in aqueous solution to give VIIa. The ring-opened derivatives VIII were also unstable in solution. For example, VIIa equilibrated with an isomeric formamidopyrimidine presumed to be IXa in H_2O at pH 9.84 (ionic strength 0.50) and 25°C in ca. 30 h (Scheme 1). The reactions in both directions obeyed pseudo-first-order kinetics ($k_2 = 1.49 \times 10^{-3} \text{ min}^{-1}$; $k'_2 = 0.84 \times 10^{-3} \text{ min}^{-1}$; $K_{\text{eq}} = k_2/k'_2 = 1.77$). Under the same conditions the ring opening of VIIa

TABLE I. Rate Constants (k_1) for the Ring Opening of VII in H₂O at pH 9.84, 25°C, and Ionic Strength 0.50

no.	substrate		ring opening	
	R ¹	R ²	$k_1 \times 10^4, \text{min}^{-1}$	rel. rate
VIIa	Me	Me	54.7	1
VIIb	Me	Et	6.72	0.12
VIIc	Me	PhCH ₂	190	3.47
VII d	Et	Me	23.8	0.44
VIIe	Et	Et	2.63	0.05
VII f	Et	PhCH ₂	79.4	1.45
VII g	PhCH ₂	Et	83.1	1.52

(X = ClO₄) to give VIIIa took place at a rate of $5.47 \times 10^{-3} \text{ min}^{-1}$. Equilibration between VIIIa and IXa and the rearrangement of VIIa (X = I) to Xa through VIIIa seem to proceed via a common intermediate (XII). Table I assembles the rates of the ring opening of VIIa,b,d-f (X = ClO₄), VIIc (X = Br), and VIIg (X = ClO₄).³ It may be seen that the replacement of the Me group at the 7- or the 9-position by the Et group retards the ring opening but to a greater extent by the 7-Et group. On the other hand, the benzyl group at either position accelerates the reaction.

In conclusion, the above results have established a general synthetic route to N⁶,7-dialkyladenines (X) from 1-alkoxy-9-alkyladenines through 7,9-dialkyladeninium salts (VII).¹³ They also render a solid help to understanding the chemical behavior of agelasine¹ upon which the correctness of its 7,9-disubstituted adenine structure has relied.

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5. We prefer not commit ourselves as to tautomeric forms by the designation of structure employed herein, since there has been certain spectroscopic evidence in support of the 6-imino-1H-purine structure. The details will be published elsewhere at a later date.
6. Both the amidine group and the N(3) atom of the imidazole ring in Ia and II d were considered to be the sites susceptible to alkylation. For reviews on such susceptibility, see (a) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. I, W. A. Benjamin, New York, 1965, p. 181;
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8. Ref. 6b, p. 167 and p. 241.
9. All new compounds have been characterized by spectral means and gave satisfactory C, H, N analyses.
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13. Alternative syntheses of N⁶,7- and 7,9-disubstituted adenines from 7,9-disubstituted N⁶-acyladenines (prepared from 9-substituted N⁶-acyladenines by a 7-alkylation procedure) have been disclosed quite recently by Maki and his co-workers.^{12c}

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