7,9-DIALKYLADENINIUM SALTS. AN ALTERNATIVE SYNTHESIS, RING OPENING, AND REARRANGEMENT TO N^6,7-DIALKYLADENINES

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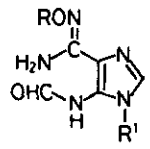
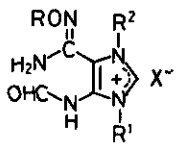
Abstract —— Alkylation of N'-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidine (type I or II) (in the absence of any base) followed by hydrogenolysis of the N'-alkoxy group and cyclization (or vice versa) yielded the corresponding 7,9-dialkyladeninium salts (type VII), which readily rearranged to N^6,7-dialkyladenines (type X) in boiling 1 N NaOH. Under milder basic conditions, VII underwent hydrolysis to produce 4-alkylamino-6-amino-5-formamidopyrimidines (VIII). The $NaBH_4$ 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 synthesis[2] of 7,9-dimethyladeninium perchlorate (VIIa, X = ClO_4) to other alkyl analogues have led to the establishment of a general synthetic route to VII from N^6-alkoxy-9-alkyladenines.[3] This communication describes an alternative synthesis of the salts VII as well as their unique chemical behavior observed.

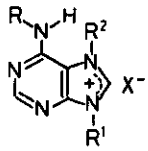
Alkylations of the formamidoimidazoles Ia[4a] and IId,[4a] the readily isolable intermediates[4] in the Dimroth rearrangement of 1-methoxy-9-methyladenine and 1-ethoxy-9-ethyladenine, with MeI, EtI, and $PhCH_2Br$ (Ia only) in $HCONMe_2$ at 30–50°C afforded the corresponding 3-substituted imidazolium 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 N^6-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 H_2 and Raney Ni have already been shown[3] to furnish the corresponding 7,9-dialkyladeninium



I, R = Me
II, R = Et

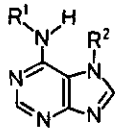


III, R = Me
IV, R = Et

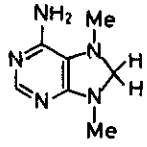


V, R = MeO
VI, R = EtO
VII, R = H

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



X

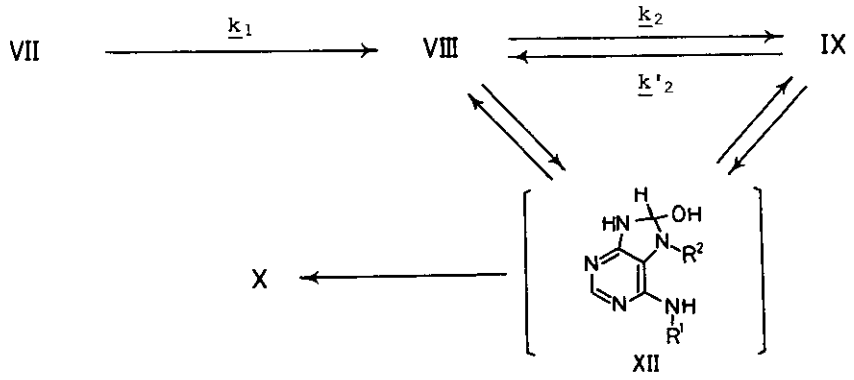


XI

a, $R^1 = R^2 = Me$ b, $R^1 = Me$; $R^2 = Et$ c, $R^1 = Me$; $R^2 = PhCH_2$ d, $R^1 = Et$; $R^2 = Me$
e, $R^1 = R^2 = Et$ f, $R^1 = Et$; $R^2 = PhCH_2$ g, $R^1 = PhCH_2$; $R^2 = Et$

salts [VIIa,b (X = I), VIIc (X = Br)] in acceptable yields. The N^6-ethoxy derivatives VId,e (X = I) were likewise hydrogenolyzed to VIId,e (X = I) in 63–82% yields. Alternatively, similar hydrogenolyses of the N'-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 IId). Preferential 3-substitution[6] on the imidazole ring of Ia and IId presents a contrast to the previous finding[7] that the formamidoimidazoles (type I) are alkylated almost exclusively on the 5-formamido nitrogen atom when treated with alkyl halide in the presence of K_2CO_3.

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 ($X = ClO_4$)[3] were indeed unstable under basic conditions. Treatment of their aqueous solutions with Na_2CO_3 (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: VIIIa,[9] mp 247–248°C (dec.) [uv λ_{max} (95% EtOH) 223 nm (ε 44800), 257 (5600); λ_{max} (H_2O) (pH 1) 223 (29500), 268 (12900); λ_{max} (H_2O) (pH 7) 221 (41200), 258 (6100); λ_{max} (H_2O) (pH 13) 221 (41200), 257 (6050)]; VIIIb, mp 206–208°C (dec.); VIIIc, mp 191–192°C (dec.); VIIId, mp 205–207°C (dec.); VIIIe, 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 Me_2SO-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 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 N^6,7-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 N^6,7-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 reported[10] for N^6,7-dimethyladenine, and identity of Xb with a sample synthesized from 6-chloro-7-ethylpurine[11] and $MeNH_2$. Cyclization of VIIIa in 1 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 (Me_2SO-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 VIIIa. The ring-opened derivatives VIII were also unstable in solution. For example, VIIIa 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 × 10^{-3} min^{-1}; k'_2 = 0.84 × 10^{-3} min^{-1}; K_{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 H_2O at pH 9.84, 25°C, and Ionic Strength 0.50

substrate			ring opening	
no.	R^1	R^2	$k_1 \times 10^4$, min^{-1}	rel. rate
VIIa	Me	Me	54.7	1
VIIb	Me	Et	6.72	0.12
VIIc	Me	$PhCH_2$	190	3.47
VIId	Et	Me	23.8	0.44
VIIe	Et	Et	2.63	0.05
VIIf	Et	$PhCH_2$	79.4	1.45
VIIg	$PhCH_2$	Et	83.1	1.52

(X = ClO_4) to give VIIIa took place at a rate of 5.47×10^{-3} 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 = ClO_4), VIIc (X = Br), and VIIg (X = ClO_4).[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 N^6,7-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 agelasine[1] 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 IId 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; (b) K. Schofield, M. R. Grimmett, and B. R. T. Keene, "Heteroaromatic Nitrogen Compounds. The Azoles," Cambridge University Press, Cambridge, 1976, p. 95.

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13. Alternative syntheses of N^6,7- and 7,9-disubstituted adenines from 7,9-disubstituted N^6-acyladenines (prepared from 9-substituted N^6-acyladenines by a 7-alkylation procedure) have been disclosed quite recently by Maki and his coworkers.[12c]

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