

A NEW CLASS OF PURINES. SYNTHESIS OF 3,9-DIALKYL-  
HYPOXANTHINES BY THE CYCLIZATION OF 1-ALKYL-  
5-ALKYLAMINOIMIDAZOLE-4-CARBOXAMIDES

Taisuke Itaya\* and Kazuo Ogawa

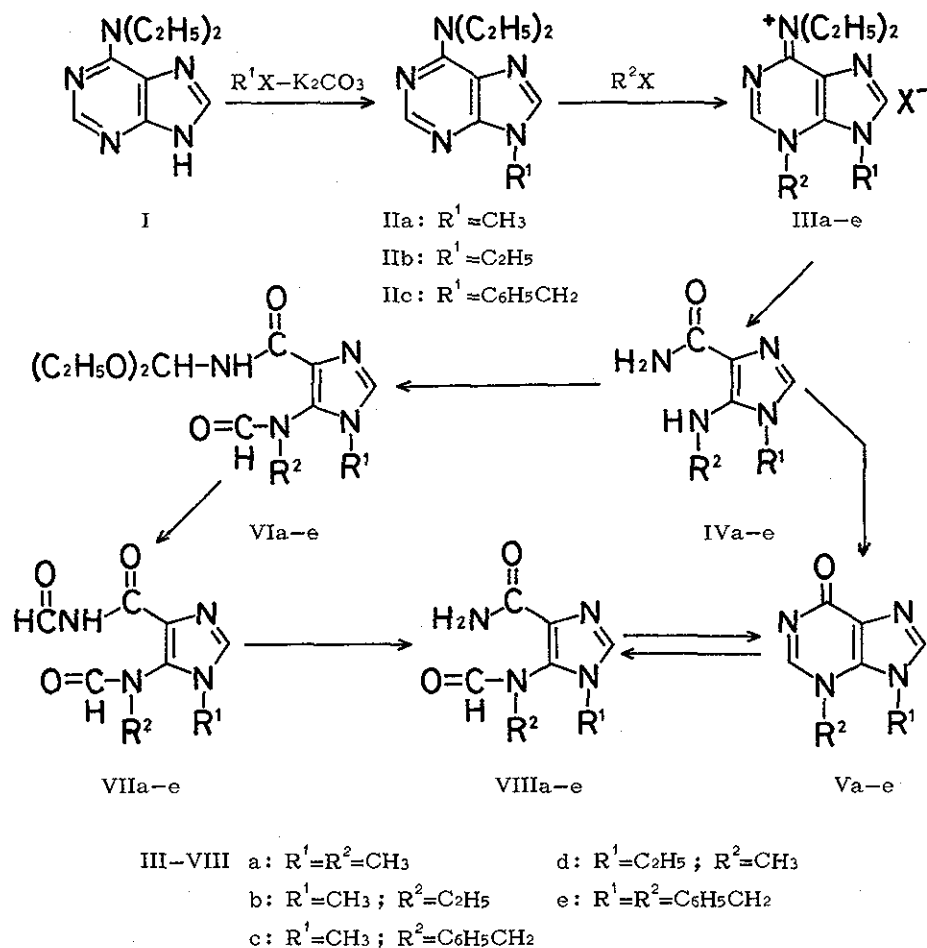
Faculty of Pharmaceutical Sciences, Kanazawa University

13-1 Takara-machi, Kanazawa 920, Japan

Alkylation of *N,N*-diethyladenine (I) with alkyl halides in the presence of potassium carbonate gave mainly *N,N*-diethyl-9-alkyladenines (II), which were converted to 1-alkyl-5-alkylaminoimidazole-4-carboxamides (IV) via *N,N*-diethyl-3,9-dialkyladeninium salts (III). Heating IV in a mixture of triethyl orthoformate and acetic anhydride produced hitherto unknown 3,9-dialkylhypoxanthines (V) as well as *N*-diethoxymethyl-1-alkyl-5-(*N*-alkylformamido)imidazole-4-carboxamides (VI).

The increasing interest in alkyl-substituted purines as biologically active substances has greatly multiplied the number of known alkylated purines.<sup>1</sup> Among the six possible *N,N*-dialkylhypoxanthines, the 3,9-dialkyl compounds still have remained unknown, although a cyclic derivative, 2',3'-*O*-isopropylidene-3,5'-cycloinosine has been reported.<sup>2</sup> We now describe the first general synthesis of 3,9-dialkylhypoxanthines (V).

At first we assumed that 3,9-dialkyladenines<sup>3</sup> would be available for synthetic precursors of V, but treatment of 3,9-dimethyladenine hydrochloride<sup>4</sup> with sodium nitrite in hydrochloric acid or in aqueous acetic acid did not give the desired



compound (Va). Consequently, we planned the cyclization of 1-alkyl-5-alkylamino-imidazole-4-carboxamides (IV).

Treatment of *N,N*-diethyladenine (I)<sup>5</sup> with ethyl iodide in *N,N*-dimethylacetamide in the presence of potassium carbonate at room temperature for 6 hr provided *N,N*,9-triethyladenine (IIb) as the major product,<sup>6</sup> as well as *N,N*,3-triethyladenine (13% yield; mp 71–72°).<sup>7</sup> The 9-ethyl structure of IIb was establish-

ed by the direct comparison of its picrate (mp 169–170°) with that of a sample synthesized from 6-chloro-9-ethylpurine<sup>8</sup> and diethylamine. N,N-Diethyl-9-methyladenine (IIa)<sup>6,9</sup> and N,N-diethyl-9-benzyladenine (IIc: 64% yield; mp 63–64°) were also obtained in a similar manner.

The second alkylation occurred at the 3-position<sup>10</sup> when the N,N-diethyl-9-alkyladenines (IIa,b) were treated again with methyl, ethyl iodide, and benzyl bromide in N,N-dimethylacetamide at 40–100°, resulting in production (57–75% overall yield from I) of the corresponding N,N,3,9-tetraalkyladeninium salts (III): N,N-diethyl-3,9-dimethyladeninium iodide {IIIa: X=I; mp 230.5–232° (dec.) [lit.<sup>11</sup> mp 230.5–232.5° (dec.)]}; N,N,3-triethyl-9-methyladeninium iodide [IIIb: X=I; mp 228–230° (dec.)]; N,N-diethyl-3-benzyl-9-methyladeninium bromide [IIIc: X=Br; mp 207–208° (dec.)]; N,N,9-triethyl-3-methyladeninium iodide [IIId: X=I; mp 213–214° (dec.)].

Alkaline hydrolysis of III in a manner similar to that of Marsico *et al.*<sup>11</sup> afforded IV (73–82% yield): 1-methyl-5-methylaminoimidazole-4-carboxamide [IVa: mp 211–213° (lit.<sup>11</sup> mp 211–213°)]; 1-methyl-5-ethylaminoimidazole-4-carboxamide (IVb: mp 195–196°); 1-methyl-5-benzylaminoimidazole-4-carboxamide (IVc: mp 161–162°); 1-ethyl-5-methylaminoimidazole-4-carboxamide (IVd: mp 176–177°).

Cyclization of IV to 3,9-dialkylhypoxanthine (V) was effected by heating IV at reflux in a mixture (previously refluxed for 1 hr) of triethyl orthoformate and acetic anhydride (8:3, v/v) for 40–60 min to produce V: 3,9-dimethylhypoxanthine (Va: 60% yield; mp >300°); 3-ethyl-9-methylhypoxanthine [Vb: 48% yield; mp 265–268° (dec.)]; 3-benzyl-9-methylhypoxanthine [Vc: 46% yield; mp 252–254° (dec.)]; 9-ethyl-3-methylhypoxanthine [Vd: 66% yield; mp 260–261° (dec.)]. Montgomery *et al.*<sup>12</sup> failed to convert 1-benzyl-5-benzylaminoimidazole-4-carboxamide (IVe) to 3,9-dibenzylhypoxanthine (Ve) under various conditions, but isolat-

ed 1-benzyl-5-(N-benzylformamido)imidazole-4-carboxamide (VIIIe) and 9-benzyl-hypoxanthine. In our hands, IVe (obtained from IIc in 28% yield via IIIe, mp 152–153° (lit.<sup>12</sup> mp 153°)) successfully cyclized to Ve (37% yield; mp 270–272° (dec.)) under the reaction conditions described above.

The somewhat low yields of V in the cyclization of IV were due to the concomitant formation of N-diethoxymethyl-1-alkyl-5-(N-alkylformamido)imidazole-4-carboxamides (VI). These compounds were obtained as unstable oily substances and their structures were assignable by means of nmr spectrum.<sup>13</sup> On being treated with alumina, the compounds (VI) were transformed into VIII through isolable intermediates, N-formyl-1-alkyl-5-(N-alkylformamido)imidazole-4-carboxamides (VII).<sup>14</sup> Thus, 1-methyl-5-(N-methylformamido)imidazole-4-carboxamide (VIIIa: 39% yield; mp 244–245°), 1-methyl-5-(N-ethylformamido)imidazole-4-carboxamide (VIIIb: 50% yield; mp 214–216°), 1-methyl-5-(N-benzylformamido)imidazole-4-carboxamide (VIIIc: 22% yield; mp 219–220°), 1-ethyl-5-(N-methylformamido)imidazole-4-carboxamide (VIIId: 13% yield; mp 195–196°), and 1-benzyl-5-(N-benzylformamido)imidazole-4-carboxamide (VIIIe: 43% yield; mp 205–207° (lit.<sup>12</sup> mp 208°)) were obtained. Heating VIIIa at 260° for 30 min furnished a further crop of Va but in only 20% yield.

The dimethylhypoxanthine (Va) had uv spectra [ $\lambda_{\max}^{95\% \text{ EtOH}}$  258 nm ( $\epsilon$  10900);  $\lambda_{\max}^{\text{H}_2\text{O}}$  (pH 1) 255 (10400);  $\lambda_{\max}^{\text{H}_2\text{O}}$  (pH 7) 261 (12200); (pH 13) unstable]<sup>15</sup> different from those of the known N,N-dimethyl isomers (1,7-,<sup>16</sup> 1,9-,<sup>17</sup> and 7,9-<sup>18</sup>) and the uv spectra of the dibenzylated product [Ve:  $\lambda_{\max}^{95\% \text{ EtOH}}$  258 nm ( $\epsilon$  12800);  $\lambda_{\max}^{\text{H}_2\text{O}}$  (pH 1) 256 (12100);  $\lambda_{\max}^{\text{H}_2\text{O}}$  (pH 7) 261 (13800); (pH 13) unstable] were unlike those of any other known N,N-dibenzyl isomers (1,3-,<sup>12</sup> 1,7-,<sup>12,19</sup> 1,9-,<sup>12,19</sup> 3,7-,<sup>19</sup> and 7,9-<sup>12</sup>). The nmr spectrum of Va in D<sub>2</sub>O solution exhibited two three-proton singlets ( $\delta$  4.08 and 4.12, two N-Me's) and two one-proton singlets ( $\delta$  7.80 and

8.06, two purinyl protons). Final identification as 3,9-dimethylhypoxanthine rested on the alkaline hydrolysis of Va leading to VIIIa (77% yield).

Synthesis of 3-alkylinosine along this line is under progress.

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- 4 Kindly gifted by Mr. T. Saito, Kanazawa University.
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- 12 J. A. Montgomery, K. Hewson, S. J. Clayton, and H. J. Thomas, J. Org. Chem., 1966, 31, 2202.
- 13 The nmr spectrum of VIb in CDCl<sub>3</sub> exhibited two triplets ( $\delta$  1.13, 3H, J=7 Hz;  $\delta$  1.24, 6H, J=7 Hz) and a multiplet ( $\delta$  3.7, 6H) (N-Et and O-Et), two singlets ( $\delta$  3.51 and 3.55, 3H, N(CH<sub>3</sub>)), two doublets ( $\delta$  5.09 and 6.01, 1H, J=8 Hz each,  $\text{>CH-NH}$ ), two singlets ( $\delta$  7.40 and 7.42, 1H, C $\alpha$ -H), a broad signal ( $\delta$  7.70, 1H, NH), and two singlets ( $\delta$  8.11 and 8.30, 1H, HCON). The appearance of the twin signals are probably due to cis-trans isomerism caused by restricted rotation about the C-N bond in the formamido group.
- 14 N-Formyl-1-methyl-5-(N-methylformamido)imidazole-4-carboxamide (VIIa: mp 197-200°) and N-formyl-1-methyl-5-(N-ethylformamido)imidazole-4-carboxamide (VIIb: mp 155-158°) were isolated.
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