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

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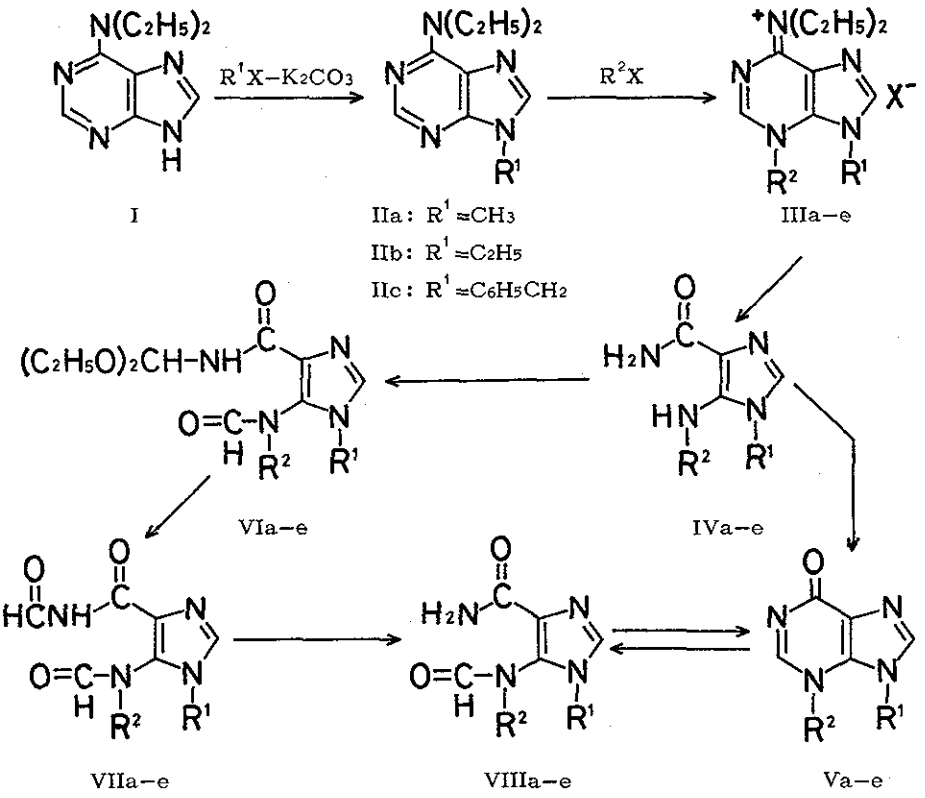
Alkylation of N,N-diethyladenine (I) with alkyl halides in the presence of potassium carbonate gave mainly N,N-diethyl-9-alkyladenines (II), which were converted to 1-alkyl-5-alkylamino-imidazole-4-carboxamides (IV) via N,N-diethyl-3,9-dialkylade-ninium salts (III). Heating IV in a mixture of triethyl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

The increasing interest in alkyl-substituted purines as biologically active substances has greatly multiplied the number of known alkylated purines.[1] 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.[2] We now describe the first general synthesis of 3,9-dialkylhypoxanthines (V).

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



III–VIII a: $R^1=R^2=CH_3$ d: $R^1=C_2H_5$; $R^2=CH_3$

b: $R^1=CH_3$; $R^2=C_2H_5$ e: $R^1=R^2=C_6H_5CH_2$

c: $R^1=CH_3$; $R^2=C_6H_5CH_2$

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

Treatment of N,N-diethyladenine (I)[5] 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,[6] as well as N,N,3-triethyladenine (13% yield; mp 71–72°).[7] 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[8] and diethylamine. N,N-Diethyl-9-methyladenine (IIa)[6,9] 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[10] 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.[11] 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.[11] afforded IV (73–82% yield): 1-methyl-5-methylaminoimidazole-4-carboxamide [IVa: mp 211–213° (lit.[11] 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.[12] 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-benzylhypoxanthine. In our hands, IVe [obtained from IIc in 28% yield via IIIe, mp 152–153° (lit.[12] 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.[13] 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).[14] 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.[12] 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 [$\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 10900); $\lambda_{max}^{H_2O}$ (pH 1) 255 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 261 (12200); (pH 13) unstable][15] different from those of the known N,N-dimethyl isomers (1,7-,[16] 1,9-,[17] and 7,9-[18]) and the uv spectra of the dibenzylated product [Ve: $\lambda_{max}^{95\%EtOH}$ 258 nm (ε 12800); $\lambda_{max}^{H_2O}$ (pH 1) 256 (12100); $\lambda_{max}^{H_2O}$ (pH 7) 261 (13800); (pH 13) unstable] were unlike those of any other known N,N-dibenzyl isomers (1,3-,[12] 1,7-,[12,19] 1,9-,[12,19] 3,7-,[19] and 7,9-[12]). The nmr spectrum of Va in D_2O solution exhibited two three-proton singlets (δ 4.08 and 4.12, two N-Me's) and two one-proton singlets (δ 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.

5 This compound was obtained by treating 6-chloropurine with diethylamine {97% yield; mp 221–222° [lit. (R. K. Robins and B. E. Christensen, J. Am. Chem. Soc., 1952, 74, 3624) mp 222–223°]}.

6 Obtained as an oil which was contaminated by N,N-dimethylacetamide.

7 Complete analytical and/or spectral data were obtained for all new compounds reported.

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13 The nmr spectrum of VIb in $CDCl_3$ exhibited two triplets (δ 1.13, 3H, J=7 Hz; δ 1.24, 6H, J=7 Hz) and a multiplet (δ 3.7, 6H) (N-Et and O-Et), two singlets (δ 3.51 and 3.55, 3H, N(3)-Me), two doublets (δ 5.09 and 6.01, 1H, J=8 Hz each, >CH-NH), two singlets (δ 7.40 and 7.42, 1H, C(2)-H), a broad signal (δ 7.70, 1H, NH), and two singlets (δ 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.

15 Although Israelite chemists claimed that 3,9-dimethylhypoxanthine (Va) was formed on treatment of 3,9-dimethyl-6-thiopurine with cold 50% nitric acid (Z. Neiman and F. Bergmann, Israel J. Chem., 1965, 3, 161), the uv spectra reported therein are different from those of our present sample.

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