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SYNTHESIS OF 7,9-DISUBSTITUTED ADENINES: THE USE OF THE METHOXYL GROUP AS A DIRECTING GROUP IN N-ALKYLATION OF THE ADENINE RING

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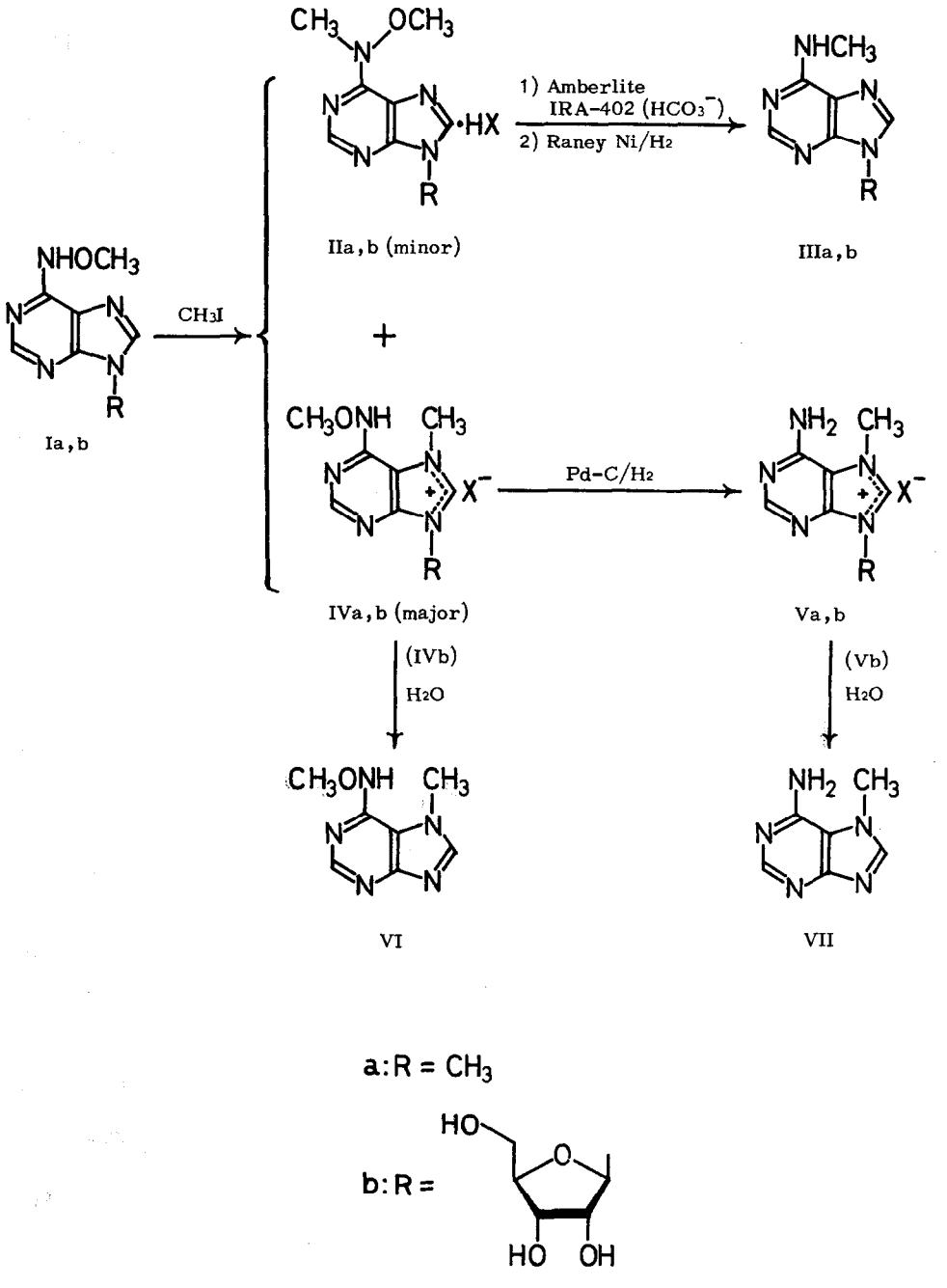
The compelling interest in the naturally-occurring N-substituted purines has greatly multiplied the number of known alkylated purines.[1] Among the eleven possible N,N-disubstituted adenines, however, the 1,3- and 7,9-dialkyl compounds still have remained unknown. In the present communication we wish to report the synthesis of 7,9-dimethyladenine perchlorate (Va: X = ClO_4), the prototype of one of the remaining two disubstituted adenines, which utilizes the N^6-methoxyl group as a directing group in methylation of N^6-methoxy-9-methyladenine (Ia);[2] an extension of this methylation to the nucleoside analogue (Ib)[3] is also included.

Treatment of Ia with methyl iodide in N,N-dimethylacetamide at 30° for 7 hr produced N^6-methoxy-7,9-dimethyladenine hydriodide (IVa: X = I), m.p. 250–251° (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 291 nm (ε 8500); $\lambda_{max}^{H_2O}$ (pH 1) 226 (19000), 283 (9300); $\lambda_{max}^{H_2O}$ (pH 7) 226 (18900), 283 (9200); $\lambda_{max}^{H_2O}$ (pH 13) unstable, as the major product (59%), as well as N^6-methoxy-N^6,9-dimethyladenine hydriodide (IIa: X = I) (24%), m.p. 170.5–171.5° (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 277 nm (ε 16500); $\lambda_{max}^{H_2O}$ (pH 1) 220 (22900), 276 (15700); $\lambda_{max}^{H_2O}$ (pH 7) 220 (25500), 276 (17400); $\lambda_{max}^{H_2O}$ (pH 13) 276 (16800). The N^6-methyl structure (IIa) of the minor product was assignable by hydrogenolysis using hydrogen and Raney nickel on the corresponding free base to N^6,9-dimethyladenine (IIIa),[4] m.p. 183–186°, identified by direct comparison. Since the UV spectra of IIa were quite distinct from those of other possible isomers, N^6-methoxy-1,9-dimethyladenine[5] and 1-methoxy-N^6,9-dimethyladenine,[5] the possibility that compound IIIa might be formed from these isomers through a Dimroth-type rearrangement during the process could be excluded.

The major product (IVa: X = I) was converted into the perchlorate (IVa: X = ClO_4), m.p. 257–259° (dec.), which was then subjected to catalytic hydrogenolysis over 10% palladium-on-carbon. The


NHOCH3
CH3I
Ia,b
CH3 N OCH3
•HX
R
IIa,b (minor)
1) Amberlite IRA-402 (HCO3−)
2) Raney Ni/H2
NHCH3
IIIa,b
+
CH3ONH CH3
X−
IVa,b (major)
Pd-C/H2
NH2 CH3
Va,b
(IVb)
H2O
(Vb)
H2O
VI
VII

a: R = CH_3

b: R =

HO
O
HO
OH

product (Va: X = ClO_4), m.p. 276–277° (dec.), was unlike the previously known perchlorates of N,9-dimethyladenine isomers (1,9-[4] and 3,9-[6]) and had UV spectra [$\lambda_{max}^{95\% EtOH}$ 273 nm (ε 11500); $\lambda_{max}^{H_2O}$ (pH 1) 268 (11900); $\lambda_{max}^{H_2O}$ (pH 7) 269 (12100); $\lambda_{max}^{H_2O}$ (pH 13) 257 (5800)] different from those[4] of the N^6,9-dimethyl isomer (IIIa). The NMR spectrum of Va (X = ClO_4) in deuterated dimethyl sulfoxide solution exhibited two three-proton singlets at 6.15 and 5.86 τ (two N-CH_3's), a fairly sharp two-proton peak at 2.11 τ (NH_2, exchanged with D_2O), two one-proton singlets at 1.60 ($C_{(2)}$-H) and 0.50 τ ($C_{(8)}$-H). Final identification as 7,9-dimethyladenine perchlorate rested on the analogous methylation of the adenosine derivative (Ib) and subsequent reactions of the major product leading to 7-methyladenine (VII), which are briefly outlined below.

Methylation of Ib in the same way as that described above for Ia and treatment of the product with Amberlite CG-400 (HSO_4^-) gave N^6-methoxy-7-methyladenosine sulfate (IVb), m.p. 128–129° (dec.), and the N^6-methyl isomer (IIb) as a hard oil. Hydrogenolysis of the free base obtained from IIb was effected as in the case of IIa (X = I), giving N^6-methyladenosine (IIIb)[7] in 33% yield (based on the starting nucleoside).

On the other hand, low-pressure catalytic hydrogenation of sulfate IVb over palladium-on-carbon yielded a hygroscopic solid presumed to be 7-methyladenosine sulfate (Vb), which furnished VII[8] when treated with water at 100° for 40 min. A similar hydrolysis of sulfate IVb afforded N^6-methoxy-7-methyladenine (VI), m.p. 232–233° (dec.); UV $\lambda_{max}^{95\% EtOH}$ 277 nm (ε 13400); $\lambda_{max}^{H_2O}$ (pH 1) 228 (6800), 278 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 275 (13800); $\lambda_{max}^{H_2O}$ (pH 13) 296 (13200).

It has been well known[1,7,9] that a substituent at the 9-position of adenine orients further alkylation to the 1-position. The observed alteration by the N^6-methoxyl group in such a directing effect is particularly noteworthy in this connection and will be of considerable utility for chemical modification of the adenine ring.

Further investigation along these lines is now under way.

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6. This isomer has recently been prepared in the form of the corresponding perchlorate in our laboratory (T. Fujii, T. Itaya, K. Mohri, and T. Saito, J. C. S. Chem. Comm., submitted.) from N′-methoxy-1-methyl-5-formamidoimidazole-4-carboxamidine, the readily isolable intermediate in the Dimroth rearrangement of 1-methoxy-9-methyladenine,[2,4] by reduction with $LiAlH_4$ followed by cyclization with ethyl orthoformate and removal of the methoxyl group by catalytic hydrogenolysis. Part of the work will be presented at the 6th Symposium on the Chemistry of Heterocyclic Compounds organized by Society of Synthetic Organic Chemistry, Japan, and Pharmaceutical Society of Japan, Nagoya, Japan, November 1–2, 1973.

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