SYNTHESES OF 9-ALLYLADENINE 1-OXIDE AND 9-(Δ^2-ISOPENTENYL)ADENINE 1-OXIDE

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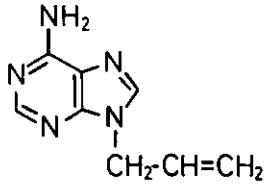
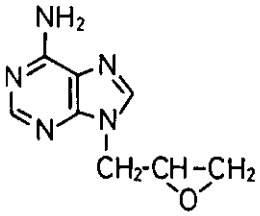
Abstract— An unequivocal synthesis of 9-allyladenine 1-oxide (III) has been accomplished by an initial alkylation of 1-ethoxyadenine (VI) with allyl bromide and the Et—O bond cleavage of the resulting 9-allyl-1-ethoxyadenine hydrobromide (VII) with pyridine. 9-(Δ^2-Isopentenyl)adenine 1-oxide (IX) was also prepared in a similar manner.

Oxidation of 9-allyladenine (I) with perbenzoic acid was reported by Kondo et al.[1] to give 9-(2,3-epoxypropyl)adenine (II) in 63% yield, although the uv spectrum of the oxidized material was suggestive of the 1-N-oxide structure (III). The recent communication by DiMenna and Piantadosi[2] reported that a similar oxidation of I with m-chloroperbenzoic acid produced 9-allyladenine 1-oxide (III) and not the epoxypropyl derivative II as claimed by the Japanese workers. However, the evidence adduced by the American group for assignment of the 1-N-oxide structure also seemed somewhat inconclusive. This prompted us to prepare the N-oxide III through an unambiguous synthetic route that should not include a step to expose the allylic side chain to oxidation.

The starting material selected in the present synthesis was 1-ethoxyadenine (VI),[3] which was easily obtainable by the peracetic acid oxidation of adenine (IV)[3,4] followed by ethylation of the resulting 1-N-oxide V.[3] Treatment of VI with allyl bromide in $AcNMe_2$ at room temperature (26–32°C) for 48 h furnished the allylated product VII [mp 204–208°C (dec.); $\lambda_{max}^{95\%\ EtOH}$ 259 nm (ε 12700); $\lambda_{max}^{H_2O}$ (pH 1) 260 (12900); $\lambda_{max}^{H_2O}$ (pH 7) 260 (12800); $\lambda_{max}^{H_2O}$ (pH 13)[5] 258 (13400), 265 (sh) (12000)][6] in 67% yield. The assignment of the 9-substituted structure was based on the generalization that 1-alkoxyadenines undergo alkylation mainly at the 9-position[3] and on the uv spectra



I



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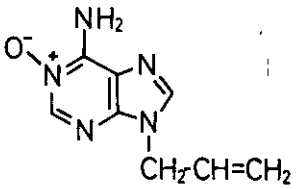
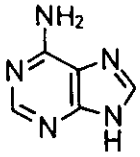
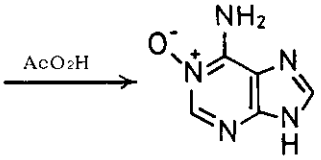


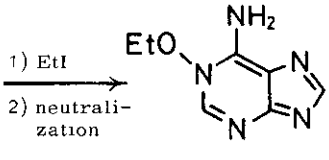
III



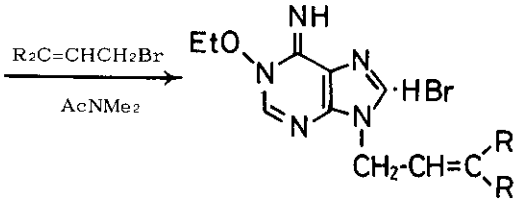
IV



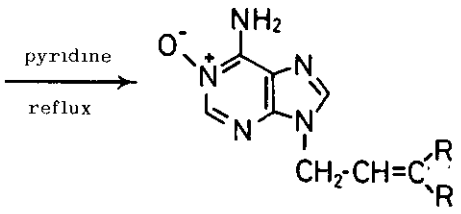
V



VI



VII, R = H
VIII, R = Me



III, R = H
IX, R = Me

similar to those[3,7] of 1-alkoxy-9-alkyladenines. Removal of the ethyl group from VII was then effected with boiling pyridine (1 h) to give the desired N-oxide III [mp 265–269°C (dec.)] in 86% yield. The easy cleavage of the Et—O linkage was in general agreement with the facile dealkylation[8,9] of 1-alkoxy-9-alkyladenine salts on nucleophilic attack. The structure of III was supported by similarity of its uv spectra [$\lambda_{max}^{95\%\ EtOH}$ 235 nm (ε 42300), 263 (8000), 300 (2100); $\lambda_{max}^{H_2O}$ (pH 1) 259 (12300); $\lambda_{max}^{H_2O}$ (pH 7) 232 (45300), 262 (8100), 292 (2100); $\lambda_{max}^{H_2O}$ (pH 13) 232 (28500), 269 (8700), 305 (4100)] to those[7] of 9-alkyladenine 1-oxides and by its nmr spectrum [(CF_3CO_2D) δ: 5.16 (2H, d, J = 6 Hz, $NC\underline{H}_2CH$), 5.62 (1H, d, J = 17.5 Hz, trans CH=$C\underline{H}_2$), 5.66 (1H, d, J = 9 Hz, cis CH=$C\underline{H}_2$), 5.80–6.32 (1H, m, $CH_2C\underline{H}=CH_2$), 8.92 and 9.17 (1H each, s, purine protons)] indicating that the allylic side chain was kept intact.

The synthetic generality of the above scheme was then checked by a parallel synthesis of 9-(Δ^2-isopentenyl)adenine 1-oxide (IX), the 1-N-oxide of one of the positional isomers of triacanthine.[10] Alkylation of VI with 3-methyl-2-butenyl bromide ($AcNMe_2$, 29–33°C, 12 h) produced the salt VIII [mp 207.5–210.5°C (dec.)] in 66% yield. On treatment with boiling pyridine for 1 h, VIII afforded the N-oxide IX [88% yield; mp 266.5–268.5°C (dec.); nmr (CF_3CO_2D) δ: 1.96 (6H, s, CMe_2), 5.15 (2H, d, J = 8 Hz, $NC\underline{H}_2CH$), 5.59 (1H, t, J = 8 Hz, $CH_2C\underline{H}$=C), 8.94 and 9.24 (1H each, s, purine protons)]. The uv spectra of VIII and IX matched those of VII and III, respectively.

Thus, the present results have demonstrated the synthetic utility of the 1-ethoxy group for preparation of adenine 1-oxide derivatives possessing unsaturated side chains at the 9-position.

ACKNOWLEDGMENT Financial support of this work by a Grant-in-Aid for Cancer Research (to Professor D. Mizuno) from the Ministry of Education, Science and Culture, Japan, is gratefully acknowledged. We also wish to thank Mr. M. Naruse, Kyowa Hakko Kogyo Co., for a generous gift of adenine.

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received, 17th September, 1979