

Hydrogen Fluoride Treatment of Protected Dipeptides—Protected dipeptide (50 mg) and excess anisole (110 mg) were placed in a Toho Kasei Hydrogen fluoride apparatus and 5 ml of anhydrous hydrogen fluoride was introduced. After 1 hr stirring at various temperature (see Table), hydrogen fluoride was completely distilled off *in vacuo*. The residue was dissolved in water and extracted with ethyl acetate. The aqueous layer was lyophilized. The white residue was dissolved in aqueous 1% ammonium hydrogen carbonate and stood at 40° for 24 hr. After lyophilization of the reaction mixture, the product was applied on paper chromatography (Toyo No. 50 and in butanol: acetic acid: water=2:1:1). Amino acid analysis of α and β -aspartylserine. α , Asp_{1.09}, Ser_{1.00}; β , Asp_{1.05}, Ser_{1.00} (6N HCl at 110° for 24 hr).

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Purines. X.¹⁾ A Convenient Method for Synthesis of 2',3'-O-Isopropylidene-adenosine 1-Oxide

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The preparation of 2',3'-O-isopropylideneadenosine 1-oxide (III) from 2',3'-O-isopropylideneadenosine (II)³⁾ by the 1-N-oxidation was first reported in 1958 by Brown and co-workers.⁴⁾ In a continuing study of the chemistry of 1-alkoxy-9-alkyladenine salts^{1,5)} we had occasion to examine an alternative synthesis of this N-oxide (III), which constitutes the major portion of this paper.

The starting material selected for the present synthesis was adenosine 1-oxide (IV),^{4,6)} and it was prepared from adenosine (I) in 65% yield according to the procedure reported by Stevens *et al.*⁴⁾ except that the excess of hydrogen peroxide and peracetic acid were removed by passing the reaction mixture in the cold (2–5°) through a column packed with Amberlite CG-120 (H⁺) and the column was eluted with dilute aqueous ammonium hydroxide. Since we have noticed that the original procedure often requires stirring a few days long with palladium-on-charcoal for destroying the peroxides, this modification will prove of great use.

In order to prepare isopropylidene derivative III, condensation of IV with acetone in the presence of *p*-toluenesulfonic acid was then attempted under conditions patterned after those³⁾ employed for the synthesis of II from I. However, the *p*-toluenesulfonate of IV that formed was only sparingly soluble in acetone, and the desired reaction seemed to occur only very slowly. Accordingly, we next tried to use perchloric acid as a catalyst in a mixture of acetone and 2,2-dimethoxypropane because of its simplicity, ready availability, and the ease with which it could convert certain nucleosides into the corresponding isopropylidene derivatives.⁸⁾ Treatment of IV with acetone containing 2,2-dimethoxypropane and 70%

1) Part IX: T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.* (Tokyo), **20**, 1818 (1972).

2) Location: 13-1 Takara-machi, Kanazawa 920, Japan.

3) A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961), and references cited.

4) M.A. Stevens, D.I. Magrath, H.W. Smith, and G.B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958).

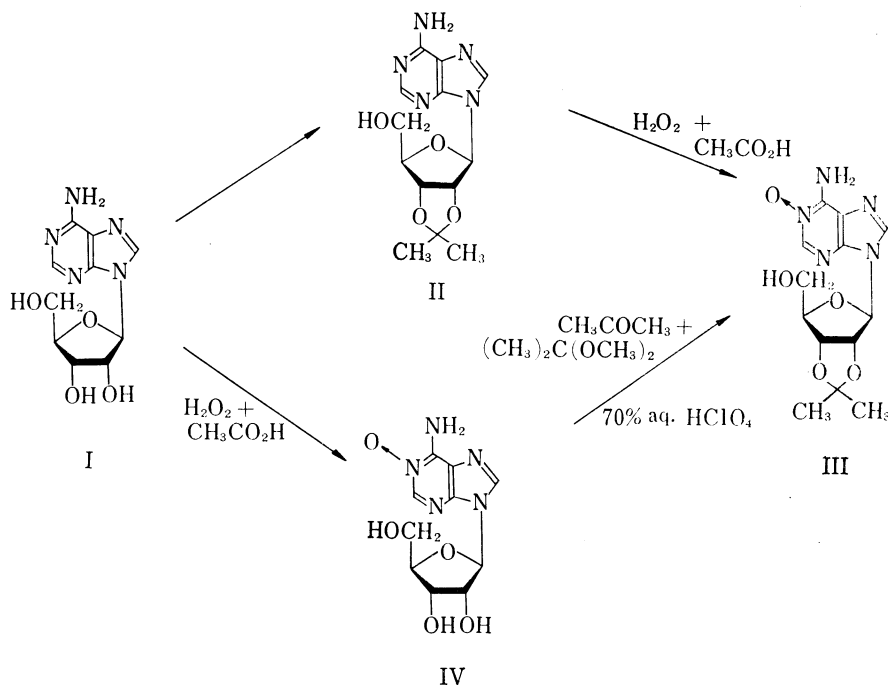
5) T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.* (Tokyo), **20**, 958 (1972), and earlier papers cited therein.

6) For a monohydrate of N-oxide IV, see footnote 8 in ref. 7.

7) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).

8) a) J.A. Zderic, J.G. Moffatt, D. Kau, K. Gerzon, and W.E. Fitzgibbon, *J. Med. Chem.*, **8**, 275 (1965);

b) T. Ueda, Y. Iida, K. Ikeda, and Y. Mizuno, *Chem. Pharm. Bull.* (Tokyo), **16**, 1788 (1968).



aqueous perchloric acid at room temperature for 45 min afforded, after neutralization with triethylamine, the desired product (III), mp 240–241° (decomp.), in 83% yield. This sample was identical with an authentic specimen of III prepared by the earlier method.⁴⁾

It may be noted that the present alternative route (I→IV→III) can produce compound III more easily in better yield and on a larger scale than the previous synthesis (I→II→III). Thus, adequate amounts of this isopropylidene N-oxide (III), required for our current work, can be prepared readily by following the procedure described below.

Experimental⁹⁾

Adenosine 1-Oxide (IV)—A solution of adenosine (40.0 g, 0.15 mole) in a mixture of acetic acid (2 liters) and 30% aqueous H₂O₂ (200 ml) was kept at 30° for 5 days. The resulting mixture was diluted with H₂O (4 liters) under cooling and the cold solution was immediately passed through a column of Amberlite CG-120 (type I, H⁺) (240 ml, 0.46 mole eq) in a freezing room (2–5°). The column was then washed with cold H₂O (2 liters) until a test with potassium iodide-starch paper indicated the absence of peroxides in the latest portion of the washings. Next the column was eluted successively with cold 2% aqueous NH₃ (1 liter) and cold 5% aqueous NH₃ (2 liters). The ammoniacal eluates were combined and evaporated *in vacuo* to dryness to leave a colorless solid. Two recrystallizations from H₂O and drying over P₂O₅ at 60° and 3 mm Hg for 14 hr gave colorless prisms (29.2 g, 65%) of a monohydrate⁹⁾ of IV, mp 224–225° (decomp.), shown to be homogeneous by paper chromatography (PPC). This sample was recrystallized from 99% aqueous ethanol to give anhydrous IV as colorless minute needles, mp 220–222° (decomp.), identical to an authentic specimen⁴⁾ by comparison of the infrared (IR) spectra.

2',3'-O-Isopropylideneadenosine 1-Oxide (III)—To a mixture of dry acetone (700 ml) and 2,2-dimethoxypropane (70 ml) was added 70% aqueous HClO₄ (8 ml). After 5 min, adenosine 1-oxide monohydrate (IV·H₂O) (20.0 g, 66.4 mmoles) was added in one portion with continuous stirring. The mixture

9) All melting points were obtained on a Yamato MP-1 capillary melting point apparatus and are corrected. Paper chromatographies were developed as described previously.⁷⁾ See also ref. 7 for details of instrumentation and measurement. Elemental analyses were carried out by Mr. Y. Itatani and Miss S. Toyoshima at Kanazawa University.

was stirred at room temperature and the oxide went into solution within 10 min. After 45 min, the resulting orange solution was cooled and triethylamine (40 ml) was added, giving colorless gelatinous precipitates. The mixture was evaporated under vacuum to leave a gel. The residue was triturated with boiling 99% aqueous ethanol (200 ml) and the mixture was allowed to stand at room temperature for 2 hr and then in a refrigerator for 2 hr. The insoluble solid was filtered off, washed with 99% aqueous ethanol, and dried over conc. H_2SO_4 at room temperature and 18 mm Hg for 15 hr to give an anhydrous sample of III, mp 239—240° (decomp.), shown to be pure by means of PPC. Yield, 17.8 g (83%). Recrystallization from 99% aqueous ethanol and drying over P_2O_5 at 110° and 3 mm Hg for 3 hr furnished an analytical sample as colorless needles, mp 240—241° (decomp.) [lit.⁴⁾ mp 176—178° (decomp.)]; $[\alpha]_D^{20} -51.4^\circ$ ($c=1.00$, $l=0.5$, H_2O); UV $\lambda_{\text{max}}^{\text{aq. EtOH}}$ $m\mu$ (ϵ): 235 (40700), 264 (7800), 301 (2300); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1)¹⁰⁾ 258 (12100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7)¹¹⁾ 233 (40800), 262 (8000), 296 (2100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13)¹²⁾ 232 (22500), 269 (8400), 310 (4100). Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_5\text{N}_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.29; H, 5.44; N, 21.86. Identity of this sample with the one obtained by the earlier method⁴⁾ was established by mixed melting-point test, PPC, and ultraviolet and IR spectra.

Replacement of the monohydrate ($\text{IV}\cdot\text{H}_2\text{O}$) by an anhydrous sample in this reaction could not increase the yield of III.

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10) Measured in 0.1N HCl.

11) Measured in 0.005M phosphate buffer.

12) Measured in 0.1N NaOH.

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Studies on Phenothiazinyl Radicals

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During the course of numerous studies on phenothiazine radicals, it has been indicated by electron spin resonance (ESR) method that neutral phenothiazinyl radical which is rather unstable can be produced from phenothiazine by several methods.²⁻⁴⁾ However, any work has not been published regarding the electronic absorption spectrum of these radicals. This may be chiefly because, as seen in general, measuring and assigning the spectrum of such unstable radical are seriously prevented from coexistence of various radical decay products. In this note we shall report the electronic absorption spectra of non-substituted and 1-methyl-substituted phenothiazinyl radicals which are generated in degassed dimethylsulfoxide-acetic anhydride mixture. By referring to the ESR spectra in the same systems and by performing theoretical calculations on the electronic transition of the radicals, a brief comment will be given to the assignment of the new absorption maxima in the electronic absorption spectra.

Experimental

1-Methylphenothiazine was prepared from thionation of the corresponding diarylamine by the method described in the literature.⁵⁾ (mp 136°. Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{NS}$: C, 73.20; H, 5.20; N, 6.57. Found:

1) Location: *Oshika, Shizuoka-shi.*

2) H.J. Shine and E.E. Mach, *J. Org. Chem.*, **30**, 2130 (1965).

3) B.C. Gilbert, P. Hanson, R.O.C. Norman, and B.T. Sutcliffe, *Chem. Comm.*, **1966**, 161.

4) Y. Tsujino, *Tetrahedron Letters*, **1968**, 4111.

5) S.P. Massie and P.K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).