A Lithiation Approach to Cordycepin Analogues Variously Substituted at the C-8 Position

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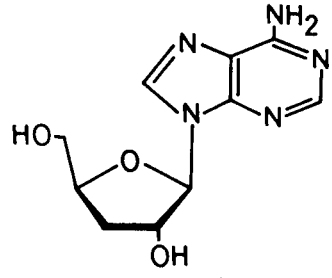
Received October 6, 1988

Several 8-substituted cordycepins were prepared *via* LDA lithiation of 2',5'-bis-*O*-(*t*-butyldimethylsilyl)-cordycepin and successive reactions of its C-8 lithiated species with various types of electrophiles. Wittig reaction of the 8-formyl derivative was also examined.

J. Heterocyclic Chem., **26**, 189 (1989).

Cordycepin (**1**) is an antibiotic isolated first from the mould *Cordyceps militaris* [1]. After disputes on its structure, it was unambiguously proved to be 3'-deoxyadenosine by chemical synthesis [2].



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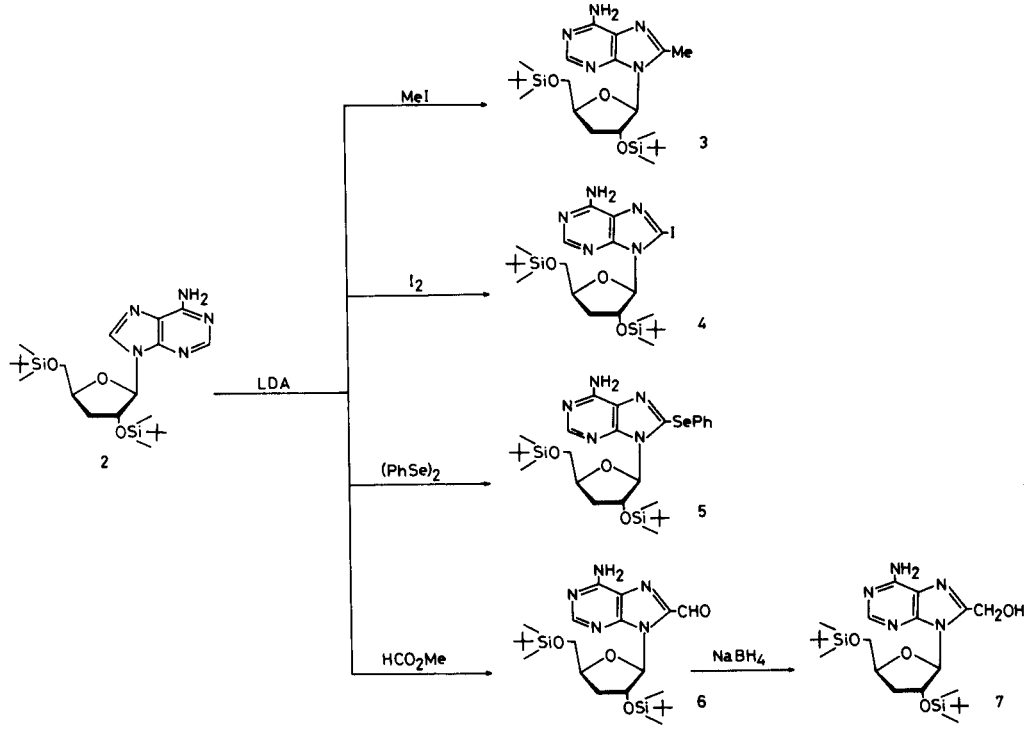
Because of its biological effects on methyltransferase [3], purines biosynthesis [4], and RNA biosynthesis [5], chemical modification of this compound [6] and preparation of a number of purine nucleosides bearing 3-deoxy-D-ribofuranosyl moiety [7-12] have been undertaken with the directed aim to obtain chemotherapeutically viable derivatives. However, the chemical alteration of cordycepin at the C-8 position is unprecedented to our knowledge.

Quite recently, we reported that naturally-occurring purine nucleosides could be lithiated at the C-8 position with lithium diisopropylamide (LDA) to a practical extent, when their sugar hydroxyls were protected with *t*-butyldimethylsilyl (TBDMS) group. Subsequent reactions of their lithiated species with carbon electrophiles furnished a method for 8-carbon-substituted purine nucleosides [13]. The anticipated simplicity and generality of the LDA lithiation procedure combined with lack of 8-substituted cordycepin analogues in literature led us to investigate the present study.

Scheme 1



The two sugar hydroxyls were protected with TBDMS group by treatment of **1** with TBDMSCl and imidazole in *N*,*N*-dimethylformamide to give **2** in almost quantitative yield, as reported earlier [14]. The C-8 lithiation of **2** was carried out by using 5 equivalents of LDA in tetrahydrofuran (THF) at below −70°, after which a clear solution of the lithiated species resulted.

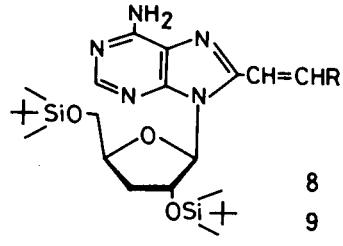
Introduction of a methyl group was performed by treating the lithiated species with 2 equivalents of methyl iodide at the low temperature for 1 hour to give **3** (Scheme 1) in 34% yield after column chromatography on silica gel. The mass spectral pattern of **3** was consistent with its structure, showing two characteristic fragment ion peaks, m/z 478 ($M^+ - Me$) and m/z 436 ($M^+ - Bu\text{-}t$), of a TBDMS derivative and the presence of the base, m/z 149 (B + 1). The ^{1}H-nmr spectrum of **3** in deuteriochloroform exhibited a singlet corresponding to a methyl group at δ 2.65 ppm, which was coincidental with the reported value of 2-methyladenosine in pyridine-d_5 [15]. However, comparison of **2** and **3** at H-2′ revealed a significant deshilding, 0.7 ppm in the latter compound. This observation is explicable in terms of the *syn*-glycosidic conformational preference of 8-substituted purine nucleosides, where the N^3-atom can exert an anisotropic effect to the H-2′ [16].

As depicted in Scheme 1, the iodination and phenylselenenylation were carried out in a similar manner by using iodine and diphenyl diselenide, respectively, as an electrophile. The 8-iodocordycepin derivative **4**, a suitable intermediate for the preparation of 8-alkynylated cordycepins [17], was isolated in 59% yield, while the yield of 8-phenylselenenyl derivative **5** was 50%.

When the lithiated species was subjected to the reaction with methyl formate, three products were detected by tlc (benzene:ethyl acetate = 1:1). After column chromatographic isolation, the two faster-running products were found to be convertible to **2** upon treatment with methanolic ammonia at room temperature for 20 hours. The ^{1}H-nmr spectrum of the third product showed the presence of a singlet at δ 10.00 ppm, which was not deuterium oxide-exchangeable, in addition to an aromatic proton (δ 8.40 ppm) and two amino protons (δ 5.95 ppm). Another feature of the spectrum was that the H-1′ appeared at δ 6.68 ppm, which was deshielded by 0.68 ppm and 0.92 ppm, respectively, as compared to the signals of **2** and **3**. These ^{1}H-nmr observations enabled us to confirm the 8-formyl structure **6** of the third product. The above mentioned deshielding of its H-1′ can be rationalized by assuming the carbonyl group being constrained predominantly in *s-trans* structure in the *syn*-glycosidic conformation. The isolated yield of **6** was 36%.

A functionalized alkyl group, the hydroxymethyl group, can be introduced simply by reducing **6** with sodium borohydride. In a practical sense, it is not necessary to isolate **6**. Thus, an intact reaction mixture containing **6** was quenched with acetic acid, diluted by ethanol, and then treated with sodium borohydride at room temperature for 15 minutes to give **7** in 40% overall yield.

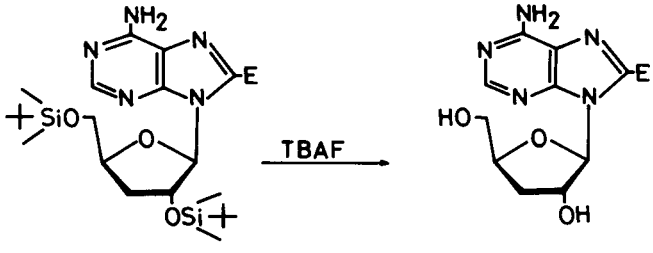
We next examined the Wittig reaction by the use of isolated **6**. When **6** was treated, in turn, with carbethoxymethylene triphenylphosphorane and cyanomethylene triphenylphosphorane in THF for 1 hour, highly fluorescent **8** (73%) and **9** (70%) were obtained as the sole reaction products. (*E*)-Stereochemistry of these products was deduced from their large coupling constants between vinylic protons (**8**: J = 15.6 Hz, **9**: J = 16.1 Hz).



8 R= CO_2Et
9 R= CN

Finally, as shown in Scheme 2, deprotection of 2′,5′-bis-*O*-TBDMS 8-substituted cordycepins was conducted by treatment with tetrabutylammonium fluoride (TBAF) in THF to produce the corresponding free nucleosides **10-15** in good yields.

Scheme 2



10 E= Me
11 E= I
12 E= SePh
13 E= CH_2OH
14 E= $CH{=}CHCO_2Et$
15 E= CH=CHCN

We believe the method described herein would be of potential usefulness for the preparation of biologically active cordycepin analogues due to its simplicity and generality.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. The ^{1}H-nmr spectra were measured with an internal standard of TMS with either a JEOL JNM-FX 100 or a JEOL JNM-GX 400 nmr spectrometer. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Ultraviolet spectra were recorded on a

Shimadzu UV-240 spectrophotometer. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). Tlc was performed on silica gel (precoated silica gel plates F_{254}, Merck).

General Procedure for the LDA Lithiation of **2** and Successive Reactions with Electrophiles.

LDA (5 equivalents), prepared from equimolar amounts of butyllithium and diisopropylamine at below −70° in THF, was placed in a three-necked flask equipped with a gas inlet adaptor, thermometer, and rubber septum. To this, a solution of **2** in THF was added, under positive pressure of dry argon, at a rate such that the internal temperature did not exceed −70°. After the mixture was stirred for 1 hour, an electrophile was added either in a THF solution or neat, while maintaining the temperature below −70°. The reaction mixture was stirred for 1 hour at the low temperature, quenched with acetic acid and evaporated to dryness. The whole residue was chromatographed on a silica gel column to give the respective 2',5'-bis-*O*-TBDMS 8-substituted cordycepin.

8-Methyl-2',5'-bis-*O*-TBDMS Cordycepin (**3**).

The following amounts of reagents and 491 mg (1.02 mmoles) of **2** in THF (10 ml) were used: 5.1 mmoles of LDA in THF (10 ml), 0.13 ml (2.04 mmoles) of freshly distilled methyl iodide. Column chromatography (benzene:ethyl acetate = 5:1) gave 171 mg (34%) of **3** as a foam; uv (methanol): λ max 258 nm, λ min 228 nm; ^{1}H-nmr (deuteriochloroform): δ 0.00 (s, 12H, SiMe), 0.82 and 0.85 (each as s, 18H, SiBu-*t*), 1.97-2.14 and 2.48-2.78 (each as m, 2H, CH_2-3'), 2.65 (s, 3H, 8-Me), 3.73-3.82 (m, 2H, CH_2-5'), 4.40 (m, 1H, H-4'), 5.33 (m, 1H, H-2'), 5.60 (br, 2H, NH_2), 5.76 (d, 1H, J = 3.9 Hz, H-1'), 8.27 (s, 1H, H-2); ms: (m/z) 478 (M^+ − Me), 436 (M^+ − Bu-*t*), 149 (B + 1).

8-Iodo-2',5'-bis-*O*-TBDMS Cordycepin (**4**).

The following amounts of reagents and 492 mg (1.03 mmoles) of **2** in THF (10 ml) were used: 5.15 mmoles of LDA in THF (10 ml), 254 mg (1.55 mmoles) of iodine in THF (5 ml). Column chromatography (chloroform) gave 347 mg (59%) of **4** as a foam; uv (methanol): λ max 266 nm, λ min 235 nm; ^{1}H-nmr (deuteriochloroform): δ 0.01 and 0.02 (each as s, 12H, SiMe), 0.87 (s, 18H, SiBu-*t*), 1.93-2.16 and 2.63-2.90 (each as m, 2H, CH_2-3'), 3.80-3.85 (m, 2H, CH_2-5'), 4.37-4.51 (m, 1H, H-4'), 5.38-5.48 (m, 1H, H-2'), 5.67 (br, 2H, NH_2), 5.80 (d, 1H, J = 3.4 Hz, H-1'), 8.24 (s, 1H, H-2); ms: (m/z) 590 (M^+ − Me), 548 (M^+ − Bu-*t*).

8-Phenylselenenyl-2',5'-bis-*O*-TBDMS Cordycepin (**5**).

The following amounts of reagents and 502 mg (1.04 mmoles) of **2** in THF (7 ml) were used: 5.20 mmoles of LDA in THF (10 ml), 487 mg (1.56 mmoles) of diphenyl diselenide in THF (5 ml). Column chromatography (chloroform) gave 328 mg (50%) of **5** as a syrup; uv (methanol): λ max 275 nm, λ min 245 nm; ^{1}H-nmr (deuteriochloroform): δ −0.15, −0.06, and 0.00 (each as s, 12H, SiMe), 0.81 and 0.85 (each as s, 18H, SiBu-*t*), 2.01 and 2.65-2.71 (each as m, 2H, CH_2-3'), 3.79 (m, 2H, CH_2-5'), 4.39 (m, 1H, H-4'), 5.40 (m, 1H, H-2'), 5.62 (br, 2H, NH_2), 6.04 (s, 1H, H-1'), 7.32 and 7.60 (each as m, 5H, SePh), 8.25 (s, 1H, H-2); ms: (m/z) 634 (M^+), 619 (M^+ − Me), 577 (M^+ − Bu-*t*).

8-Formyl-2',5'-bis-*O*-TBDMS Cordycepin (**6**).

The following amounts of reagents and 501 mg (1.04 mmoles) of **2** in THF (7 ml) were used: 5.20 mmoles of LDA in THF (10 ml), 0.64 ml (10.4 mmoles) of freshly distilled methyl formate. Column chromatography (chloroform) gave 153 mg (36%) of **6** as a foram; uv (methanol): λ max 262 nm, λ min 230 nm; ^{1}H-nmr (deuteriochloroform): δ −0.05, −0.01, 0.00, and 0.01 (each as s, 12H, SiMe), 0.82 and 0.85 (each as s, 18H, SiBu-*t*), 1.99-2.05 and 2.66-2.73 (each as m, 2H, CH_2-3'), 3.79 and 3.83 (each as dd, 2H, CH_2-5'), 4.42-4.46 (m, 1H, H-4'), 5.22-5.26 (m, 1H, H-2'), 5.95 (br, 2H, NH_2), 6.68 (d, 1H, J = 3.3 Hz, H-1'), 8.40 (s, 1H, H-2), 10.00 (s, 1H, CHO); ms: (m/z) 492 (M^+ − Me), 450 (M^+ − Bu-*t*).

8-Hydroxymethyl-2',5'-bis-*O*-TBDMS Cordycepin (**7**).

The following amounts of reagents and 503 mg (1.05 mmoles) of **2** in THF (10 ml) were used for the preparation of **6**: 5.25 mmoles of LDA in THF (10 ml), 0.45 ml (7.3 mmoles) of freshly distilled methyl formate. After being quenched with acetic acid (0.4 ml), the reaction mixture containing **6** was diluted by ethanol (20 ml) and treated with sodium borohydride (397 mg, 10.5 mmoles) for 15 minutes at room temperature. Evaporation of the solvents followed by column chromatography (2% methanol in chloroform) gave 214 mg (40%) of **7** as a syrup; uv (methanol): λ max 260 nm, λ min 230 nm; ^{1}H-nmr (deuteriochloroform): δ −0.14, −0.07, 0.03, and 0.04 (each as s, 12H, SiMe), 0.81 and 0.86 (each as s, 18H, SiBu-*t*), 1.97-2.03 and 2.47-2.54 (each as m, 2H, CH_2-3'), 3.68 and 3.88 (each as dd, 2H, CH_2-5'), 4.42-4.45 (m, 1H, H-4'), 4.88 and 4.93 (each as d, 2H, J = 14.3 Hz, 8-CH_2OH), 5.25-5.28 (m, 1H, H-2'), 5.84 (br, 2H, NH_2), 5.95 (d, 1H, J = 4.0 Hz, H-1'), 8.29 (s, 1H, H-2); ms: (m/z) 509 (M^+), 494 (M^+ − Me), 452 (M^+ − Bu-*t*).

8-(*E*)-Carbethoxyvinyl-2',5'-bis-*O*-TBDMS Cordycepin (**8**).

To an ice-cooled suspension of carbethoxymethylene triphenylphosphorane (209 mg, 0.6 mmole) in THF (2 ml), a THF (2 ml) solution of **6** (152 mg, 0.3 mmole) was added under positive pressure of dry argon and the mixture was stirred at room temperature for 15 hours. After partition between ether and saturated aqueous sodium chloride, the organic layer separated was dried, evaporated, and chromatographed on a silica gel column (chloroform) to give 129 mg (73%) of **8** as a powder; uv (methanol): λ max 240 nm and 333 nm, λ min 265 nm, λ shoulder 290 nm; ^{1}H-nmr (deuteriochloroform): δ 0.00 and 0.03 (each as s, 12H, SiMe), 0.86 (s, 18H, SiBu-*t*), 1.39 (t, 3H, $CO_2CH_2CH_3$), 1.97-2.30 and 2.55-2.82 (each as m, 2H, CH_2-3'), 3.79-3.85 (m, 2H, CH_2-5'), 4.24-4.53 (m, 3H, H-4' and $CO_2CH_2CH_3$), 5.40-5.46 (m, 1H, H-2'), 5.74 (br, 2H, NH_2), 5.95 (d, 1H, J = 3.4 Hz, H-1'), 7.07 and 7.81 (each as d, 2H, J = 15.6 Hz, vinyl), 8.33 (s, 1H, H-2); ms: (m/z) 562 (M^+ − Me), 520 (M^+ − Bu-*t*).

8-(*E*)-Cyanovinyl-2',5'-bis-*O*-TBDMS Cordycepin (**9**).

This compound was prepared from **6** (372 mg, 0.73 mmole) by usng cyanomethylene triphenylphosphorane (356 mg, 1.18 mmoles) as described in the preparation of **8**. Column chromatography (chloroform) gave 268 mg (70%) of **9**, which was crystallized from ethanol, mp 161-162°; uv (methanol): λ max 243 nm (ε 24600) and 341 nm (ε 14200), λ min 271 nm (ε 5000), λ shoulder 290 nm (ε 6700); ^{1}H-nmr (deuteriochloroform): δ −0.03, −0.01, and 0.00 (each as s, 12H, SiMe), 0.81 and 0.83 (each as s, 18H, SiBu-*t*), 2.00-2.06 and 2.47-2.54 (each as m, 2H, CH_2-3'), 3.68 and 3.85 (each as dd, 2H, CH_2-5'), 4.44-4.48 (m, 1H, H-4'), 5.28-5.32 (m, 1H, H-2'), 5.81 (br, 2H, NH_2), 5.88 (d, 1H, J = 4.0 Hz, H-1'), 6.67 and 7.66 (each as d, 2H, J = 16.1 Hz, vinyl), 8.32 (s, 1H, H-2); ms: (m/z) 515 (M^+ − Me), 473 (M^+ − Bu-*t*).

Anal. Calcd. for $C_{25}H_{42}N_6O_3Si_3$ (530.58): C, 56.59; H, 7.98; N, 15.84. Found: C, 56.81; H, 8.11; N, 15.79.

General Procedure for Deprotection of the 2',5'-bis-*O*-TBDMS Groups.

A 2',5'-bis-*O*-TBDMS 8-substituted cordycepin was dissolved in THF and treated with 2.5 equivalents of tetrabutylammonium fluoride trihydrate for 1 hour at room temperature. After evaporation of the solvent, the whole residue was chromatographed on a silica gel column to give the respective free nucleoside.

8-Methylcordycepin (**10**).

This compound was obtained in 89% yeild after column chromatography (2% methanol in chloroform). Crystallization from methanol-ethyl acetate gave an analytical sample, mp 191-192°; uv (methanol): λ max 260.5 nm (ε 17000), λ min 229 nm (ε 4200); ^{1}H-nmr (DMSO-d_6): δ 1.89-2.12 and 2.29-2.50 (each as m, 2H, CH_2-3'), 2.54 (s, 3H, 8-Me), 3.30-3.72 (m, 2H, CH_2-5'), 4.18-4.36 (m, 1H, H-4'), 4.80-5.02 (m, 1H, H-2'), 5.44-5.56 (m, 2H, 2'-OH and 5'-OH), 5.70 (d, 1H, J = 4.4 Hz, H-1'), 7.17 (br, 2H, NH_2), 8.05 (s, 1H, H-2).

Anal. Calcd. for $C_{11}H_{15}N_5O_3$ (265.27): C, 49.80; H, 5.70; N, 26.40. Found: C,49.98; H, 5.70; N, 26.15.

8-Iodocordycepin (**11**).

This compound was obtained in 87% yield after column chromatography (5% methanol in chloroform). Crystallization from ethanol gave an analytical sample, mp 202-205°; uv (methanol): λ max 268 nm (ε 18100), λ min 236.5 nm (ε 5500); ^{1}H-nmr (DMSO-d_6): δ 1.90-2.20 and 2.35-2.62 (each as m, 2H, CH_2-3'), 3.38 (m, 2H, CH_2-5'), 4.18-4.40 (m, 1H, H-4'), 4.95-5.15 (m, 1H, H-2'), 5.40-5.60 (m, 2H, 2'-OH and 5'-OH), 5.67 (d, 1H, J = 4.4 Hz, H-1'), 7.49 (br, 2H, NH_2), 8.05 (s, 1H, H-2).

Anal. Calcd. for $C_{10}H_{12}IN_5O_3$ (377.14): C, 31.85; H, 3.21; N, 18.57. Found: C, 32.07; H, 3.18; N, 18.28.

8-Phenylselenenylcordycepin (**12**).

This compound was obtained in 78% yield after column chromatography (3% methanol in chloroform). Crystallization from ethanol gave an analytical sample, mp 177-178°; uv (methanol): λ max 275.5 nm (ε 15800), λ min 242.5 nm (ε 10200); ^{1}H-nmr (DMSO-d_6): δ 1.99-2.17 and 2.35-2.67 (each as m, 2H, CH_2-3'), 3.35-3.66 (m, 2H, CH_2-5'), 4.20-4.37 (m, 1H, H-4'), 4.96-5.13 (m, 1H, H-2'), 5.36-5.51 (m, 2H, 2'-OH and 5'-OH), 5.99 (d, 1H, J = 4.4 Hz, H-1'), 7.31-7.42 (m, 3H, SePh), 7.51-7.60 (m, 4H, SePh and NH_2), 8.12 (s, 1H, H-2).

Anal. Calcd. for $C_{16}H_{17}N_5O_3Se$ (406.30): C, 47.30; H, 4.22; N, 17.24. Found: C, 47.55; H, 4.16; N, 17.19.

8-Hydroxymethylcordycepin (**13**).

This compound was obtained in 87% yield after column chromatography (5% methanol in chloroform). Crystallization from methanol-water gave an analytical sample, mp 123-124°; uv (methanol): λ max 263 nm (ε 19500), λ min 230.5 nm (ε 4800); ^{1}H-nmr (DMSO-d_6): δ 1.94-2.12 and 2.33-2.51 (each as m, 2H, CH_2-3'), 3.30-3.74 (m, 2H, CH_2-5'), 4.18-4.37 (m, 1H, H-4'), 4.66 (d, 2H, J = 5.4 Hz, 8-C*H*$_2$OH), 5.45-5.74 (m, 3H, 2'-OH, 5'-OH, and 8-CH_2O*H*), 5.94 (d, 1H, J = 4.9 Hz, H-1'), 7.29 (br, 2H, NH_2), 8.08 (s, 1H, H-2).

Anal. Calcd. for $C_{11}H_{15}N_5O_4$ (281.27): C, 46.97; H, 5.38; N, 24.90. Found: C, 46.76; H, 5.62; N, 24.81.

8-(*E*)-Carbethoxyvinylcordycepin (**14**).

This compound was obtained in 81% yield after column chromatography (3% methanol in chloroform). Crystallization from methanol gave an analytical sample, mp 184-185°; uv (methanol): λ max 240 nm (ε 25800) and 334 nm (ε 15700), λ min 268 nm (ε 5700), λ shoulder 294 nm (ε 8100); ^{1}H-nmr (DMSO-d_6): δ 1.29 (t, 3H, $CO_2CH_2CH_3$), 2.00-2.06 and 2.50 (each as m, 2H, CH_2-3'), 3.41-3.48 and 3.56-3.61 (each as m, 2H, CH_2-5'), 4.24 (q, 2H, $CO_2CH_2CH_3$), 4.30-4.34 (m, 1H, H-4'), 4.85-4.92 (m, 1H, H-2'), 5.19-5.27 (m, 1H, 5'-OH), 5.55 (d, 1H, 2'-OH), 5.96 (d, 1H, J = 4.8 Hz, H-1'), 6.91 and 7.77 (each as d, 2H, J = 15.8 Hz, vinyl), 7.56 (br, 2H, NH_2), 8.15 (s, 1H, H-2); ms: (m/z) 349 (M^+), 233 (B + 1).

Anal. Calcd. for $C_{15}H_{19}N_5O_5$ (349.34): C, 51.57; H, 5.48; N, 20.05. Found: C, 51.29; H, 5.34; N, 19.98.

8-(*E*)-Cyanovinylcordycepin (**15**).

This compound was obtained in 71% yield after column chromatography (3% methanol in chloroform). Crystallization from ethanol gave an analytical sample, mp 251-252°; uv (methanol): λ max 243 nm (ε 23600), 283 nm (ε 6900), and 339 nm (ε 13400), λ min 272 nm (ε 6700) and 297 nm (ε 6700); ^{1}H-nmr (DMSO-d_6): δ 1.96-2.03 and 2.39-2.45 (each as m, 2H, CH_2-3'), 3.43-3.48 and 3.60-3.65 (each as m, 2H, CH_2-5'), 4.30-4.35 (m, 1H, H-4'), 4.76-4.83 (m, 1H, H-2'), 5.32-5.35 (m, 1H, 5'-OH), 5.52 (d, 1H, 2'-OH), 6.62 (d, 1H, J = 15.8 Hz, vinyl), 7.59 (br, 2H, NH_2), 8.13 (d, 1H, J = 15.8 Hz, vinyl), 8.16 (s, 1H, H-2); ms: (m/z) 302 (M^+), 186 (B + 1).

Anal. Calcd. for $C_{13}H_{14}N_6O_3$ (302.29): C, 51.65; H, 4.67; N, 27.80. Found: C, 51.93; H, 4.71; N, 28.05.

Acknowledgement.

The authors are deeply grateful to Miss Masami Mayumi for her skillful technical assistance.

REFERENCES AND NOTES

[1] K. G. Cunningham, S. A. Hutchinson, W. Manson, and F. S. Spring, *J. Chem. Soc.*, 2299 (1951).

[2] A. Todd and T. L. V. Ulbricht, *J. Chem. Soc.*, 3275 (1960).

[3] R. I. Glazer and A. L. Peale, *Biochem. Biophys. Res. Commun.*, **81**, 521 (1978).

[4] D. Hunting and J. F. Henderson, *Biochem. Pharmacol.*, **27**, 2163 (1978).

[5] H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, **240**, 806 (1965).

[6] E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965).

[7] S. R. Jenkins, F. W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965).

[8] M. J. Dickinson, F. W. Holly, E. Walton, and M. Zimmerman, *J. Med. Chem.*, **10**, 1165 (1967).

[9] N. J. Leonard and M. Rasmussen, *J. Org. Chem.*, **33**, 2488 (1968).

[10] J. J. K. Novák and F. Šorm, *Collect. Czech. Chem. Commun.*, **38**, 1173 (1973).

[11] M. J. Robins, J. R. McCarthy, Jr., R. A. Jones, and R. Mengel, *Can. J. Chem.*, **51**, 1313 (1973).

[12] H. S. El Khadem and El S. H. El Ashry, *Carbohydr. Res.*, **32**, 339 (1974).

[13] H. Hayakawa, K. Haraguchi, H. Tanaka, and T. Miyasaka, *Chem. Pharm. Bull.*, **35**, 72 (1987).

[14] H. Hayakawa, H. Tanaka, K. Haraguchi, M. Mayumi, M. Nakajima, T. Sakamaki, and T. Miyasaka, *Nucleosides Nucleotides*, **7**, 121 (1988).

[15] A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **33**, 2583 (1968).

[16] L. Dudycz, R. Stolarski, R. Pless, and D. Shugar, *Z. Naturforsch.*, **34c**, 359 (1979).

[17] S. Koyama, Z. Kumazawa, and N, Kashimura, *Nucleic Acids Symposium Series*, **11**, 41 (1982).