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Author(s)	Matsuda, Akira; Muneyama, Kei; Nishida, Takako et al.
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A new synthesis of 5'-deoxy-8,5'-cyclo-adenosine and -inosine: conformationally-fixed purine nucleosides (nucleosides and nucleotides. XVI)[1].

Akira Matsuda, Kei Muneyama, Takako Nishida, Tatsuo Sato and Tohru Ueda

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060, Japan

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ABSTRACT

A versatile method for the synthesis of 5'-deoxy-8,5'-cycloadenosine, a conformationally-fixed "anti" type of adenosine, was presented. Irradiation of 2',3'-O-isopropylidene-5'-deoxy-5'-phenylthioadenosine with 60W Hg vapor lamp afforded 2',3'-O-isopropylidene-5'-deoxy-8,5'-cycloadenosine in high yield. The use of other 5'-alkylthio derivatives also gave the cycloadenosine, though the yields were rather poor. Deacetonation of the cyclo compound with 0.1N HCl gave 5'-deoxy-8,5'-cycloadenosine. The cycloinosine derivative was similarly prepared. The nmr, mass and CD spectra of 5'-deoxy-8,5'-cycloadenosine were given and discussed with the previously reported results.

INTRODUCTION

In recent years several cyclonucleosides bearing a carbon-carbon linkage between the sugar and the aglycon moieties have been prepared and utilized as the conformationally-fixed analogs of nucleosides and nucleotides. The first carbon bridged cyclonucleoside was reported by Hogenkamp[2] and Johnson and co-workers[3] in the anaerobic photolysis of 5'-deoxyadenosylcobalamin affording 5'-deoxy-8,5'-cycloadenosine. By the similar procedure 5'-deoxy-8,5'-cycloinosine was prepared[3]. Photolysis of 2',3'-O-isopropylidene-5'-deoxyuridinylcobalamin afforded the 6,5'-cyclo-5,6-dihydrouridine derivative[4]. γ-Irradiation of adenosine 5'-phosphate was reported to yield a small amount of 8,5'-cycloadenosine 5'-phosphate[5]. Treatment of 2',3'-O-isopropylideneadenosine-5'-carboxylic acid with methyllithium gave the 8,5'-cyclo-5'-ketoadenosine derivative in low yield, which was converted to the diastereomeric mixture of 2',3'-O-isopropylidene-8,5'-cycloadenosine[6]. A 2,2'-methylene-cyclopyrimidine nucleoside[7] and 6,5'(S)-cyclo-5-hydroxyuridine[8] are the C-cyclopyrimidine nucleosides prepared so far. We have encountered, during the photochemical investigation of sulfur-containing nucleosides, an interesting cyclization reaction leading to give 5'-deoxy-8,5'-cyclopurine nucleosides as will be described[9].

RESULTS

A solution of 2',3'-O-isopropylidene-5'-deoxy-5'-phenylthioadenosine(Ia)[10] and trimethyl phosphite in acetonitrile was irradiated with 60W low-pressure Hg vapor lamp for 1.5 hours. A survey of the reaction mixture with a thin-layer chromatography(silica gel; $CHCl_3$-EtOH, 10:1) showed that the reaction proceeded almost completely to leave a new product(Rf 0.51) and the spots of the starting material(Rf 0.70) or minor products were found to be practically negligible. After evaporation of the solvent the product was obtained as hygroscopic crystals from hot ethanol in 66% yield. The structure of the product was assigned as 2',3'-O-isopropylidene-5'-deoxy-8,5'-cycloadenosine(II) from the following evidence . The ultraviolet absorption (UV) spectra of II were closely similar to those of 8-alkyladenines[11]. The mass spectra of II showed a peak of the molecular ion at m/e 289(relative intensity 36%). Proton magnetic resonance(pmr) spectra showed that the C-8 proton in Ia was disappearing and the signal of anomeric proton appeared as a singlet. The 5'-methylene protones appeared as the ABX type signals. All these were well indicative of the presence of an cyclo linkage between C-8 and C-5' as shown in II.

Studies of the course of this photocyclization reaction were performed in some extent. The omission of trimethyl phosphite in this reaction resulted in a decrease of the yield of II due to the formation of unidentified by-products, which implies that trimethyl phosphite is acting as an effective trapping agent of the liberated phenylthiyl radical[12]. Photolysis of the 5'-benzylthio derivative(Ib) instead of Ia proceeded very slowly under irradiation with the low-pressure Hg lamp. The use of 100W high-pressure Hg lamp(for 3 hours) improved the yield of II(44%) from Ib. Photolysis of 5'-allylthio and 5'-propylthio derivatives(Ic and Id, respectively) gave rather poor results in either irradiations. From these observations it can be assumed that the phenylthio group in Ia is photo-activated initially, rather than the adenine moiety, to yield an 5'-methylene intermediate(A) and phenylthiyl radical. The intermediate A cyclized to the next intermediate(B) followed by the release of hydrogen radical to give the product II. In the case of the reaction of Ib-d such exclusive cleavage between the 5'-methylene and the alkylthio group cannot be expected.

It is to be emphasized here that the irradiation of 5'-deoxy-5'-phenylthioadenosine itself resuted in an extensive degradation and did not give the 8,5'-cyclo derivative in a measurable amount. The fixation of the 2'- and 3'-hydroxyl group in a form of a five-membered ring such as in Ia

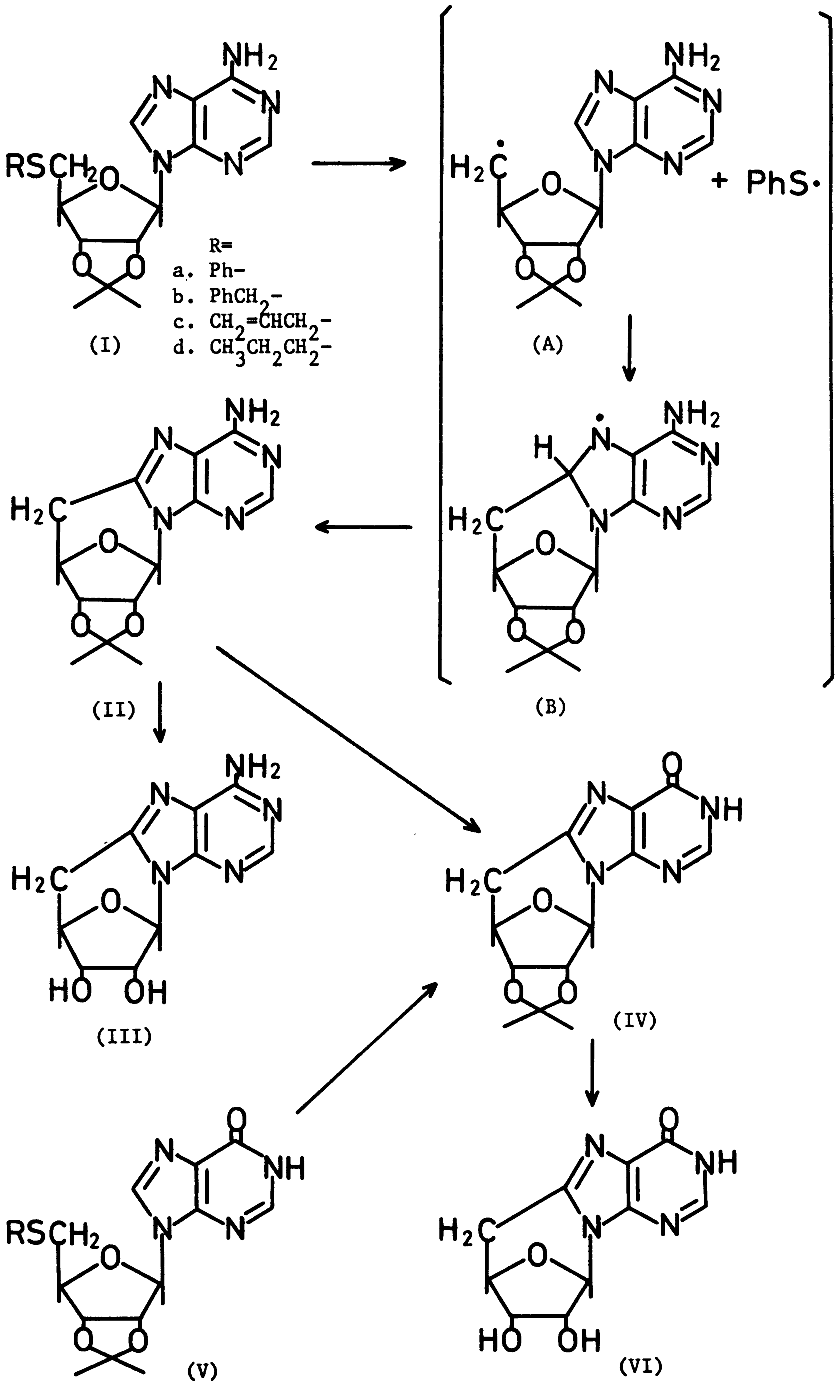

NH2
N
N
N
N
RSCH2
O
O
O
R=
a. Ph-
b. PhCH2-
c. CH2=CHCH2-
d. CH3CH2CH2-
(I)
H2C
+ PhS·
(A)
H
(B)
(II)
(III)
HO
OH
NH
(IV)
(V)
(VI)

Figure 1. Proton Magnetic Resonance Spectrum of 5'-Deoxy-8,5'-cycloadenosine

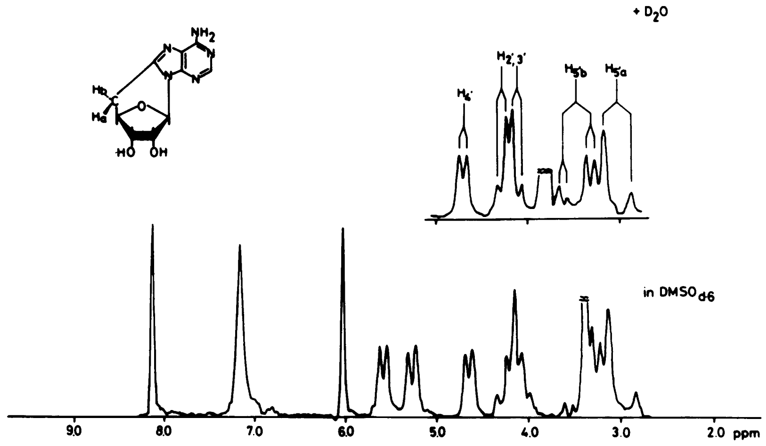
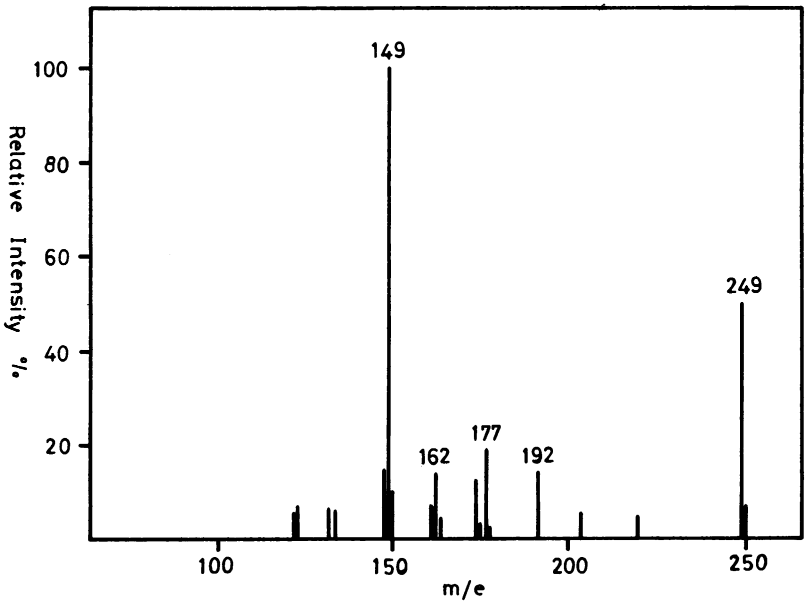


Figure 2. Mass Spectrum of 5'-Deoxy-8,5'-cycloadenosine



seemed to be sterically essential to bring about the intramolecular cyclization in the intermediate A to B.

Treatment of II with 0.1N HCl at 90° for one hour gave 5'-deoxy-8,5'-cycloadenosine(III) in a yield of 71%, as has been described in a preceding report[3]. Compound III showed well resolved signals in its pmr spectra(Fig.

1) for H-5'a, H-5'b and H-4' as the ABX system at 3.02, 3.45 and 4.69ppm, respectively, with the coupling constants of $J_{5'a,5'b}$= 18Hz, $J_{5'b,4'}$= 4.5Hz and $J_{5'a,4'}$= 0Hz. No coupling between H-4' and H-3' was observed. These results are consistent with the expected structure by inspecting a Dreiding model of III in that the dihedral angles of H-5'a and H-4', and H-4' and H-3' were nearly 90°, respectively, with the sugar puckering of 1'-O-exo type.

Some comments are to be made on the mass spectrum of III(Fig. 2). Law and Wood have already reported[13] the mass fragmentation pattern of III prepared by the photolysis of 5'-deoxyadenosylcobalamin. In its spectrum the mass number of 135(adenine$^+$) was the base peak and the mass number of 108 was reported to be derived from the former. In our spectrum these two fragment peaks were missing, instead, mass number of 149(8-methyladenine$^+$) was the base peak. Since we have confirmed that the fragmentation of 8-methyladenine did not give the peaks corresponding to 135 or 108 and did give those of 149 and 122, the sample obtained by the photolysis of 5'-deoxyadenosylcobalamin must have been contaminated with some C-8 unsubstituted adenine derivatives. It is known that adenosine and adenine derivatives gave the fragment ions at 135 and 108[14].

The circular dichroism(CD) spectra of III exhibited a strong negative band($[\theta]$=-19800) around its main absorption region which was consistent with those of "anti"-oriented adenine nucleosides[15]. This is to be contrasted with the results of 8,5'-O- and -S-cycloadenosines, which showed positive dichroic bands at their main absorption regions, though these are regarded as "anti"-fixed models of purine nucleosides[16].

Treatment of II with sodium nitrite in aqueous acetic acid afforded the hypoxanthine derivative, 2',3'-O-isopropylidene-5'-deoxy-8,5'-cycloinosine(IV). Compound IV was also prepared by the photolysis of 2',3'-O-isopropylidene-5'-deoxy-5'-phenyl(and benzyl)thioinosine(V) in a similar manner as described in the synthesis of II. Deacetonation of IV in acidic solution afforded free 5'-deoxy-8,5'-cycloinosine(VI). After completion of our works the alternative method of synthesis of II, which involved the treatment of 2',3'-O-isopropylidene5'-deoxy-5'-iodoadenosine with tri-n-butyltin hydride , has appeared[17].

Studies of the synthesis of the cycloguanosine derivative as well as the reactions leading to the introduction of various substituents into the 5'-position of III are being undertaken and will be reported elsewhere.

EXPERIMENTAL

The UV spectra were recorded on a Shimazu UV-300 recording spectrophotometer. Pmr spectra were taken on a Hitachi H-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer. CD spectra were measured on a JASCO J-40 spectropolarimeter with 8 times accumulations. The photo-reactions were carried out with apparatus of Eikosha PIL-60 low-pressure Hg vapor lamp or Ushio UM-102 100W high-pressure Hg vapor lamp(quartz filter).

2',3'-O-Isopropylidene-5'-deoxy-8,5'-cycloadenosine(II)----a). 2',3'-O-Isopropylidene-5'-deoxy-5'-phenylthioadenosine[10] (Ia, 340mg) and trimethyl phosphite(1 ml) were dissolved in 300ml of acetonitrile and argon gas was bubbled through the solution for 30min. This was irradiated with a 60W low-pressure Hg lamp for 90min under argon bubbling. Thin layer chromatography of the reaction mixture(silica gel, $CHCl_3$-EtOH, 10:1) revealed a spot at Rf 0.51 and the spot at Rf 0.70(Ia) disappeared. The solution was concentrated to leave a residue, which was taken up in hot EtOH. After cooling the separated crystals(160mg, 65.8%) of II were collected, mp 230.5-231.5°(reported mp, 233-235°[3]). Anal. Calcd. for $C_{13}H_{15}N_5O_3 \cdot 1/4\ H_2O$: C, 53.12; H, 5.33; N, 23.84. Found: C, 53.21; H, 5.25; N, 24.01. Mass m/e: 289(M^+). pmr(DMSO-d_6), δ ppm: 8.10(s, 1, H-2), 7.07(bs, 2, 6-NH_2), 6.15(s, 1, H-1'), 4.79(dd, 1, H-4', $J_{4',5'b}$= 5.5Hz, $J_{4',5'a}$= 1Hz), 4.82(d, 1, H-2', $J_{2',3'}$= 6Hz), 4.62(d, 1, H-3'), 3.43(dd, 1, H-5'b, $J_{5'a,5'b}$= 18Hz), 2.98(dd, 1, H-5'a), 1.46 and 1.25(s, 6, Me_2C).

b). The photolysis of 416mg of Ia and 0.5ml of trimethyl phosphite in 500ml of acetonitrile with the irradiation of 100W high-pressure Hg lamp for 5 hours afforded 205mg(69.6%) of II after the similar work-up.

c). The photolysis of 413mg of 2',3'-O-isopropylidene-5'-deoxy-5'-benzylthioadenosine(Ib) and 5ml of trimethyl phosphite in 500ml of acetonitrile with 100W Hg lamp for 3 hours afforded 128.4mg(44.3%) of II after similar work-up. The irradiation in a same scale except trimethyl phosphite was omitted for 10 hours gave 50.5mg(17.5%) of II.

d). The photolysis of compound Ic and Id with trimethyl phosphite with 60W or 100W Hg lamp by the similar manner as described in a section a) for 10 hours gave a trace of II as checked by the thin layer chromatography. Most of the starting material was recovered.

5'-Deoxy-8,5'-cycloadenosine(III)---- Compound II(330mg) was dissolved in 50ml of 0.1N HCl and heated on a water bath at 85-90° for 1 hour. After neutralization by the addition of 2N-NH_4OH the solution was concentrated to dryness, the residue crystallized from hot water to leave 202mg(71%) of III, mp>290°. Anal. Calcd. for $C_{10}H_{11}N_5O_3.H_2O$: C, 44.92; H, 4.91; N, 26.22. Found: C, 44.88; H, 4.82; N, 26.15. UV λ max(H_2O): 264nm(ε, 17450); λ max (0.5N HCl): 261.5nm(ε, 17000); λmax(0.5N NaOH): 265nm(ε, 18000). CD in H_2O, nm([θ]): 260(-19800), 217(0), 205(+24500). pmr: See Fig. 1. Mass: See Fig. 2.

2',3'-O-Isopropylidene-5'-deoxy-5'-benzylthioinosine(V, R=$PhCH_2$)---- a). 2',3'-O-Isopropylidene-5'-O-tosylinosine(1.32g)[18] was added to the liquid ammonia previously dissolved 150mg of Na and 0.5ml of benzylmercaptan and kept overnight in a flask stoppered with a sodium hydroxide tube. The residue was neutralized with the addition of NH_4Cl solution, partitioned with $CHCl_3/H_2O$ and the organic layer was separated, dried over sodium sulfate, and evaporated. The residue was crystallized from hot EtOH affording 857mg (72.5%) of IV, mp 119-121°. Anal. Calcd. for $C_{20}H_{22}N_4O_4S$: C, 57.94; H, 5.36; N, 13.52; S, 7.73. Found: C, 58.00; H, 5.31; N, 13.70; S, 7.91. Mass m/e : 414(M^+). pmr(DMSO-d_6) δ ppm: 12.50(bs, 1, N_1-H), 8.35(s, 1, H-8), 8.12(s, 1, H-2), 7.30(s, 5, phenyl), 6.18(d, 1, H-1', $J_{1',2'}$= 2Hz), 5.43(dd, 1, H-2', $J_{2',3'}$= 6Hz), 4.95(dd, H-3', $J_{3',4'}$= 3Hz), 4.26(m, 1, H-4'), 3.76(s, 2, $-CH_2$-Ph), 2.71(bd, 2, H-5', $J_{4',5'}$= 7.5Hz), 1.54 and 1.33(s, 6, Me_2C).

b). Compound V(R=$PhCH_2$) was also obtained by the treatment of the tosylate (462mg) with 0.5ml of benzylmercaptan and 2ml of N-NaOMe in dimethylformamide(5ml) at room temperature overnight. After neutralization of the solvent with N-HCl and evaporation the residue was crystallized from hot EtOH to give 410mg(quant.) of V(R=$PhCH_2$).

2',3'-O-Isopropylidene-5'-deoxy-5'-phenylthioinosine(V, R=Ph)----2',3'-O-Isopropylidene-5'-O-tosylinosine(2g) was dissolved in liquid ammonia previously dissolved 200mg of Na and 2ml of thiophenol and kept overnight in a flask stoppered with sodium hydroxide tube. After similar work-up as described in the previous section the final residue was crystallized from hot EtOH to give 1.52g(87%) of the product(V, R=Ph), mp 225-227°. Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.97; H, 5.05; N, 13.99; S, 8.00. Found: C, 57.23; H, 5.17; N, 14.27; S, 8.03. Mass m/e: 400(M^+). pmr(DMSO-d_6) δ ppm: 12.44(bs, 1, N_1-H), 8.32(s, 1, H-8), 8.12(s, 1, H-2), 7.5-7.1(m, 5, Ph), 6.18(d, 1, H-1', $J_{1',2'}$= 2Hz), 5.45(dd, 1, H-2', $J_{2',3'}$= 6Hz), 5.03(dd, 1, H-3', $J_{3',4'}$= 3Hz), 4.26(dt, 1, H-4', $J_{4',5'}$= 7.5Hz), 3.26(bd, 2, H-5'), 1.51 and 1.33(s, 6, Me_2C).

2',3'-O-Isopropylidene-5'-deoxy-8,5'-cycloinosine(IV)---- a). Compound V(R = $PhCH_2$), 400mg, and trimethylphosphite, 1 ml, in 500ml of acetonitrile were irradiated with 100W Hg lamp for 5 hours. After the work-up as described in the synthesis of II the product was crystallized from hot EtOH to give 162mg(57.8%) of IV, mp>300°. Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.75; H, 4.90; N, 19.11. UV λmax(H_2O): 251.5 nm(ε, 14050), λmax(0.5N HCl): 252nm(ε, 12650), λmax(0.5N NaOH): 256.5nm (ε, 14600). Mass m/e: 290(M^+). CD in H_2O, nm([θ]): 250(-13900), 227(0), 222 (+1400), 216(0), 210(-5300). CD in 0.5N HCl: 249(-11100), 223(0), 210(+5000).

b). A solution of V(R=Ph), 350mg, and 1 ml of trimethyl phosphite in 350ml of acetonitrile was irradiated with 60W Hg lamp for 90min. After the similar work-up the product IV was obtained in 72.2%(249mg) yield.

c). To a solution of 100mg of II in 10ml of 80% acetic acid 100mg of $NaNO_2$ was added and stirred for 24 hours. After further addition of 100mg of $NaNO_2$ and stirring for 3 days the solvent was evaporated and the residue was taken in a hot water from which crystals of IV(68mg, 68%) was obtained.

5'-Deoxy-8,5'-cycloinosine(VI)---- Compound IV, 80.6mg, was heated in 0.1N HCl(7ml) at 85-90° and after 60min this was neutralized with ammonia and evaporated to leave a mass. This was crystallized from hot water to give 32.1mg(46%) of VI. Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.91; H, 4.08; N, 20.97. Mass m/e: 250(M^+). pmr(DMSO-d_6) δ ppm: 7.97(s, H-2), 5.95(s, 1, H-1'), 4.62(dd, 1, H-4', $J_{4',5'b}$= 5.5Hz, $J_{4',5'a}$= 1.5Hz), 4.24(d, 1, H-2', $J_{2',3'}$= 6Hz), 4.10(d, 1, H-3'), 3.32(dd, 1, H-5'b, $J_{5'b,5'a}$= 17.5Hz), 2.90(dd, 1, H-5'a).

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