Some Transformations of DL-Phenylalanine Ortho Esters and *N*-Benzyloxycarbonyl-L-phenylalaninal[1]

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Glycine ortho esters have found a wide use[2] in the synthesis of glycyl derivatives of ribonucleosides,[2a,b] ribonucleotides,[2c] and ribooligonucleotides.[2d-h] The application of the ortho ester exchange method which provides the basis of the synthetic approach[2a] to the above mentioned compounds for amino acids other than glycine has been hampered for a long time by a lack of general method for the preparation of amino acid ortho esters.[3]

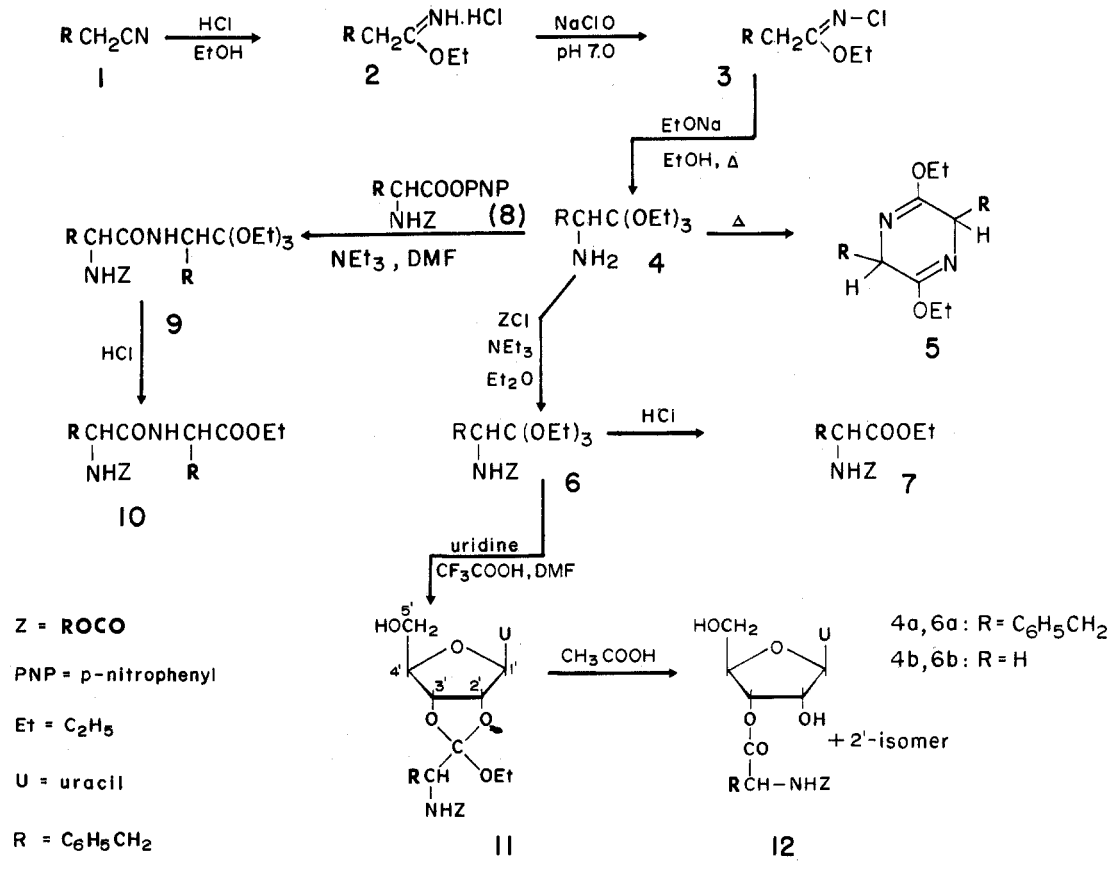
A brief report[4] describing a synthesis of some amino acid ortho esters has prompted us to investigate (a) N-protection of such derivatives, (b) synthesis of dipeptide ortho esters, and (c) synthesis of 2′(3′)-*O*-aminoacyl ribonucleosides via the corresponding cyclic ortho ester derivatives. The resuls from all three areas are the subject of this communication. In addition, a facile preparation of *N*-benzyloxycarbonyl-L-phenylalaninal dimethyl acetal (**17**) as well as the reaction of aldehyde **16** with adenosine in the presence of ethyl orthoformate is also described.

Ethyl DL-orthophenylalaninate (**4a**) was prepared as indicated in Scheme I (**1** → **2** → **3** → **4a**) according to a procedure described briefly for some other amino acid ortho esters.[4] Hydrocinnamonitrile (**1**) was converted in 98% yield to the corresponding imido ester hydrochloride[5] (**2**) which, in turn, was chlorinated[6] with aqueous NaClO at pH 7.0 to give an *N*-chloroimido ester (**3**) in 98% yield. The latter afforded the ortho ester **4a** by heating with sodium ethylate in ethanol for 2 h at 80 °C in 99% yield. Thus, the overall yield (**1** → **4a**) was 95%. The structure of **4a** was confirmed by ir which revealed a strong band at 1065 cm^{-1} indicating C–O–C grouping but absence of ester. NMR indicated the undistilled **4a** to be of a high (ca. 95%) purity. Distillation of **4a** afforded an analytical sample but led to an extensive decomposition. From the higher boiling fraction, a pyrazine derivative **5** was obtained and characterized by ir and NMR spectra. This observation contradicts the claim of the Soviet literature[7] that amino acid ortho esters as free bases are "very stable compounds and do not change even on long heating".

The reaction of ortho ester **4a** with benzyloxycarbonyl chloride in ether and in the presence of triethylamine gave ethyl *N*-benzyloxycarbonyl-DL-orthophenylalaninate (**6a**) in 66% yield. The same reaction was extended to the preparation of ethyl *N*-benzyloxycarbonylorthoglycinate[2a] (**6b**) from ortho ester[4] **4b** in 38% yield.

The structure of **6a** was confirmed by ir (urethane carbonyl band, strong C–O–C absorption) and NMR spectra. The latter showed the methyl protons of the ethoxy function as a sharp triplet; however, the signal for the methylene protons (quartet) was split (Figure 1), which was not the case in ethyl *N*-

Scheme I



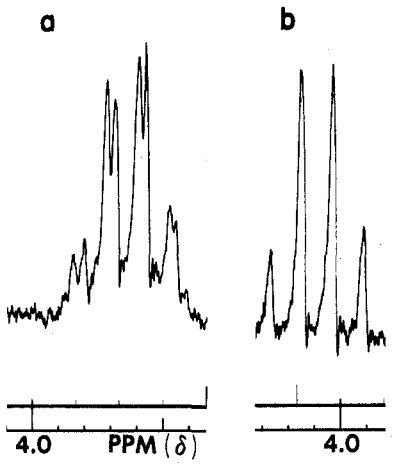
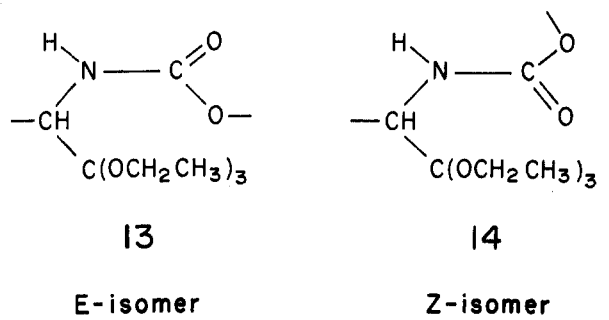


Figure 1. (a) Methylene proton signal of ethoxy group in ortho ester **6a**; (b) methylene proton signal of ethoxy group in ester **7**.

benzyloxycarbonylorthoglycinate (**6b**) or ethyl *N*-benzyloxycarbonyl-DL-phenylalaninate (**7**). The splitting pattern observed in our case (Figure 1) is also different from that described for some alicyclic ethyl esters.[8,9] The most likely explanation for the splitting is the assumption of *Z–E* isomerism of the urethane bond[10] (cf. formulas **13** and **14**). Additional



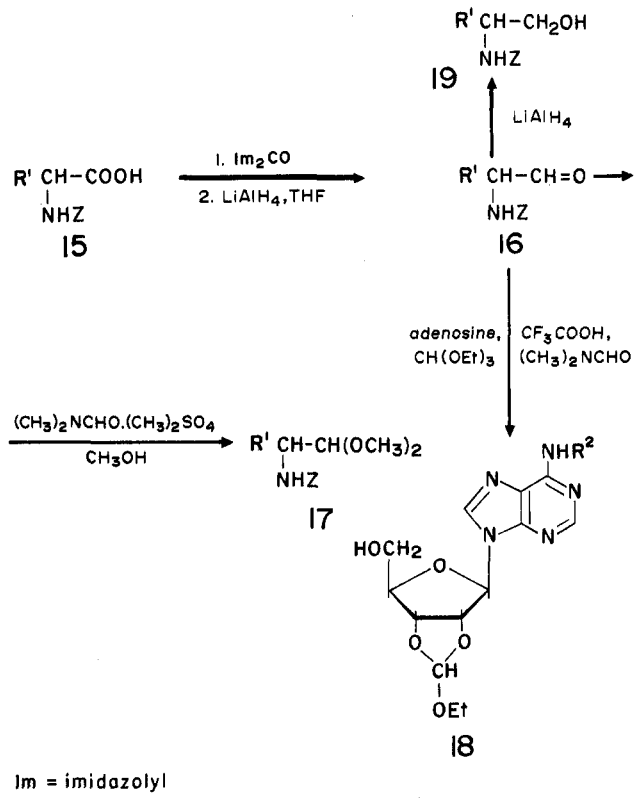
confirmation for the structure of **6a** derives from its hydrolysis with 10% HCl to the corresponding known[11] ester **7**.

The condensation of ortho ester **4a** with *N*-benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester[12] (**8**) in the presence of triethylamine in CH_2Cl_2 gave the dipeptide ortho ester **9** in 63% yield. The latter was characterized by spectral (ir and NMR) data which confirmed the presence of urethane and amide groups in addition to ethoxy functions. Compound **9** was hydrolyzed with 10% HCl to the corresponding dipeptide ester **10** whose structure was corroborated by NMR spectrum. Again, a secondary splitting of the methylene protons of the ethoxy group in **9** was observed although the resolution was lower than in the case of ortho ester **6a**. Thus, the situation is analogous to that noted with the urethane derivative **6a**. In addition to *Z–E* isomerism of the urethane grouping, a possibility of a similar isomerism can readily be visualized for **9** in view of the fact that the partial double bond character of the peptide bond is well established.[13] However, this case is more complex because **9** is a mixture of two diastereoisomers.

It is also of interest to utilize *N*-benzyloxycarbonyl ortho ester **6a** for the synthesis of 2′(3′)-*O*-phenylalanylribonucleosides. As shown previously, an ortho ester exchange reaction of ethyl *N*-benzyloxycarbonylorthoglycinate (**6b**) with ribonucleosides or ribonucleotides can be readily accomplished in dimethylformamide (DMF) using CH_3SO_3H[2a] or CF_3COOH[2c] as catalysts. In a model experiment with uridine (catalysis with CF_3COOH), compound **6a** afforded the expected 2′,3′-cyclic ortho ester **11** in 51% yield. The starting ortho ester **6a** is a racemate (DL mixture) and formation of the 2′,3′-cyclic ortho ester creates a new asymmetric center at the "ortho ester" carbon which presents the possibility of four diastereoisomers for compound **11**. TLC indicated, however, that such a mixture would be difficult to resolve. Compound **11** moved as a single spot.[14] Hydrolysis of **11** in dioxane–acetic acid–water (2:3:3) mixture gave 2′(3′)-*O*-(*N*-benzyloxycarbonyl)-DL-phenylalanyluridine[15] (**12**) in 95% yield which had the same mobility on TLC as the corresponding L-phenylalanyl derivative.[3a]

In connection with our experiments on the ortho ester exchange of **6a** with ribonucleosides, it was of interest to examine an analogous acetalation reaction of aldehyde **16**. *N*-Benzyloxycarbonyl-L-phenylalanine (**15**) was converted to the corresponding imidazolide which was reduced in situ with $LiAlH_4$ to aldehyde **16** in 50% yield following the procedure described for N^{α}-benzyloxycarbonyl-N^{ω}-nitroargininal.[16] In addition, *N*-benzyloxycarbonyl-L-phenylalaninol (**19**)[17,18] was also obtained (23% yield) as the final reduction product of aldehyde **16** (Scheme II). The ir spectrum of **16** showed distinctly separate aldehyde and urethane carbonyl bands. The assignments follow from the spectrum of acetal **17** which contains only a urethane carbonyl band. The NMR exhibited a typical low-field singlet of an aldehyde group. The fact that the optical rotation of **19** was slightly higher than that of an authentic sample[17,18] indicates that no racemization of the aldehyde **16** occurred during reaction with $LiAlH_4$. However, after isolation (chromatography on silica gel[19]) the aldehyde was almost completely (93%) racemized[19] as shown by $LiAlH_4$ reduction to alcohol **19** and comparing its rotation with optically pure L-compound. The reaction of **16** with dimethylformamide–dimethyl sulfate complex and methanol following the procedure[20] for acetalation of simple aliphatic aldehydes gave the corresponding acetal **17** in 60% yield.[21] Both the ir

Scheme II



and NMR spectra of **17** lack the bands characteristic of an aldehyde. It is of interest to note that the NMR spectrum of **17** exhibits two separate signals (singlets) for acetal methoxy groups. This finding probably reflects *Z–E* isomerism of the urethane bond[10] (cf. formulas **13** and **14**). A similar splitting of signals was observed with ortho ester **6a** (see Figure 1).

Acetalation of adenosine with aldehyde **16** in the presence of ethyl orthoformate and trifluroacetic acid as catalyst in DMF afforded only 2′,3′-*O*-ethoxymethyleneadenosine[22] (**18a**) in 73% yield in addition to the N,O mixed acetal **18b** obtained in 21% yield. The structure of the latter followed from analysis and uv max which is bathochromically shifted relative to **18a**. NMR shows the presence of two phenyl groups and two ethoxy functions. The absence of a free amino group was confirmed by the failure of **18b** to react with dimethylformamide dimethyl acetal.[23,24] In acid, compound **18b** is hydrolyzed[24] to adenosine 2′(3′)-formate and aldehyde **16**.

It is of interest to note that a similar reaction (formation of N,O mixed acetal derivative) was observed when adenosine was treated with *p*-nitrobenzaldehyde under similar conditions.[24] It appears therefore that alkoxycarbonium ions (see Scheme I, ref 24) derived from aldehydes carrying an electronegative substituent in the vicinity of aldehyde function are less reactive toward 2′,3′-cis diol grouping of adenosine than toward a weakly basic amino group of the adenine moiety. Contrariwise, the corresponding dialkoxycarbonium ions derived from analogous ortho esters [e.g., from ethyl *N*-benzyloxycarbonyl-DL-orthophenylalaninate (**6a**)] react smoothly with the 2′ and 3′ hydroxy groups of ribonucleosides (cf. compound **11**).

Experimental Section

General Methods. Evaporations were carried out in a Büchi rotary evaporator in vacuo at a bath temperature below 40 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Samples for analysis were dried at 10^{-3} mm over P_2O_5 at room temperature. Thin layer chromatography (TLC) was performed on 6 × 2 cm precoated silica gel F-254 aluminum foils (Merck, Darmstadt, Germany) in solvent S_1 (diethyl ether–petroleum ether, 1:1), S_2 (chloroform–methanol, 9:1), S_3 (chloroform–methanol, 4:1), S_4 ($CHCl_3$), and S_5 ($CHCl_3$–MeOH, 97:3). Preparative TLC and column chromatography were performed with silica gel 70–325 mesh ASTM (Merck, Darmstadt, Germany); for TLC 1% (w/w) fluorescent indicator, Lumilux Grün ZS Super (Riedel-De Haën AG, Seelze-Hannover, Germany) was added. Detection was performed in uv light (Mineralight) or with iodine vapors. Petroleum ether was of a 30–60 °C boiling range. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. The ir spectra were measured in CCl_4 in a Perkin-Elmer Model 21 spectrometer. NMR spectra were obtained using a Varian A-60A spectrometer in CCl_4 or CD_3COCD_3, unless stated otherwise; $(CH_3)_4Si$ was used as an internal standard. Ethanol and DMF were dried with Linde molecular sieves. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ and stored over sodium wire. *N*-Benzyloxycarbonyl-L-phenylalanine was a product of Sigma Chemical Co., St. Louis, Mo. *N*-Benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester was prepared according to the literature.[12] Hydrocinnamonitrile was a product of Eastman Kodak Co., Rochester, N.Y.

Ethyl Hydrocinnamimidate Hydrochloride (2). The described procedure[5] was modified as follows. A solution of hydrocinnamonitrile [**1**, freshly distilled from P_2O_5 immediately before use, bp 98–100 °C (0.1 mm), 23.93 g, 0.182 mol] in ethanol (12.7 ml, 0.22 mol) was cooled in an ice bath and a slow stream of HCl was introduced directly from a tank with stirring to saturation. The resultant thick oil was kept overnight at 0 °C. The white, crystalline product **2** was filtered off after addition of dry ether (ca. 500 ml), and washed with ether and dried in vacuo over P_2O_5 and KOH in a desiccator: yield 38.41 g (98%); mp 144 °C dec (lit.[5] 130 °C); NMR (CD_3SOCD_3, sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard) δ 7.33 (s, 5, C_6H_5), 4.46 (q, 2, OCH_2), 1.32 (t, 3, CH_3).

Ethyl *N*-Chlorohydrocinnamimidate (3). The procedure described[6] for the preparation of ethyl *N*-chlorophenylacetimidate was followed. To the cooled (5 °C) solution of NaClO freshly made from NaOH (100 g, 2.5 mol) and chlorine (114.4 g, 1.61 mol) in water (800 ml) compound **2** was added portionwise with stirring (32.1 g, 0.15 mol) at 0–10 °C (ice–salt bath was used). It is imperative to keep the pH of the NaClO solution at 7.0 (pH meter) during the addition of hydrochloride **2** to avoid concomitant hydrolysis to the corresponding ester. The mixture was then stirred for 30 min, petroleum ether (100 ml) was then added, and the layers were separated. The aqueous portion was extracted with petroleum ether, and the combined extracts were dried ($MgSO_4$) and evaporated to give **3** as a colorless oil: 31.04 g (98%); n^{30}D 1.5210; ir no absorptionat 1650–1800 (absence of CO ester) and 3100–4000 (absence of NH), 1600 cm^{-1} (strong, C=N—Cl, cf. ref 6); NMR (CCl_4) δ 7.17 (s, 5, C_6H_5), 4.09 (q, 2, OCH_2), 2.84 (s, 4, CH_2), 1.20 (t, 3, CH_3).

Ethyl DL-Orthophenylalaninate (4a) and 2,5-Dibenzyl-3,6-diethoxy-2,5-dihydropyrazine (5). The procedure[4] for preparation of amino acid ortho esters was extended to the phenylalanine derivative **4a**. The solution of compound **3** (21.17 g, 0.1 mol) in ethanol (50 ml) was added dropwise with stirring and external ice cooling to 1.25 M sodium ethylate (freshly prepared from sodium, 2.88 g, 0.125 mol, and 100 ml of ethanol). The solution was stirred for 1.5 h at 30–40 °C (bath temperature, NaCl started to precipitate) and 2 h at 80 °C. The reaction mixture was kept overnight at room temperature, poured into water (250 ml), and extracted with dichloromethane (3 × 100 ml). Combined organic layers were dried ($MgSO_4$) and evaporated to give **4a** as a yellow, rumlike smelling oil: n^{28}D 1.4790; 26.46 g (99%); ir no absorption between 1650 and 1800 (absence of CO ester), 1065 cm^{-1} (strong, C–O–C); NMR (CCl_4) δ 7.13 (s, 5, C_6H_5), 3.65 (q, 6, OCH_2), 3.03 (m, 2, CH_2) 2.35 (q, 1, CH), 1.13 (t, 11, CH_3 overlapped with NH_2, after addition of D_2O the triplet became symmetric and it integrated for 9 protons). This product was sufficiently pure (ca. 95%) to be used in subsequent steps (preparation of **6a** and **9**) without further purification. Distillation of this product at 107–110 °C (0.25 mm) afforded ortho ester **4a** in two fractions (5.32 g, 20%). The second fraction (n^{27}D 1.4813) was analyzed.

Anal. Calcd for $C_{15}H_{25}NO_3$ (267.4): C, 67.38; H, 9.43; N, 5.24. Found: C, 67.30; H, 9.27; N, 5.48.

Continued distillation afforded an additional fraction (2.1 g) of **4a** contaminated, according to ir, with **5**. The last fraction (thick syrup, n^{25}D 1.5469), which was analyzed, was dissolved in petroleum ether and the solution cooled to −20 °C to give **5** (0.975 g, 5.6%): mp 40–100 °C; ir 1703 cm^{-1} (C=N); NMR (CCl_4) δ 7.05 (m, 10, C_6H_5), 4.07 (m, 4, CH_2 of C_2H_5O), 1.23 (m, 6, CH_3 of C_2H_5O).[25]

Anal. Calcd for $C_{22}H_{26}N_2O_2 \cdot \frac{1}{4}H_2O$ (355.0): C, 74.44; H, 7.53; N, 7.89. Found: C, 74.50; H, 7.35; N, 8.15.

Ethyl *N*-Benzyloxycarbonyl-DL-orthophenylalaninate (6a). A solution of benzyloxycarbonyl chloride (7.5 g, 0.044 mol) in dry ether (200 ml) was added dropwise with stirring and external ice cooling to a mixture of ortho ester **4a** (10.68 g, 0.04 mol), triethylamine (12 ml, 0.12 mol), and dry ether (200 ml) during 40 min. The stirring continued for 1 h at 0 °C and after addition of ethanol (10 ml) for 30 min at room temperature. The precipitate (riethylamine hydrochloride) was filtered off and washed with ether and the filtrate was extracted with water (150 ml). Dried ($MgSO_4$) ether layer was evaporated and the resultant solid crystallized from petroleum ether (40 ml) at 0 °C to give 10.49 g (66%) of ortho ester derivative **6**: mp 77–79 °C; ir 3500 (NH), 1735 (CO, urethane), 1512, 1520 (amide II band of urethane plus aromatics), 1058 cm^{-1} (C–O–C); NMR (CCl_4) δ 7.15 (2 s, 10, C_6H_5), 4.9 (s, 2, CH_2 of $C_6H_5CH_2O$), 3.65 (d of q, 6, CH_2 of C_2H_5O), 2.8 (m, 2, CH_2), 1.13 (t, 9, CH_3 of C_2H_5O).

Anal. Calcd for $C_{23}H_{31}NO_5$ (401.5): C, 68.80; H, 7.78; N, 3.49. Found: C, 68.98; H, 7.90; N, 3.48.

Ethyl *N*-Benzyloxycarbonylorthoglycinate (6b). The procedure described for ortho ester **6a** was followed starting from ethyl orthoglycinate[4] **4b** (12.63 g, 0.071 mol) to give, after crystallization from petroleum ether, the *N*-benzyloxycarbonyl derivative **6b** (11.82 g, 38%), mp 35–40 °C (lit.[2a] 38–40 °C), which was identical with an authentic specimen:[2a] NMR (CCl_4) δ 7.19 (s, 5, C_6H_5), 4.98 (d, 2, CH_2 of $C_6H_5CH_2O$), 3.50 (q, 6, CH_2 of C_2H_5O, partially overlapped with CH_2 of the glycine portion), 3.32 (d, 2, CH_2 of glycine, partially overlapped with CH_2 of C_2H_5O).

Ethyl *N*-Benzyloxycarbonyl-DL-phenylalaninate (7). A solution of ortho ester **6a** (0.2 g, 0.5 mmol) in CH_2Cl_2 (20 ml) was stirred with 10% HCl (10 ml) for 30 min at room temperature. The layers were then separated, and the CH_2Cl_2 portion was washed with water (2 × 10 ml) and saturated solution of $NaHCO_3$ (10 ml). The dried ($MgSO_4$) organic phase was evaporated to a syrup which was dissolved in ether (5 ml). Petroleum ether (5 ml) was added and the mixture containing a syrupy precipitate was kept overnight at −20 °C whereupon it crystallized. Evaporation in vacuo gave crystalline ester **7**: mp 77–79 °C (lit.[11] 77–79 °C); mixture melting point with ortho ester **6a** was 65

°C; 0.13 g (80%); NMR (CCl_4) δ 7.25 and 7.14 (2 s, 10, C_6H_5), 5.03 (s, 2, CH_2 of $C_6H_5CH_2O$), 4.53 (m, 1, CH), 4.09 (q, 2, CH_2 of C_2H_5O), 1.17 (t, 3, CH_3 of C_2H_5O).

Ethyl *N*-Benzyloxycarbonyl-L-phenylalanyl-DL-orthophenylalaninate (9). The cooled solution of ortho ester **4a** (0.536 g, 2 mmol) and triethylamine (0.202 g, 2 mmol) in dichloromethane (10 ml) was treated with *p*-nitrophenyl ester[12] **8** (0.925 g, 2.2 mmol) in dichloromethane (10 ml). The reaction mixture was kept for 5 h at room temperature, whereupon it was extracted with a saturated solution of $NaHCO_3$ (3 × 10 ml) and NH_4OH (dilute 1:1, 3 × 10 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a solid which as filtered after addition of ethanol: 0.69 g (63%), homogeneous on TLC (S_1); mp 114–118 °C was unchanged after recrystallization from cyclohexane; $[\alpha]^{24}D$ −27.4° (*c* 0.5, acetone); ir (KBr) 3370 (NH), 1705 (CO, urethane), 1660 (CO, amide), 1553, 1543 cm^{-1} (amide II bands of urethane and peptide bond and aromatics); NMR (CD_3COCD_3) δ ca. 7.22 (m, 15, C_6H_5), 4.95 (s, 2, CH_2 of $C_6H_5CH_2O$), 3.63 (poorly resolved d of q, 6, CH_2 of C_2H_5O), 1.08 (t, 9, CH_3).

Anal. Calcd for $C_{32}H_{40}N_2O_6$ (548.7): C, 70.05; H, 7.35; N, 5.11. Found: C, 70.07; H, 7.38; N, 5.13.

Ethyl *N*-Benzyloxycarbonyl-L-phenylalanyl-DL-phenylalaninate (10). A solution of dipeptide ortho ester **9** (70 mg, 0.13 mmol) in CH_2Cl_2 (10 ml) was stirred with 10% HCl (10 ml) for 30 min at room temperature. The layers were separated, the aqueous one was extracted with CH_2Cl_2 (10 ml), and the combined organic portions were washed with a saturated solution of $NaHCO_3$ (10 ml) and water (10 ml). The dried ($MgSO_4$) solution was evaporated, leaving a white solid **10**, mp 100–103 °C, TLC (S_1) homogeneous and different (slower) from ortho ester **9**. Crystallization from benzene–cyclohexane (2:1) gave 25 mg (40%) of material:[26] mp 128–130 °C; $[\alpha]^{24}D$ + 1.75° (*c* 0.91, ethyl acetate); NMR (CD_3COCD_3) δ 7.27 and 7.20 (2 s, 15, C_6H_5), 4.98 (s, 2, CH_2 of $C_6H_5CH_2O$), 4.55 (m, 2, CH), 4.09 (q, 2, CH_2 of C_2H_5O), 1.31 (t, 3, CH_3 of C_2H_5O).

Reaction of Uridine with Ortho Ester 6a. A solution of uridine (0.12 g, 0.5 mmol), ortho ester **6a** (0.4 g, 1 mmol), and CF_3COOH (5 drops) in DMF (5 ml) was kept for 15 h at room temperature. Triethylamine (0.5 ml) was then added, the solution was evaporated at 0.1 mm, and the residue was partitioned between CH_2Cl_2 (20 ml) and saturated $NaHCO_3$ (10 ml). The aqueous layer was extracted with CH_2Cl_2 (10 ml), and the combined organic portions were dried ($MgSO_4$) and evaporated. The syrupy residue was chromatographed on one 20 × 20 cm 2-mm thick layer of Stahl's silica gel GF-254 in solvent S_2 (0.1 ml of triethylamine/100 ml). The major slower moving uv-absorbing band was eluted with the 4:1 mixture of the same solvents and the eluate was evaporated to give a syrup. Trituration with ether–petroleum ether afforded 2′,3′-cyclic ortho ester **11** as an amorphous solid, 0.14 g (51%), homogeneous on TLC (S_2, S_3), uv max (ethanol) 260 nm (ε 8700), min 230 (ε 1800).

Anal. Calcd for $C_{28}H_{31}N_3O_9$ (553.6): C, 60.75; H, 5.65; N, 7.59. Found: C, 60.61; H, 5.90; N, 7.33.

2′(3′)-*O*-(*N*-Benzyloxycarbonyl-DL-phenylalanyl)uridine (12). A solution of 2′,3′-cyclic ortho ester **11** (83 mg, 0.15 mmol) in dioxane–acetic acid–water (2:3:3) mixture (4 ml) was kept for 22 h at room temperature. The solution was then lyophilized, the residue dissolved in $CHCl_3$, and ether–petroleum ether added to precipitate **12** as an amorphous powder, 77 mg (95%); the mobility on TLC (S_2, S_3) was identical with that of an authentic sample[3a] of the corresponding L-phenylalanyl derivative.

***N*-Benzyloxycarbonyl-L-phenylalaninal (16) and *N*-Benzyloxycarbonyl-L-phenylalaninol (19).** A solution of *N*-benzyloxycarbonyl-L-phenylalanine (**15**, 7 g, 0.023 mol) in tetrahydrofuran (45 ml) was cooled to 10 °C and *N,N′*-carbonyldiimidazole (4 g, 0.025 mol) was added. The resulting mixture was stirred for 20 min at 10 °C, then cooled to −20 °C and a solution of $LiAlH_4$ (1.9 g, 0.050 mol) in tetrahydrofuran (80 ml) was added dropwise over a period of 30 min. The stirring of the reaction mixture then continued for 15 min at −20 °C whereupon 2 M HCl (80 ml) was added. Evaporation in vacuo gave a solid which was extracted with chloroform (total 350 ml). The combined extracts were washed with water (100 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in chloroform (10 ml) and the solution was put on the top of the column made from silica gel (120 g, 3 × 30 cm). Elution with chloroform (250 ml) after evaporation gave a crystalline solid which was crystallized from ether–petroleum ether (1:2) to afford aldehyde **16** (3.3 g, 50%): mp 76–77 °C; $[\alpha]^{22}D$ −1.8° (*c* 0.45, $CHCl_3$);[19] ir (KBr) 3370 (NH), 1736 (CO, aldehyde), 1683 cm^{-1} (CO, urethane); NMR ($CDCl_3$) δ 9.35 (s, 1, CH=O), 7.31–6.94 (m, 10, C_6H_5), 5.03 (s, 2, CH_2 of benzyloxycarbonyl), 4.37 (q, 1, CH), 3.04 (d, 2, CH_2).

Anal. Calcd for $C_{17}H_{17}NO_3$ (283.3): C, 72.07; H, 6.05; N, 4.94. Found: C, 71.91; H, 6.08; N, 4.87.

Further elution with chloroform (100 ml) gave *N*-benzyloxycarbonyl-L-phenylalaninol (**19**, 1.53 g, 23%), mp 92–92.5 °C (lit.[17,18] 90–92 and 90 °C, respectively), $[\alpha]^{22}D$ −45.9° [lit.[17] −41.5° (*c* 1.4, ethanol)], $[\alpha]^{22}D$ −44.6° [lit.[18] −42° (*c* 2.0 methanol)].

The reduction of aldehyde **16** in a standard fashion (see above) with $LiAlH_4$ gave alcohol **19**, mp 76–77 °C, $[\alpha]^{22}D$ −3.4° (*c* 1.4, ethanol), ir corresponded to that of optically pure **19**.

***N*-Benzyloxycarbonyl-L-phenylalaninal Dimethyl Acetal (17).** Aldehyde **16** (0.4 g, 1.4 mmol) was added portionwise to a mixture of dimethylformamide dimethyl sulfate complex[28] (0.31 g, 1.55 mmol) and anhydrous methanol (65 mg, 2 mmol) at room temperature with stirring which then continued for 2.5 h. The mixture was kept overnight, and the crystallized product was washed with petroleum ether and recrystallized from petroleum ether–ether (1:1) to give acetal **17** (0.28 g, 60%): mp 58–60 °C; $[\alpha]^{22}D$ −8.4° (*c* 1.22, $CHCl_3$); ir (KBr) 3350 cm^{-1} (NH), 1690 (CO, urethane), 1550 (amide II band, urethane); NMR ($CDCl_3$) δ 7.25 and 7.16 (two s, 10, C_6H_5), 5.00 (s, 2, CH_2 of benzyloxycarbonyl), 4.08 (m, 2, CH), 3.41 and 3.35 (two s, 6, OCH_3), 2.85 (m, 2, CH_2).

Anal. Calcd for $C_{19}H_{23}NO_4$ (329.4): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.20; H, 7.10; N, 4.17.

Reaction of Adenosine, Aldehyde 16, and Ethyl Orthoformate. A solution of aldehyde **16** (0.4 g, 1.4 mmol), ethyl orthoformate (0.46 g, 3.1 mmol), adenosine (0.376 g, 1.4 mmol), and trifluoroacetic acid (0.24 g, 2.1 mmol) in DMF (10 ml) was kept at room temperature for 39 h. Triethylamine was then added to adjust pH to 8–9 (indicator paper) and the volatile components were evaporated at 0.1 mm and room temperature. The residue was chromatographed on two loose layers of silica gel (35 × 15 cm, 3 mm thick) in solvent S_5 containing 0.2% of triethylamine (double development). The faster moving band was eluted with the solvent and evaporated to give amorphous product **18b** (0.185 g, 21%): TLC (S_2) homogeneous; uv max (ethanol) 265 nm (ε 16 500), min 228 (2100); NMR (CD_3COCD_3 + D_2O) δ 8.15 (s, 2, H_8 + H_2), 7.13 (m, 10, C_6H_5), 6.35 (d, 1, J = 3.5 Hz, $H_{1'}$), 1.10 and 1.42 (two t, CH_3 of C_2H_5O).

Anal. Calcd for $C_{32}H_{38}N_6O_8$ (634.7): C, 60.55; H, 6.04; N, 13.24. Found: C, 60.41; H, 6.17; N, 13.13.

Elution of the slower moving band with solvent S_2 containing 0.2% of triethylamine gave 2′,3′-*O*-ethoxymethyleneadenosine (**18a**, 0.33 g, 73%) identical with an authentic sample[22] (TLC, uv, and melting point).

Attempted Reaction of 18b with Dimethylformamide Dimethyl Acetal. A solution of compound **18b** (2 mg) and dimethylformamide dimethyl acetal (0.05 ml) in DMF (0.2 ml) was kept for 16 h at room temperature.[23] After evaporation the uv spectrum of the residue (ethanol) was identical with that of starting material **18b**.

Hydrolysis of Compound 18b. A solution of **18b** (5 mg) in 80% formic acid (0.5 ml) was kept at room temperature for 30 min. A sample of the mixture was chromatographed (TLC) in solvents S_4 and S_5 along with authentic samples of **18b**, adenosine 2′(3′)-*O*-formate prepared in situ from **18a** by the same procedure,[24] and aldehyde **16**.

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Registry No.—**1**, 645-59-0; **2**, 52353-64-7; **3**, 59830-53-4; **4a**, 59830-54-5; **4b**, 24595-61-7; **5**, 59830-55-6; **6a**, 59830-56-7; **6b**, 13347-35-8; **7**, 3588-57-6; **8**, 2578-86-1; **9**, 59830-57-8; **10**, 59830-58-9; **11**, 59830-59-0; **15**, 1161-13-3; **16**, 59830-60-3; **17**, 59830-61-4; **18b**, 59830-62-5; NaClO, 7681-52-9; sodium ethylate, 141-52-6; benzyloxycarbonyl chloride, 501-53-1; uridine, 58-96-8; *N,N′*-carbonyldiimidazole, 530-62-1; dimethylformamide, 68-12-2; adenosine, 58-61-7; ethyl orthoformate, 122-51-0.

References and Notes

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Orientation of the Nitrogen Lone-Pair Electrons in Cannivonine

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The structure of cannivonine b (1) has been reasonably established using ^1H NMR spectra recorded in the presence of shift reagents.[1-3] The cannivonine b is a tricyclic alkaloid having a 1-cyclohexen-3-ol ring fixed on the azabicyclo-[2.2.2]octane skeleton. Such a tricyclic compound can undergo syn–anti equilibration (Scheme I).

In the presence of the shift reagents, syn oriented nitrogen lone-pair electrons contribute to the formation of the eight-coordinate two donor atoms complex that involves O and N.[3] Recently Morishima and Yoshikawa[4] have found that the nitrogen lone pair of *N*-methyl-2-azabicyclo[2.2.2]oct-5-ene (and its dihydro derivative) is oriented in an anti position.

The NMR spectra, ^1H and ^{13}C, recorded in the presence of nickel bisacetylacetonate do not show the orientation of the metal relative to the double bond. The CNDO–MO calculations, carried out by the same authors, confirmed the preferential anti position of the nitrogen lone pair.[5,6] However, for cannivonine b, acetylacetonate can easily lie between the nitrogen and oxygen atoms and force the nitrogen lone pair into syn orientation (endo using Morishima nomenclature).

The syn orientation of the nitrogen lone pair is deduced from the ^{13}C NMR spectra of cannivonine (Table I).

The acetylacetonate relative induced shift of β carbons, with respect to the lone pair, is bigger if the lone pair is oriented trans (anti-coplanar) to this carbon. However, the gauche or eclipsed orientation shows a rather small contact shift (Scheme II). There are four carbons atoms β to the nitrogen lone pair (C-4, C-8, C-10, and C-11) and two β to the oxygen lone pairs (C-5 and C-7). Thus, the large C-10 relative induced shift of −1.38 is now understandable compared with the C-11, C-8, or C-4 induced shifts.

The oxygen atom has lone pairs oriented in such a manner that at the same time they are trans and eclipsed to C-5 and C-7. As a result, an average (~0.4) relative induced shift is observed.[7]

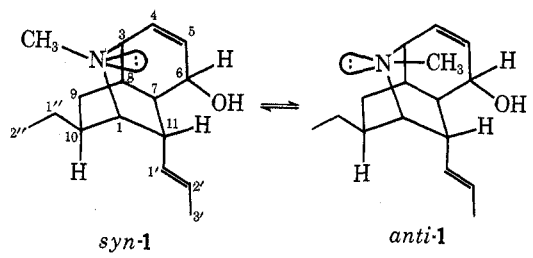
Finally, examination of steric repulsion in the 1-syn and 1-anti conformers shows that the syn conformers is effectively more stable. The interaction of 10-ethyl–NCH_3 and H-9β–NCH_3 in the syn conformer is smaller than the total interac-

Table I. Ni(acac)$_2$ Induced ^{13}C Contact Shifts for 1 [a]

C	δ_C	Relative induced shift
1	52.17	+1.00
NCH_3	43.81	+1.62
3	56.24	+1.40
4	129.73	−0.52
5	131.34	−0.44
6	65.51	+0.84
7	25.40	+0.40
8	26.87	−0.33
9	25.65	+0.02
10	24.92	−1.38
11	25.17	−0.41
1′	130.71	+0.08
2′	121.37	−0.17
3′	13.41	+0.14
1″	25.02	+0.08
2″	12.10	0.00

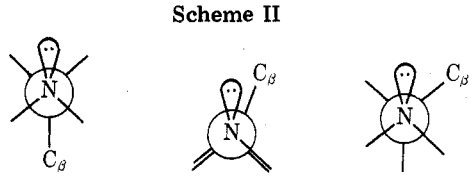
[a] Identification from off-resonance ^1H; see Experimental Section for details of calculations.

Scheme I



syn-1 *anti*-1

Scheme II



trans anti-coplanar eclipsed gauche

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