Photochemical Oxidation of Selected Nucleosides and Related Carbohydrates[1]

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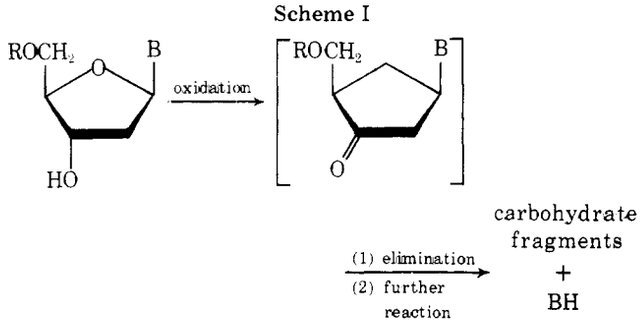
A recently developed photochemical oxidation technique has been used to convert four nucleoside derivatives, 5′-*O*-tritylthymidine (**8**), 5′-*O*-benzoylthymidine (**10**), 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**9**), and 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**11**), into the corresponding 3′-keto compounds. The conditions for these oxidations were sufficiently mild that the 3′-ketonucleosides, relatively unstable structures which easily experience β elimination, were isolated and characterized. A fifth compound, 3′-*O*-acetylthymidine (**16**), was oxidized to 3′-*O*-acetylthymidine-5′-aldehyde (**18**). In addition to these five nucleoside derivatives, four related carbohydrates (**1–4**) have been successfully oxidized using the photochemical oxidation technique.

Aldehydo- and ketonucleosides are types of compounds whose significance has become increasingly apparent in recent years. These structures represent key intermediates in the laboratory synthesis of such biologically important molecules as cyclonucleosides,[2] antiviral and antifungal nucleosides and related structures,[3-5] derivatives of adenosine 3′,5′-cyclic phosphate,[6] and adenosine 5′-phosphate and 5′-triphosphate.[7] Also, certain ketonucleosides are known to inhibit cancerous cell growth.[8] The significance of these compounds is evident.

Several years ago Pfitzner and Moffatt noted in their pioneering work on nucleoside oxidation that a severe limitation existed to the successful synthesis of certain ketonucleosides and ketonucleotides, particularly the 3′-keto compounds.[9] Hydroxyl to carbonyl oxidation, a logical process for obtaining keto derivatives, resulted in molecular decomposition of many compounds[10] (e.g., thymidine 5′-phosphate, adenosine 5′-phosphate, uridine 5′-phosphate, 5′-*O*-acetylthymidine, and 5′-*O*-*p*-nitrobenzoylthymidine). (To account for this instability, the reaction sequence shown in Scheme I was proposed.[11]) It was clear that a significant need existed for an oxidation process which was sufficiently mild to permit general hydroxyl to carbonyl oxidation in nucleosides and their derivatives without further reaction.

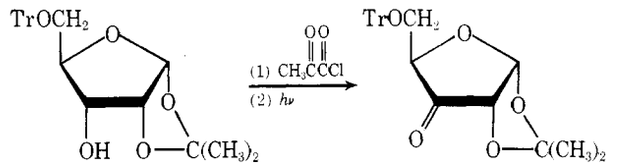
Two years ago we reported a photochemical process for oxidation of carbohydrates which was conducted under quite mild reaction conditions.[13] This process seemed well suited for situations in which oxidation products were known to be relatively unstable. Recently, successful photochemical oxidation of three tetraacetates of D-glucopyranose[14] demonstrated that, in fact, this technique was useful in preparing relatively unstable carbonyl compounds.[15] Such a finding suggested that similar transformations producing reactive aldehydo- and ketonucleosides also might be successful. In preparation for nucleoside oxidation, four model systems, 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranose (**1**), 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-xylofuranose (**2**), methyl 2-deoxy-5-*O*-trityl-α-D-*erythro*-pentofuranoside (**3**), and methyl 2-deoxy-5-*O*-trityl-β-D-*erythro*-pentofuranoside (**4**), were investigated.

Scheme I

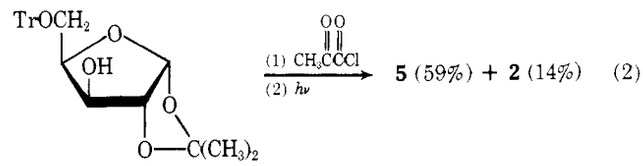


R = H, PO_3H_2, OAc, ETC; B = nitrogenous base

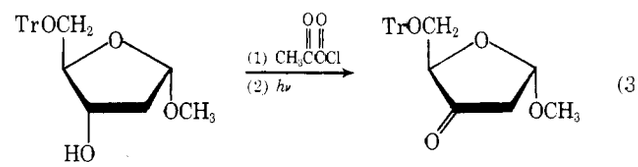
The same general procedure was used for the oxidation of all four alcohols **1–4**. Pyruvoyl chloride was added to a benzene solution of the alcohol and pyridine, resulting in ester formation which was immediate and quantitative. Each pyruvate ester (3.00 mmol) in 350 mL of benzene was irradiated for 1 h under nitrogen through a Pyrex filter with a 450-W mercury vapor lamp. The solvent was removed in vacuo below 25 °C and the resulting material was chromatographed on silica gel to afford the products in percent yields shown in eq 1–4.



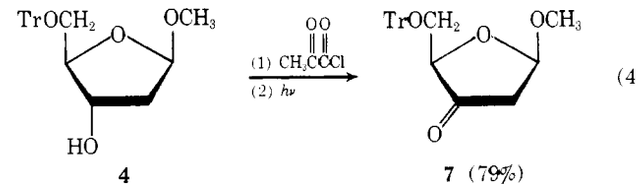
+ **1** (37%) + **2** (8%) (1)



(2)



(3)



(4)

Tr = $C(C_6H_5)_3$

Product identities were established by comparison with authentic samples. The alcohols recovered from photochemical reactions of **1** and **2** were not simply unreacted starting materials since pyruvate ester formation was complete prior to

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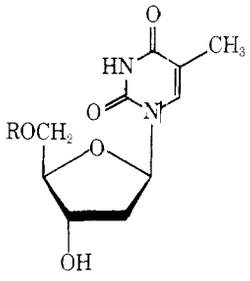
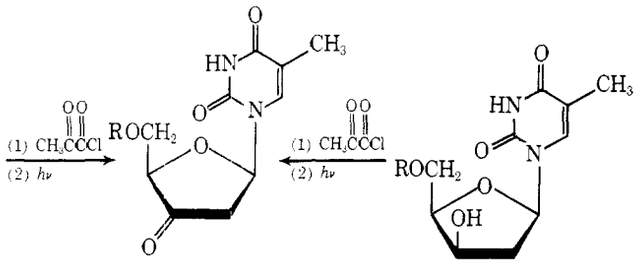
irradiation; further, product alcohols did not arise from hydrolysis of unreacted esters during workup since the starting esters were consumed totally during photolysis.

Following successful oxidation of compounds 1–4, four nucleoside derivatives (8–11) were studied. Reaction of the first of these, 5′-*O*-tritylthymidine (8), resulted in the formation of a single product from the oxidation process. Chromatography was unnecessary since after solvent removal, the photoproduct crystallized from chloroform–carbon tetrachloride. The IR spectrum of the photoproduct showed a carbonyl absorption at 1778 cm^{-1} (carbonyl in a five-membered ring). The ^1H-NMR spectrum of the photoproduct was similar to the starting alcohol (8) except that absorptions due to the hydroxyl proton and the proton on C_3' were absent; also, the patterns exhibited by the hydrogens attached to C_2' and C_4' were simplified. These data and the elemental analysis indicated the 3′-keto-5′-*O*-tritylthymidine (12) structure for



8

10



12

13

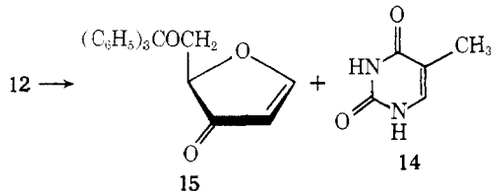
9

11

8, 9, 12, R = $C(C_3H_5)_3$ 10, 11, 13, R = $C(=O)C_6H_5$

the photoproduct. This structure (12) was confirmed by reduction of the photoproduct with sodium borohydride to yield 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (9). The yield of crystalline 12 from oxidation of 8 was 61%.

The work of Pfitzner and Moffatt correctly suggested that compounds such as 12 should be unstable under certain mild conditions. That the ketonucleoside 12 was unstable under rather mild conditions was evidenced by the fact that dissolving it in triethylamine at 25 °C or chromatographing it on silica gel resulted in immediate formation of thymine (14) and an unsaturated sugar. (Pyridine caused a similar change over a period of 2 days.) The enone 15 seemed the most reasonable possibility for the structure of the unsaturated sugar. This possibility was clearly supported by the quite simple ^1H NMR spectrum of the new sugar, in particular the coupled doublet absorptions for H_1 and H_2 (δ 8.24 and 5.54 ($J_{1,2}$ = 3 Hz)). In-



15

14

dependent synthesis of 15 by silica gel catalyzed elimination of methanol from 6 made certain the structural assignment.

Three related nucleoside derivatives were oxidized successfully using the photochemical oxidation procedure. Compound 9 reacted to give 12 in 57% yield. 5′-*O*-Benzoylthymidine (10) was oxidized to a compound, mp = 87–92 °C, for which the structure 5′-*O*-benzoyl-3′-ketothymidine (13) was tentatively assigned on the basis of elemental and ^1H NMR analysis and analogy to the oxidation of compound 8. The assignment of structure 13 to the oxidation product from 10 was confirmed by oxidation of 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (11) to the same product (13) under identical conditions. The yields of 13 from 10 and 11 were 68 and 57%, respectively.

Photochemical oxidation of two additional nucleoside derivatives (3′-*O*-acetylthymidine (16) and 2′,3′-*O*-isopropylidineuridine (17)) was undertaken in order to study the formation of aldehydonucleosides. Oxidation of 3′-*O*-acetylthymidine (16) was successful; however, oxidation of 17 was thwarted by its extreme insolubility in benzene, the normal irradiation solvent. Photolysis of 17 was attempted in other solvents such as acetone, chloroform, and dichloromethane; unfortunately, TLC analyses of the crude reaction mixtures indicated them to be complex and ^1H NMR analyses of these mixtures gave no indication of aldehyde formation. The irradiation products from 17 were not further characterized.

When the results from the present study are combined with those from previous investigations,[1,13,14] it is clear that the photochemical oxidation procedure can be useful in the oxidation of a variety of carbohydrates and appears to be a promising technique for oxidation of the carbohydrate portions of nucleosides. This process should be particularly valuable in forming products which are themselves relatively unstable.

Experimental Section

General Information. Two esterification procedures were used. For compounds 1–4 procedure I was used while for 8–11 procedure II was employed. The photolysis of all compounds was carried out in the same manner. These procedures are described in a general form below. ^1H NMR spectra were obtained ($(CH_3)_4Si$, δ 0 ppm) from a Varian T-60 spectrometer (coupling constants, J, are given in hertz; s, d, t, and m indicate singlet, doublet, triplet, and multiplet, respectively). Mass spectra were measured on a Finnigan 1015-D mass spectrometer using both electron impact (ionizing voltage of 70 eV) and chemical ionization with methane as the reagent gas at a pressure of 1.00 Torr and an ionizing voltage of 110 eV. Column chromatography effluents were monitored with an ISCO UA-2 ultraviolet analyzer.

Esterification Procedure I. The alcohol to be esterified (0.03 mol) and dry pyridine (0.033 mol) were dissolved in 25 mL of anhydrous benzene. Pyruvoyl chloride[16] (0.04 mol) in 10 mL of dry benzene was added in a dropwise manner with stirring. Precipitation of pyridinium hydrochloride was immediate. Cooling with cold water was necessary to keep the reaction mixture below 10 °C. After stirring for 15 min, the pyridinium hydrochloride was removed by filtration and the benzene was distilled in vacuo to yield the pyruvate ester contaminated with pyridinium hydrochloride. The contaminant could be removed by shaking the reaction mixture in 25 mL of carbon tetrachloride, allowing it to stand for a few hours, and filtering the insoluble material. When the carbon tetrachloride was evaporated from the filtrate, the resulting ester (^1H NMR analysis showed each alcohol to be completely esterified) was subjected immediately to irradiation.

Esterification Procedure II. A solution of 0.5 g of pyruvoyl chloride[16] in 5 mL of benzene was added dropwise to a stirred solution of 1.0 mmol of alcohol in 10 mL of anhydrous pyridine. After 15 min, 50 mL of chloroform was added and the solution was extracted with two 50-mL portions of water and dried over anhydrous sodium sulfate. Distillation of the chloroform and pyridine in vacuo left a yellow oil (^1H NMR analysis showed that esterification was complete in each case) which was irradiated without further purification.

Irradiation Procedure. The pyruvate ester was dissolved in 350 mL of dry benzene and the solution was purged with nitrogen for 2.0 h. The nitrogen purge was continued during Pyrex-filtered irradiation with a 450-W medium-pressure Hanovia mercury lamp. After 1 h, the

irradiation was stopped, the reaction mixture was analyzed by TLC, the benzene was removed by distillation, and ^{1}H NMR analysis was conducted prior to chromatography or crystallization.

Oxidation of 1,2-*O*-Isopropylidene-5-*O*-trityl-α-D-ribofuranose[17] (1). After esterification of 1 according to procedure I followed by irradiation and solvent removal, the residual material was chromatographed on a 90 × 2.5 cm silica gel (60–200 mesh) column slurry packed in 1:9 ether–hexane; 60 mL fractions were collected. The column was eluted as follows: 0.5 L of 1:9 ether–hexane, 1.0 L of 1:4 ether–hexane, and 1.0 L of 1:1 ether–hexane.

Fractions 10–18 afforded 489 mg (1.14 mmol, 38%) of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose[17] (**5**), identical in NMR, mass, and IR spectra with a known sample. Fractions 20–26 gave 495 mg (1.11 mmol, 37%) of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranose (**1**), and fractions 27–32 yielded 104 mg (0.24 mmol, 8%) of 1,2-isopropylidene-5-*O*-trityl-α-D-xylofuranose[17] (**2**). Compounds 1 and 2 were identified by comparison with known samples.

Oxidation of 1,2-*O*-Isopropylidene-5-*O*-trityl-α-D-xylofuranose[17] (2). After esterification of **2** according to procedure I and irradiation and solvent removal, the residual material was chromatographed in a manner identical to the chromatography of the reaction mixture from the oxidation of **1**. Fractions 10–18 afforded 776 mg (1.77 mmol, 59%) of **5** while fractions 27–35 gave 181 mg (0.42 mmol, 14%) of **2**.

Oxidation of Methyl 2-Deoxy-5-*O*-trityl-α-D-*erythro*-pentofuranoside[18] (3). After esterification of **3** according to procedure I, irradiation, and solvent removal, a material remained which by ^{1}H NMR analysis appeared to be at least 90% methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**6**).

Chromatography of the reaction mixture on a 4.0 × 20 cm column of 200–300 mesh silica gel with 500 mL of 60% ether–hexane produced **6** in 80% yield. The identity of the photoproduct was established as methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**6**) by comparison with an authentic sample.[18]

Oxidation of Methyl 2-Deoxy-5-*O*-trityl-β-D-*erythro*-pentofuranoside[18] (4). The oxidation and isolation procedure for **4** was the same as used for **3**. A 79% yield of methyl 2-deoxy-5-*O*-trityl-β-D-*glycero*-pentofuranosid-3-ulose (**7**), identified by comparison with an authentic sample,[18] was obtained.

Oxidation of 5′-*O*-tritylthymidine[19] (8). After esterification of **8** according to procedure II and irradiation, the cloudy reaction mixture was filtered and the benzene was distilled in vacuo to leave a residue which was dissolved in 10 mL of chloroform. Carbon tetrachloride (20 mL) was slowly added, and after standing for 12 h 305 mg of crystals formed, mp 171–4 °C. The photoproduct had ^{1}H NMR (60 MHz) absorptions ($CDCl_3$) at δ 8.55 (NH, broad s), 7.47–7.11 (aromatic and H_6, m), 6.55, 3.04, 2.85 ($H_{1'}$, $H_{2'}$, $H_{2''}$, ABX pattern, $J_{1',2'}$ = 7 Hz, $J_{1',2''}$ = 9.5 Hz), 4.14, 3.64, 3.36 ($H_{4'}$, $H_{5'}$, $H_{5''}$, ABX pattern $J_{4',5'}$ = $J_{4',5''}$ = 3 Hz, $J_{5',5''}$ = 10 Hz), and 1.52 (CH_3, s). Also, the photoproduct exhibited an IR absorption at 1778 cm^{-1}.

Anal. Calcd for $C_{29}H_{26}O_5N_2$: C, 72.18; H, 5.43; N, 5.80. Found: C, 72.00; H, 5.49; N, 5.71.

The spectral evidence and the elemental analysis indicated the photoproduct to be 3′-keto-5′-*O*-tritylthymidine (**12**). Sodium borohydride reduction of it to compound **9** confirmed this structural assignment.

Photoproduct (200 mg) was dissolved in 15 mL of ethanol and 100 mg of sodium borohydride was added. After 1 h at room temperature, the solution was partitioned between chloroform (25 mL) and water (25 mL) and the chloroform layer was extracted with water (25 mL) and dried over sodium sulfate. Evaporation of the chloroform left 160 mg of 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymidine[20] (**9**).

The yield of crystalline **12** from the oxidation of **8** was 61%.

Oxidation of 1-(2-Deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine[20] (9). The oxidation of **9** was conducted in the same manner as that of **8**. The yield of the oxidation product **12** was 57%.

Reaction of 3′-Keto-5′-*O*-tritylthymidine (12) with Triethylamine. 3′-Keto-5′-*O*-tritylthymidine (100 mg) was dissolved in 5 mL of methanol and 1 mL of triethylamine was added. After 1 h the solvent was removed in vacuo and the residue was partitioned between water (5 mL) and ethyl ether (10 mL). Evaporation of the dried ether layer (sodium sulfate) produced 55 mg of colorless oil which showed ^{1}H NMR absorptions (C_5D_5N) at δ 8.24 ($H_{1'}$, d, $J_{1,2}$ = 3 Hz), 7.50–6.76 (aromatic, m), 5.54 ($H_{2'}$, d), 4.43 ($H_{4'}$, t, $J_{4,5}$ = $J_{4,5'}$ = 4 Hz), 3.33 ($H_{5'}$, $H_{5''}$, d). The mass spectrum (electron impact) showed a small parent peak at *m/e* 256. These spectral data indicated **15** as the structure of the colorless oil.

Compound **15** was independently synthesized from methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**6**) by stirring 100 mg of **6** for 1 h in 25 mL of ethyl ether in which 1 g of silica gel was suspended. Washing the silica gel with an additional 25 mL of ether followed by evaporation of the ether yielded 80 mg of **15**.

Oxidation of 5′-*O*-Benzoylthymidine[21] (10) and 1-(5-*O*-Benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine[22] (11). Following esterification of **10** according to procedure II and irradiation, the cloudy reaction mixture was filtered and the benzene was distilled in vacuo to leave a residue which was dissolved in 5 mL of chloroform. Addition of carbon tetrachloride (15 mL) caused precipitation of 270 mg of a material which was reprecipitated in the same manner to yield 232 mg of a solid, mp 87–92 °C. This product had ^{1}H NMR (60 MHz) absorptions at δ 8.94 (NH, broad s), 8.13–7.75 (ortho aromatic, m), 7.65–7.11 (meta and para aromatic, H_6, m), 6.30, 3.04, 2.68 ($H_{1'}$, $H_{2'}$, $H_{2''}$, ABX pattern, $J_{1',2'}$ = 7 Hz, $J_{1',2''}$ = 6.5 Hz, $J_{2',2''}$ = 10 Hz), 5.03–4.24 ($H_{4'}$, $H_{5'}$, $H_{5''}$, m), and 1.62 (CH_3, s). Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.51; H, 4.67; N, 8.21.

The analytical and spectral data suggested the 5′-*O*-benzoyl-3′-ketothymidine (**13**) structure for the photoproduct. Confirmation of this structure was obtained from oxidation of 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine[22] (**11**) in the same manner as **10** to yield the same material (**13**). The yield of **13** from **10** was 68% and from **11** it was 57%.

Oxidation of 3′-*O*-acetylthymidine[23] (16). After esterification according to procedure II and irradiation (only 75 mg of **16** was irradiated), the benzene was distilled to leave 50 mg of residue which was identified as 3′-*O*-acetylthymidine-5′-aldehyde[9] (**18**) by ^{1}H NMR and TLC comparison with a known sample.

Attempted Oxidation of 2′,3′-*O*-Isopropylideneuridine[23] (17). Photochemical oxidation of 2′,3′-*O*-isopropylideneuridine (**17**) was unsuccessful because although esterification took place (procedure II), the resulting ester was insoluble in benzene. Photolysis of the pyruvate ester of **17** in solvents in which it was soluble (acetone, chloroform, dichloromethane) resulted in quite complex reaction mixtures (by TLC analysis); further ^{1}H NMR and IR analyses showed no evidence of aldehyde formation. These reactions were not studied further.

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Registry No.—**1**, 20590-57-2; **2**, 20590-53-8; **3**, 16801-99-3; **4**, 16802-00-9; **5**, 20590-54-9; **6**, 51885-24-6; **7**, 51921-34-7; **8**, 7791-71-1; **9**, 55612-11-8; **10**, 35898-29-4; **11**, 65475-51-6; **12**, 65475-49-2; **13**, 65475-50-5; **15**, 65475-52-7; **16**, 21090-30-2; **18**, 5983-15-3.

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(22) Compound **11** was synthesized from 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine[20] according to the procedure used by Baker and Neenan[21] to synthesize **10**.
(23) ICN Pharmaceuticals, Inc., Cleveland, Ohio 44128.

Approach to the Use of Benzylpenicillinacylase for Configurational Correlations of Amino Compounds

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Benzylpenicillinacylase (BPA) from *Escherichia coli* ATCC 9637 was found capable of hydrolyzing, in addition to the *N*-acyl derivatives of α-amino acids, the *N*-phenylacetyl derivatives of a variety of primary amino compounds. An approach to the use of the stereospecific action of BPA for correlating the absolute configurations of amino compounds is described. For this purpose enzymatic hydrolysis of several *N*-phenylacetylamino derivatives with known absolute configuration was examined. Reference to a single stereomodel was made to analyze hydrolytic data. The substituents at the asymmetric carbon atoms of the preferred enantiomers were then classified in terms of position occupied inside groups of priority sequences. The priority relations found constitute an empirical guide for stereochemical predictions. For some of the substrates examined the absolute configuration was determined, in the course of the present work, by chemical methods.

The stereospecific action of enzymes of the class of the acylases, amidases, decarboxylases, and oxidases is a long-established and reliable method of determining the absolute configuration of α-amino acids. More recently, benzylpenicillinacylase (BPA) from *Escherichia coli* ATCC 9637 has been reported to show L-directed stereochemical preference in hydrolyzing *N*-phenylacetylamino acids.[2-4] In accordance with this observation we have used BPA to define and confirm the absolute configuration of some amino acids.[3,4]

On further investigation[5] BPA was found capable of (i) hydrolyzing (in addition to the *N*-phenylacetylamino acids) a variety of *N*-phenylacetylamino compounds with a primary amino group and (ii) reacting at different rates on both the enantiomers of racemic mixtures.

On the basis of these properties it seems interesting to examine the potentiality of this enzyme in the field of enzymatic hydrolysis, particularly for the resolution of racemates and for configurational correlations.

Although in the case of the enzymatic hydrolysis of *N*-acylamino acids, the configurational correlations can be defined by referring the results to the D/L system, it is evident that this assumption cannot be retained in the more general case of the enzymatic hydrolysis of *N*-acylamino compounds. As a continuation of previous work,[5] this paper presents an attempt to correlate the absolute configuration of amino compounds, by using the BPA-catalyzed hydrolysis of the amide linkage. For this purpose several *N*-phenylacetylamino compounds having known absolute configuration were tested with the acylase. Hydrolysis results of all examined substrates were then analyzed by using a single model, corresponding to the more rapidly hydrolyzed enantiomer. The relative positions of the substituents at the asymmetric carbon atom of the preferred enantiomer were examined, in order to define a method for correlating the absolute configurations.

Results and Discussion

All substrates subjected to enzymatic hydrolysis with BPA are reported in Table I (the more rapidly hydrolyzed enantiomers are also shown). Experimental details relative to the hydrolysis of compounds **1–25** were reported in previous communications.[3-6] Hydrolysis conditions and results relative to substrates examined here are summarized in Table II. *N*-Phenylacetyl derivatives were generally prepared following known methods. In the case of *N*-phenylacetylserinonitrile (**29**) and *N*-phenylacetyl-4-cyano-4-phenylacetamidobutyric acid (**32**), the syntheses were accomplished starting from (2-tetrahydropyranyloxy)acetaldehyde and 2-ketoglutaric acid, respectively. Hydrolysis experiments were performed with a purified preparation of BPA. The reactions were carried out limiting the time to avoid the complete hydrolysis of racemic substrates. The unaltered portion of the *N*-phenylacetyl derivatives was isolated from the reaction mixture and the optical activity examined (Table II). The progress of the hydrolysis was followed by determining the phenylacetic acid produced by GC.

In order to establish the stereochemical preference of the enzyme, we have determined the absolute configuration of the substrates through chemical correlation. In the case of the *N*-phenylacetyl derivatives **28, 30, 34,** and **35,** whose corresponding amino compounds have known absolute configuration, the configurational correlations were simply established by preparing the *N*-phenylacetyl derivatives of the optical active amino compounds. In the case of substrates **26, 27, 29,** and **32,** the corresponding amino compounds have unknown absolute configuration. The optically active *N*-phenylacetyl derivatives recovered from the enzymatic hydrolyses were then transformed by chemical methods into compounds having known absolute configuration, as reported in Table III. In the case of the methyl esters **31** and **33,** the absolute configurations of the corresponding acids **8** and **32** are known (the configuration of **32** was defined by us, as reported in Table III). Corresponding optically active acids were then esterified to establish the desired correlation.

To define a method for stereochemical correlations, the following approach was adopted. A single model,[7] reported in Figure 1, was defined and used to represent the configuration at the chiral center of the more rapidly hydrolyzed enantiomers. Since the absolute configuration of the enantiomer

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