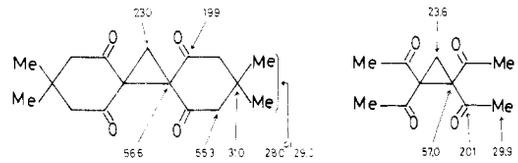

1a 3

Figure 2. ^{13}C FT-NMR spectra of **1a** and **3**.

carbonate, and water. Recrystallization from a mixture of ethanol and petroleum–ether gave **2a**, mp 205–210 °C (lit.[4] mp 211–213 °C) (4.4 g), in 78% yield.

By means of the same method, the methyl derivative of **2a** (**2b**) (mp 202–203 °C, (lit.[4] mp 197–198 °C)) and the ethyl derivative (**2c**) (mp 151–153 °C (lit. mp 149–150 °C)) were prepared in 81 and 75% yield, respectively.

3,3,10,10-Tetramethyldispiro[5.0.5.1]trideca-1,5,8,12-tetraone (1a). A solution of a dihydrofuran derivative (**2a**) (3 g) dissolved in acetonitrile (600 mL) was irradiated by low-pressure mercury arc lamp (Eiko-sha, 60 W) under a bubbling nitrogen stream at room temperature for 6 h. Evaporation of the solvent under reduced pressure left colorless product, which was recrystallized from a mixture of benzene and petroleum ether to give the tetraketone (**1a**) (mp 147–148 °C; 2.34 g) in 78% yield. If diethyl ether was used as the solvent instead of acetonitrile, **2a** was dispersed in the beginning of irradiation, then gradually dissolved in ether developing a yellow color as the reaction proceeded. But the yield of the tetraketone (**1a**) was almost the same as above.

3,3,10,10,13-Pentamethyldispiro[5.0.5.1]trideca-1,5,8,12-tetraone (**1b**), mp 109–110 °C, and 13-ethyl-3,3,10,10-tetramethyldispiro-[5.0.5.1]trideca-1,5,8,12-tetraone (**1c**), mp136–137 °C, were prepared by the same procedure as described above from **2b** and **2c**, respectively. Experimental data for these compounds are summarized in the Table I.

This photochemical rearrangement of **2a** could be accomplished within 20 min by irradiation with a high-pressure mercury lamp, contaminated with a small amount of unidentified products, when a 2.0×10^{-3} M solution in acetonitrile was used. Then, the product (**1a**) was gradually decomposed under the conditions and gave a complex mixture after irradiation for 5 h.

5-Methyl-2,2,4-triacetyl-2,3-dihydrofuran (4). Into a solution of 1,1,3,3-tetraacetylpropane (21 g, 0.10 mol)[9] dissolved in water (400 mL) containing sodium hydrogen carbonate (17 g, 0.20 mol) was added an aqueous solution (300 mL) of iodine (22.5 g, 0.10 mol) and sodium iodide (45 g, 0.30 mol) under stirring at room temperature for 1 h, then the mixture was stirred for 30 h. The resultant light-brown solution was continuously extracted with ether. Evaporation of the solvent left an oil after ordinary workup of the ether layer. The yield was lower than the former case and varied with each experiment. It showed absorption bands at 1680, 1720, and 1740 cm^{-1} in its IR spectrum (neat) and the following signals in NMR spectrum (CCl_4): two singlets at 2.25 (3 H) and 2.23 (6 H), a triplet at 2.36 (3 H, J = 2 Hz), and a quartet at 3.35 (2 H, J = 2 Hz). The sample was employed in the photochemical rearrangement without further purification.

1,1,2,2-Tetraacetylcyclopropane (3). A solution of the crude dihydrofuran (**4**) (3.0 g) dissolved in anhydrous ether (300 mL) was irradiated in the same way as above for 21 h. The product (1.0 g, 33% yield) was recrystallized from a mixture of benzene and petroleum ether, mp 96–97 °C.

Reduction of the Tetraketone (1b) with Zinc Dust in Acetic Acid. A mixture of **1b** (60 mg), zinc dust (500 mg), and glacial acetic acid (5 mL) was stirred at room temperature for 24 h. Being poured into cold water (30 mL) the mixture was extracted with chloroform. After the chloroform solution was washed with aqueous sodium hydrogen carbonate and then with water, dried solution (with anhydrous sodium sulfate) was concentrated under reduced pressure to give the product (51.4 mg). The product was sufficiently pure and identical with the authentic sample of ethylidenebis(4,4-dimethyl-2,6-dioxocyclohexyl) in all respects. Ethanol could not substitute for acetic acid in the reaction. By means of the same procedure, **1a** and **1c** gave the corresponding adducts of dimedone with aldehydes in a similar yield.

Acknowledgment. The authors wish to express their hearty thanks to Ministry of Education, Japan, for a Grant in Aid for scientific research, 154159 (1976). Skillful experimental assistance by Mr. Takashi Nagai is also acknowledged.

Registry No.—**2a**, 1984-51-6; **2b**, 19997-18-3; **2c**, 19997-19-4; **4**, 54283-17-9; methylenebis(4,4-dimethyl-2,6-dioxocyclohexyl), 2181-22-8.

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Side Reactions in Peptide Synthesis. 8.[1] On the Phenacyl Group in the Protection of the β-Carboxyl Function of Aspartyl Residues

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The ready conversion of aspartyl peptides to aminosuccinyl derivatives is one of the most disturbing side reactions in peptide synthesis. The benzyl ester grouping, a widely used form of protection for the β-carboxyl of aspartic acid, is conducive to ring closure under both acidic and basic conditions (Figure 1). Opening of the ring, e.g., with dilute alkali, is no remedy; mainly β-aspartyl peptides are obtained. Therefore, the proposal of Yang and Merrifield,[3] the application of the phenacyl group[4] for the protection of the side chain carboxyl of aspartyl residues, was a welcome contribution. These authors, however, investigated the ring closure only under the conditions of acidolysis, with HF or HBr used for the removal of completed peptide chains from the insoluble support. In solid phase peptide synthesis,[5] the intermediates are exposed to basic conditions only very briefly, namely, during the conversion of the hydrochlorides or trifluoroacetates of the partially deprotected peptidyl polymers to the corresponding free amines. On the other hand, in syntheses carried out in solution, the amine salts are often brought into reaction as such and the amino groups to be acylated are "liberated" by the addition of a tertiary amine. Thus, the often time-consuming coupling reactions are carried out in the presence of a base. Such conditions promote the formation of aminosuccinyl derivatives, especially when the aspartyl residue is followed in the sequence by serine, threonine or glycine.[1] Therefore, the proposed improvement, protection of β-carboxyls with the phenacyl group, could not be adopted for syntheses in solution without a reexamination from the point of view of ring closure under basic conditions. Also, some concern was felt about the application of phenacyl esters because they can be regarded as methyl esters substituted with the electron-withdrawing benzoyl group. Compared with benzyl esters, which are methyl esters substituted with a

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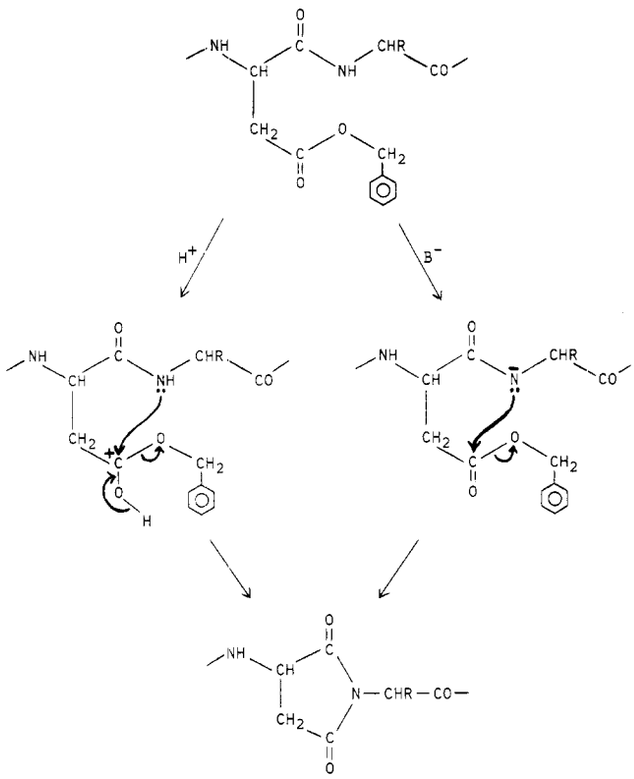

Figure 1. The acid- and base-catalyzed conversion of β-benzylaspartyl peptides to aminosuccinyl derivatives.

phenyl group, phenacyl esters a priori seemed to be more sensitive to aminolysis.[6] In fact, they may belong to a class of imperfect protecting groups, the members of which have some activated ester character. Phenyl esters,[7] trichloroethyl esters,[8] and methylsulfonylethyl esters[9] probably belong to the same category. The reactivity of these esters in aminolysis might be moderate enough to permit their application for the protection of the α-carboxyl group of a C-terminal residue. Yet, even slight reactivities might enhance the chance of ring closure in aspartyl derivatives, where the nucleophilic attack is *intramolecular* and leads to a thermodynamically favored structure[10] (Figure 1). The elimination of benzyl alcohol from the fairly unreactive benzyl esters through the attack by an amide nitrogen, which is a poor nucleophile, is strong evidence for the importance of the intramolecular reaction. Hence, the replacement of the benzyl group by the probably more reactive phenacyl grouping might not be quite innocuous. We felt that this replacement required additional experimental support.

The model peptide derivative *tert*-butyloxycarbonyl-β-benzyl-L-aspartylglycine β-naphthylamide (**1**, Figure 2) was hydrogenated in the presence of a palladium catalyst and the thus liberated acid (**2**) converted to the cesium salt.[11] The latter was allowed to react with α-bromoacetophenone in dimethylformamide. The desired β-phenacyl ester **3** could not be isolated from the reaction mixture. Instead, the aminosuccinyl derivative **4** and α-hydroxyacetophenone were obtained. Since the cesium salt was quite stable under the conditions of the ester-forming reaction, we had to conclude that **3** was formed and rapidly converted to **4**. To test this assumption, a similar experiment was carried out starting with *tert*-butyloxycarbonyl-β-benzyl-L-aspartyl-L-valine β-naphthylamide (**5**). In our recent studies,[1] this compound was found to be very resistant to ring closure. We expected, therefore, that a similar inhibition in the corresponding phenacyl ester would allow its isolation and subsequent study. Our expectations were justified; the above reaction sequence yielded *tert*-butyloxycarbonyl-β-phenacyl-L-aspartyl-L-valine β-naphthylamide (**7**) in crystalline form. Yet, on exposure to the action of an equimolar amount of triethylamine (in dimethylformamide at room temperature), conversion of **7** to the aminosuccinyl derivative **8** occurred. The half-reaction time of this ring closure was about 24 h, while about 400 h was determined[1] as $t_{1/2}$ in the conversion of **5** to **8**.

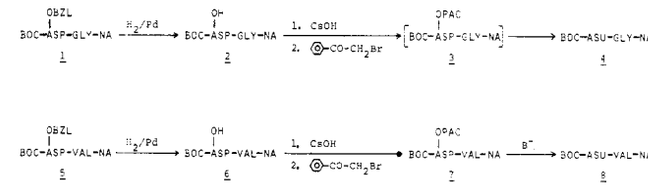

Figure 2. Attempted preparation of *tert*-butyloxycarbonyl-β-phenacyl-L-aspartylglycine β-naphthylamide (**3**), and the preparation of *tert*-butyloxycarbonyl-β-phenacyl-L-aspartyl-L-valine β-naphthylamide (**7**) and its conversion to *tert*-butyloxycarbonyl-L-aminosuccinyl-L-valine β-naphthylamide (**8**) (NA, β-naphthylamide; ASU, aminosuccinyl; PAC, phenacyl).

The results of our experiments suggest that the protection of the β-carboxyl group of aspartyl residues in the form of their phenacyl esters should not be applied in syntheses carried out in solution if basic conditions prevail during coupling[12] and particularly not in the synthesis of peptides in which an aspartyl residue is followed by glycine or a hydroxyamino acid.[1] Similar concern should be felt also about other carboxyl protecting groups which are removable with nucleophiles.

Experimental Section

For thin-layer chromatography (TLC), the following solvent systems were used: A, $CHCl_3$–CH_3OH, 8:2; B, *n*-BuOH–AcOH–H_2O, 4:1:1; C, $CHCl_3$–CH_3OH, 97:3; D, ether–CH_3OH, 40:1.

Attempted Preparation of *tert*-Butyloxycarbonyl-β-phenacyl-L-aspartylglycine β-Naphthylamide (Boc–Asp(OPac)–Gly–NA; 3). A sample of Boc–Asp(OBzl)–Gly–NA (**1**; 0.17 g, 0.33 mmol) was dissolved in methanol (20 mL) containing acetic acid (0.1 mL) and hydrogenated in the presence of a 10% Pd on charcoal catalyst (ca. 20 mg) overnight. After removal of the catalyst and solvent, the residue was triturated with hexane to give the free acid **2** as a solid (0.13 g). It gave a single spot on TLC: R_f (system A) 0.1, R_f (system B) 0.8. Compound **2** (0.41 g, 1 mmol) was converted to the cesium salt[12] by titration in aqueous ethanol with a cesium hydroxide solution to about pH 6.5. The solvent was evaporated in vacuo and the residue dried in a desiccator. (A sample of the salt dissolved in DMF produced no aminosuccinimide derivative when stored at room temperature for prolonged periods of time.) The cesium salt was dissolved in DMF (5 mL) and treated with α-bromoacetophenone (0.24 g, 1.1 mmol) at room temperature. After 30 min, TLC showed the disappearance of the cesium salt and also the presence of three major components. After removal of the solvent, chromatography of the residue on a column of silica gel (20 g) yielded some unreacted α-bromoacetophenone, followed by α-hydroxyacetophenone, both eluted by $CHCl_3$. The latter was identified by its melting point (86–87 °C) and NMR spectrum. Further elution with a mixture of $CHCl_3$–CH_3OH (20:1) gave compound **4** (mp 200–202 °C) in almost quantitative yield. It was identified by its NMR spectrum in $CDCl_3$ and by comparison (melting point and TLC) with an authentic sample prepared[13] by exposure of compound **1** to triethylamine in DMF.

***tert*-Butyloxycarbonyl-β-phenacyl-L-aspartyl-L-valine β-Naphthylamide (7).** Starting with Boc–Asp(OBzl)–Val–NA[1] (**5**), the debenzylated product and its cesium salt were prepared as described in the previous paragraph. Reaction of this salt with α-bromoacetophenone in DMF was followed by filtration from CsBr and evaporation of the solvent in vacuo. The residue was dissolved in EtOAc, and the solution was washed with H_2O, dried, and concentrated in vacuo. Trituration with ether yielded the β-phenacyl ester **7** in 85% yield: mp 179–181 °C; $[\alpha]^{25}_D$ −63.6° (*c* 0.6, MeOH); TLC, R_f (system C) 0.55, R_f (system D) 0.7. In the NMR spectrum ($CDCl_3$), the signal corresponding to the CH_2 group next to the keto carbonyl appeared as a doublet (J = 2 Hz) centered at δ 5.33. (The corresponding signal in α-hydroxyacetophenone is a singlet at δ 4.86.)

Anal. Calcd for $C_{32}H_{37}N_3O_7$: C, 66.78; H, 6.42; N, 7.30. Found: C, 66.64; H, 6.56; N, 7.01.

Conversion of Compound 7 to the Aminosuccinimide Derivative 8. To a solution of **7** (10 mg) in DMF (0.50 mL) was added a 0.2

M solution of triethylamine (0.10 mL). The mixture was kept at room temperature while samples were taken and examined (TLC, systems C and D) from time to time. For comparison, a similarly treated solution of compound **5** was used. For **7**, a half conversion time (to **8**) of about 24 h was observed, as judged from the intensities of the spots on TLC under UV. For compound **5**, a $t_{1/2}$ of about 400 h was found.[1] The elimination of α-hydroxyacetophenone was confirmed by TLC on comparison with an authentic sample. Also, both the aminosuccinimide derivative **8** and the α-hydroxyacetophenone were isolated by chromatography on a column of silica gel. Crystallization from ether yielded a sample of **8**, mp 190–192 °C, which gave the expected NMR ($CDCl_3$) spectrum.[14] The α-hydroxyacetophenone was identified by its melting point (86–87 °C) and NMR spectrum.

Acknowledgment. This study was supported by a grant from the National Science Foundation (CHE-76-15652).

Registry No.—**1**, 66515-54-6; **2**, 66515-61-5; **2** (Cs salt), 66515-60-4; **4**, 66515-55-7; **5**, 66515-58-0; **6** (Cs salt), 66515-57-9; **7**, 66515-59-1; **8**, 66515-56-8; α-hydroxyacetophenone, 582-24-1.

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(10) A sample of compound **2** was dissolved in both phases of the solvent system *n*-butanol–pyridine–acetic acid–water (4:2:1:7) and left to stand at room temperature. Gradually the aminosuccinimide derivative **4** formed. In one week, about a third of the starting material was converted. This agrees with the observation made earlier in this laboratory with the antibiotic amphomycin: M. Bodanszky, G. F. Sigler, and A. Bodanszky, *J. Am. Chem. Soc.*, **95**, 2352 (1973).
(11) B. F. Gisin, *Helv. Chim. Acta*, **56**, 1476 (1973); also cf. ref 3.
(12) The formation of a small amount (2.4%) of aminosuccinyl derivative detected by Yang and Merrifield (ref 3) could also be due to the brief exposure to basic conditions in the chain-lengthening process rather than to the treatment with strong acids in the final stages of solid phase peptide synthesis. If this is indeed the case, then repeated exposures to base in the building of long chains might become the source of major byproduct formation.
(13) To a solution of compound **1** (1 mmol) in DMF (1 mL) was added triethylamine (1 mmol). After one day at room temperature, the ring closure was complete as shown on TLC. The solvent was removed in vacuo and the residue crystallized by trituration with ether. In the NMR spectrum ($CDCl_3$; Me_4Si as an internal reference on a Varian A 60 instrument) the following signals were observed: δ 8.17 (s, NH of naphthylamide), 7.23–7.86 (7 H, naphthalene), 5.73 (d, NH peptide bond), 4.40 (s, CH_2 of glycine), 4.16 (m, α-CH of aspartic acid), 3.00 (m, CH_2 of aspartic acid), 1.42 (s, $(CH_3)_3$).
(14) In this rigid compound, the coupling constant for the doublet of the α-CH of valine (δ 4.50) is conspicuously large (9 Hz), as are the coupling constants for the two doublets of the nonequivalent CH_3 protons of this amino acid (δ 0.98 and 1.17, J_1 = 6 Hz and J_2 = 17 Hz). These values are much higher than the corresponding signals of the phenacyl derivative (two doublets at δ 0.80 and 1.90, J_1 = 2 Hz and J_2 = 7 Hz).

1,3-Dialkyluracils as a Source of Formyl Acetate for Synthesis[1]

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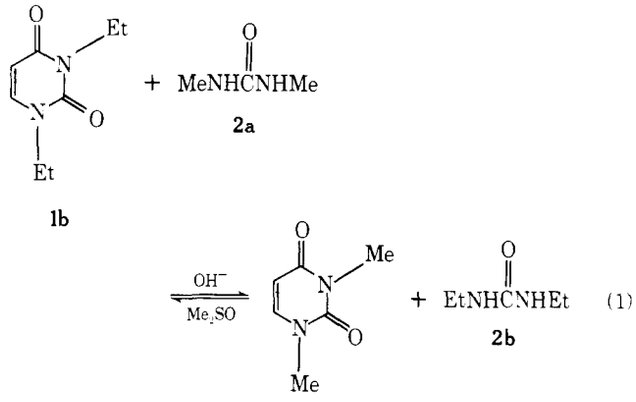
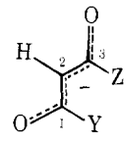
1,3-Dialkyluracils (**1**) can be used as a source of formyl acetate for the synthesis of monosubstituted uracils, for the preparation of **1** with *N*-alkyl groups different from the original ones, or for the synthesis of 2-alkyl- and 2-(dialkylamino)uracils. The favored course for these reactions involves substitution in an enolate anion intermediate.

It was shown recently[2] that 1,3-diethyluracil (**1b**) reacts with 1,3-dimethylurea (**2a**) in dimethyl sulfoxide (Me_2SO) solution in the presence of tetramethylammonium hydroxide (TMAH) to give a partial conversion to 1,3-dimethyluracil (**1a**) and 1,3-diethylurea (**2b**) (eq 1).



(1)

A mechanism was suggested for this reaction which involved condensation of the urea with the enolate anion (**3a**; Y = H,



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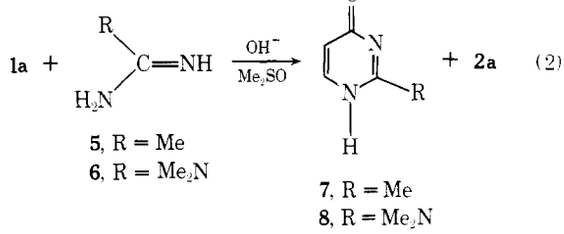
Z = RNC(O)NHR) derived from **1**. An alternative one involved direct addition of the urea to C-4 or C-6 of **1**.

The conditions required for such a reaction to take place now have been further delineated and the scope of the reaction has been extended. First, the reaction *requires* hydroxide as the base and Me_2SO as the solvent. It does not take place (TLC) with ethoxide as the base and ethanol or ethanol–Me_2SO (2:3) as the solvents, or with hydroxide as the base and water as the solvent. Second, only a catalytic amount of TMAH is necessary for the reaction of **1** with *N,N'*-dialkylureas. Third, essentially quantitative conversions of **1a**, **1b**, and 1,3-dimethylthymine to the corresponding 1- and 3-monomethyl derivatives result from the reactions of these substrates with *N*-methylurea (**4**) in the presence of an equivalent of TMAH. The requirement for 1 equiv of base in these reactions is due to the fact that the products are formed as the anions, rather than neutral molecules. Fourth, reactions analogous to eq 1 occur with acetamidine (**5**) or *N,N*-dimethylguanidine (**6**) substituted for the urea[3] (eq 2). The yield



(2)

of product, 4-hydroxy-2-methylpyrimidine (**7**), in the reaction with **5** is 39%, with a recovery of 29% of **1a**. This compares favorably with the reported yield of 33% by total synthesis.[4] The product of the reaction of **6** is 2-(dimethylamino)-4-hydroxypyrimidine. Finally, a number of modifications of

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