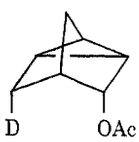
ever, would be expected to cause the **2a/2b** ratio to depart from 50:50 to a greater degree than would the **3a/3b** ratio. Since this is not observed, ion pair **9** (or



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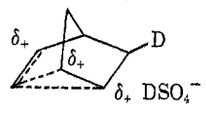

9

the ion pairs corresponding to rapidly equilibrating **7a** and **7b**) cannot be the predominant product determining intermediate(s).

Since no single one of the preceding limiting cases applies, the reaction must involve a complex set of ionic intermediates with different, ion paired, unsymmetrical precursors to each of the **2a/2b** and **3a/3b** pairs. In addition, the precursor (or precursors) to the **3a/3b** pair must cause less symmetrical product labeling than caused by the precursor(s) to **2a/2b**.

Experimental Section

Nuclear magnetic resonance spectra were determined on a Hitachi Perkin-Elmer R-20 (60 MHz) spectrometer with tetramethylsilane as a reference standard (δ 0.00 ppm). Mass spectral analyses were determined on a CEC-104 mass spectrometer under conditions previously reported.[1g] Shift reagents were obtained commercially from Norell Chemical Co., Inc. The addition of labeled acetic acid to diene **1** was carried out, and the products (**2a**, **2b**, **3**) were analyzed using conditions previously reported.[1e]

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A Facile Rearrangement of a Carbohydrate Cyclic Carbonate

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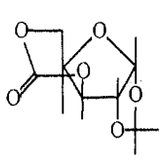
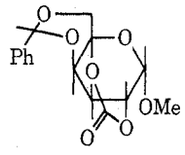
Five-membered ring carbonates are well known in the carbohydrate series and are readily prepared by treating sugars containing cis vicinal hydroxyl groups with difunctional carbonyl derivatives such as phosgene, diphenyl carbonate, and alkyl chloroformates.[1] In marked contrast to the large number of known sugar-derived ethylene carbonates, little has been reported on corresponding six-membered cyclic carbonates. In instances where alternate paths exist for five- and six-membered ring formation in the same molecule, the ethylene carbonate is formed exclusively; *e.g.*, with methyl α-D-galactopyranoside and benzyl chloroformate the only product obtained was methyl 2,6-di-*O*-benzyloxycarbonyl-α-D-galactoside-3,4-carbonate.[2] In the absence of cis vicinal hydroxyl groups an acyclic derivative usually results; *e.g.*, methyl α-D-glucopyranoside on similar treatment yields its tetra-*O*-benzyloxycarbonyl derivative.[2] Presumably the formation of a trimethylene carbonate is precluded because of additional bond strain required for forming a six-membered ring containing an sp^2 hybridized carbon atom.[3] The first six-membered ring carbonate known in the sugar series is 1,2-*O*-isopropylidene-α-D-xylofuranose-3,5-carbonate (**1**) prepared by Haworth, *et al.*, by treating



1



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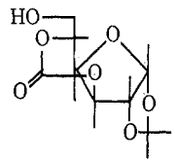


3

D-xylose with phosgene in acetone.[4] Compound **1** exhibited unusual reactivity for a sugar carbonate in that it underwent facile methanolysis at room temperature. The ease of ring opening suggested that cis-fused **1** might contain at least as much ring strain as the recently prepared trans-fused five-membered ring glucose carbonate **2**.[5,6] In support of our supposition, methyl 2,3-di-*O*-methyl-α-D-glucopyranoside-4,6-carbonate was recently prepared and shown to undergo ring opening at twice the rate of **2**.[7]

In accord with the seeming instability of six-membered ring sugar carbonates we were not able to prepare the desired 4,6-carbonate derivatives of methyl α-D-gluco- or galactopyranosides by direct reaction with phosgene in CH_2Cl_2–pyridine at −70°. In both cases only polymeric carbonates were obtained. The formation of polymer was surprising to us, since similar reaction conditions led to high yield of monomeric cyclic carbonates from 1,3-propanediol and both *cis*- and *trans*-2-hydroxymethylcyclohexanols. The possibility that a sugar 4,6-carbonate may have been first formed and then reacted intermolecularly to form polymer seemed unlikely because no reaction could be observed between methyl α-D-glucopyranoside and *cis*-2-hydroxymethylcyclohexanol carbonate in pyridine at 25° after 16 hr.

In view of the unusual behavior of the methyl glycosides toward phosgene, we decided to investigate the stability and fate of an intact, preformed six-membered carbonate ring in a sugar molecule also containing a free hydroxyl group. The compound chosen for study was 1,2-*O*-isopropylidene-α-D-glucofuranose-3,5-carbonate (**3**).

Results and Discussion

To achieve the synthesis of **3** we sought a function which could (1) be unequivocally attached to C-3 of a

(1) L. Hough, J. E. Priddle, and R. S. Theobald, *Advan. Carbohyd. Chem.*, **15**, 91 (1960).

(2) L. Hough and J. E. Priddle, *Chem. Ind. (London)*, 1600 (1959).

(3) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(4) W. N. Haworth, C. R. Porter, and A. C. Waine, *Recl. Trav. Chim. Pays-Bas*, **57**, 541 (1938).

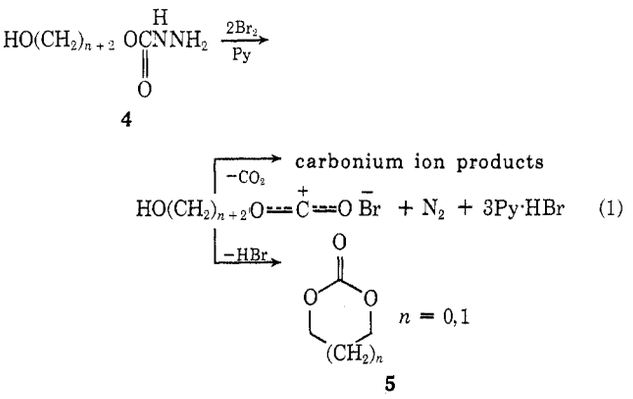
(5) W. M. Doane, B. S. Shasha, E. I. Stout, C. R. Russell, and C. E. Rist, *Carbohyd. Res.*, **4**, 445 (1967).

(6) W. M. Doane, B. S. Shasha, E. I. Stout, and C. R. Russell, *ibid.*, **11**, 321 (1969).

(7) D. Trimnell, W. M. Doane, C. R. Russell, and C. E. Rist, *ibid.*, **18**, 301 (1970).

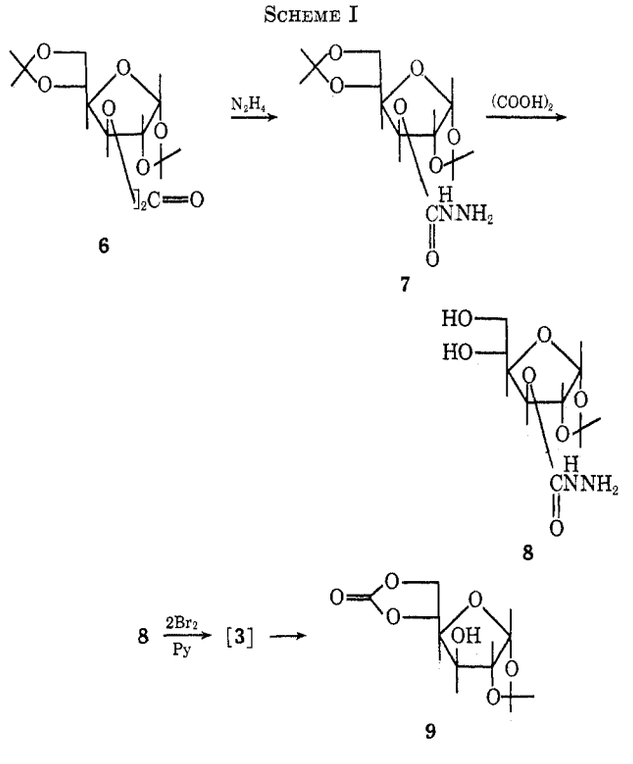
D-glucose derivative and (2) be triggered under mild conditions to effect rapid electrophilic attack and cyclization at C-5.[8]

In this connection we found that oxidation of ω-hydroxyalkyl carbazates **4** with bromine in pyridine at 0°[9] gave 49–66% yields of five- and six-membered ring carbonates **5** without concomitant polymer formation (eq 1). The principal side reaction encountered



was loss of carbon dioxide, presumably leading to ω-hydroxyalkyl bromides, pyridinium salts, or related carbonium ion derived products. Application of the carbazate oxidation in the carbohydrate series is shown in Scheme I. Reaction of the known 3,3′-diglucose

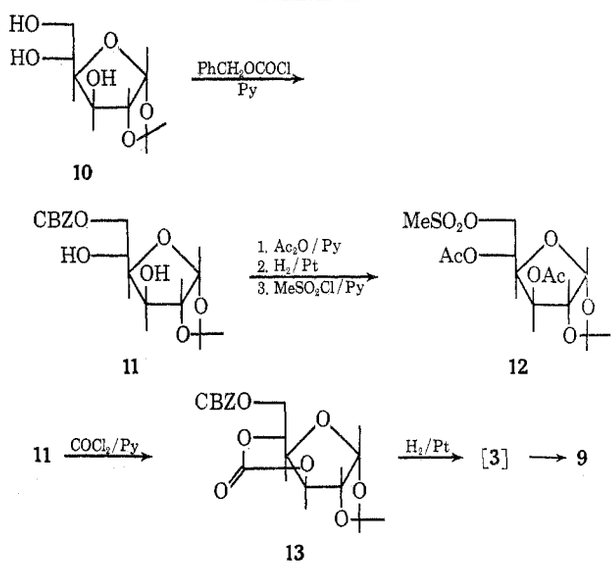
SCHEME I



carbonate **6** with hydrazine hydrate in THF at 25° gave **7** quantitatively. The carbazate structure was established by ir and nmr spectroscopy and by elemental analysis of its crystalline *p*-nitrobenzoyl derivative. Selective hydrolysis of **7** in 0.1 *N* oxalic acid at 50° gave diol **8** quantitatively after 6 hr. Treatment of an ice-cold pyridine solution of **8** with bromine (2 equiv) led to immediate gas evolution and separation of what appeared to be pyridine hydrobromide. Infrared analysis of the total crude organic product showed a single, strong carbonyl absorption at 5.63 μ.[10] This result seemed inconsistent with the expected product **3**, since trimethylene carbonate prepared by the method of Carothers and Van Natta[11] absorbed at 5.74 μ. Recrystallization gave pure 1,2-*O*-isopropylidene-α-D-glucofuranose-5,6-carbonate (**9**), mp 228.5–231°, whose ir spectrum was practically identical with that of the crude product. Thin layer chromatography (tlc) indicated two closely migrating materials in the crude product, of which the one with lower R_f corresponded to **9**.[12] Compound **9** was identified by comparison with a sample of the authentic material.[13] It seems likely that **9** was formed *via* rapid rearrangement of **3** or possibly *via* a seven-membered ring analog of **3** which would be obtained if cyclization occurred at C-6 instead of C-5.

In order to resolve the ambiguity of whether or not **3** was actually being formed and spontaneously reverting to **9** we prepared the 6-carbobenzyloxy (CBZ) derivative **13** in the hope that mild hydrogenolysis would yield **3**. The synthesis of **13** is shown in Scheme II. Treatment of 1,2-*O*-isopropylidene-α-D-glucofura-

SCHEME II



nose (**10**) with benzyl chloroformate in pyridine gave the 6-*O*-CBZ derivative **11** (63%). The structure of **11** was verified by diacetylation, hydrogenolysis, and methanesulfonation to yield the known substance **12** (52% overall). Reaction of **11** with phosgene in CH_2Cl_2/pyridine at −60° gave the cyclic carbonate **13** (85%). The structure of **13** was proven by ir, nmr, and mass spectrometry and by hydrolysis back to **11**. Also, a change in polarimetric behavior was noted in

(8) Analogous to stepwise $COCl_2$ carbonation, which presumably proceeds *via* a hydroxyalkyl chloroformate intermediate.

(9) Compare similar I_2 oxidations of acid hydrazides: Y. Wolman, P. M. Gallop, A. Patchornik, and A. Berger, *J. Amer. Chem. Soc.*, **84**, 1889 (1962).

(10) L. Hough *et al.*, *Chem. Ind. (London)*, 148 (1960).

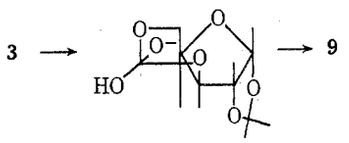
(11) W. H. Carothers and F. J. Van Natta, *J. Amer. Chem. Soc.*, **52**, 314 (1930).

(12) The fast-moving compound may have been the C-3 epimer of **9** formed as a result of inversion during oxidation.

(13) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 2796 (1929).

going from **11** to **13** which paralleled the conversion of 1,2-*O*-isopropylidene-α-D-xylofuranose to **1**. Thus **11**, with $[\alpha]D$ −7.7° became more dextrorotatory, changing to $[\alpha]D$ +59.8° on cyclic ester formation. This is similar to the α-D-xylose derivatives, in which a change from −17.5 to +7.5° was noted.[4] Ester **13** was recrystallized unchanged from boiling ethanol but underwent 83% methanolysis of the carbonate ring on refluxing in methanol for 19 hr. Reaction of **13** with 0.1 *N* $Ba(OH)_2$ or NaOH was instantaneous at 25° but complex mixtures of products were formed. Hydrogenolysis of **13** in THF or ethanol over Adams catalyst at 25° yielded the ethylene carbonate **9** as the major product (~80%). No evidence was found for **3** by periodic tlc analysis during the course of hydrogenolysis. An attempt to trap **3** with phenyl isocyanate during hydrogenolysis was also unsuccessful. The hydrogen treatment appears to involve debenzylation followed by rapid CO_2 loss and rearrangement to the stable five-membered ring carbonate. No conclusive evidence was found for hydrogenation or hydrogenolysis products of **3**; however, several minor products were observed by tlc which, in view of their high polarity; may have been formates of **10**.

The rapid rearrangement of **3** apparently results from the possible close juxtaposition of the C-6 hydroxyl to the cyclic carbonate carbonyl. In the easily adopted boat form of **3** the oxygen–carbonyl carbon internuclear distance is *ca.* 2.2 Å. The propensity of **3** to rearrange is probably related to the facile base-catalyzed rearrangement of 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranose to the isomeric 1,2,3,6-*O*-acetyl derivative[14] and other similar rearrangements involving the participation of cyclic orthoester intermediates.[15] Based on this similarity we propose that **3** rearranges *via* the tricyclic intermediate **14**.



14

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were obtained with a Varian Associates T-60 spectrometer in $CDCl_3$ containing 0.2% tetramethylsilane (TMS) as internal reference. Chemical shifts are expressed in parts per million (δ) downfield from TMS. Multiplicity is indicated by letters, where s = singlet and d = doublet. Optical rotation data were obtained using a Durrum-Jasco ORD/CD spectropolarimeter. Mass spectra derived molecular weights were determined at 70 eV with an Atlas Model CH-4 spectrometer. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Bromine Oxidation of 3-Hydroxypropyl Carbazate.—To a stirred solution of bromine (16.0 g, 0.10 mol) in pyridine (150 ml) at 0–15° was added dropwise 6.7 g (0.05 mol) of 3-hydroxypropyl carbazate[16] in 50 ml of pyridine. A mild exothermic reaction ensued during the addition (20 min) with smooth evolution of N_2 and CO_2. After 15 min 2 g of $Na_2S_2O_3$ was added and pyridine was removed under vacuum. The residue was extracted with dry THF and the filtered THF solution was concentrated to give 2.5 g (49%) of trimethylene carbonate. The ir and nmr of the product were identical with those of the authentic material.[11] In a similar experiment designed to trap CO_2 by external N_2 entrainment through 5% $Ba(OH)_2$ a 28% yield of $BaCO_3$ was obtained. Similar oxidation of 2-hydroxyethyl carbazate[16] gave ethylene carbonate in 66% yield.

1,2-*O*-Isopropylidene-α-D-glucofuranose-3-carbazate (8).—A slurry of **6**[17] (0.530 g, 0.974 mmol) in EtOH (10 ml) was treated with 0.1 ml of 100% hydrazine hydrate and stirred at 25° for 4 hr. The clear solution was concentrated to dryness under vacuum and the residue was chromatographed over 50 g of silica gel (30–70 mesh). Elution with EtOAc first gave 0.262 g of crystalline 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose identified by spectral comparison with authentic material. Further elution with EtOAc gave 0.317 g of **7** as a noncrystalline glass. The carbazate was homogeneous by tlc (silica gel, EtOAc development, H_2SO_4 charring): ir (liquid film) 2.99 (NH) and 5.76 μ (C=O); nmr[18] ($CDCl_3$) δ 1.35, 1.43, 1.53 (all s, 12, methyls), 4.58 (d, 1, J = 4 Hz, C-2 H), 5.20 (broad s, 1, C-3 H), and 5.87 ppm (d, 1, J = 4 Hz, C-1 H). Reaction of **7** with *p*-NO_2BzCl in pyridine gave the mono-*p*-nitrobenzoyl derivative, which after chromatography over silica gel eluting with benzene and 20% Et_2O/80% benzene had mp 87° dec.

Anal. Calcd for $C_{20}H_{25}N_3O_{10}$: C, 51.39; H, 5.39; N, 8.99. Found: C, 51.43; H, 5.37; N, 8.86.

For selective hydrolysis 0.818 g of freshly chromatographed **7** was dissolved in 20 ml of 0.1 *N* oxalic acid monohydrate in 1:1 THF–water and stirred at 50° for 6 hr. At this time tlc indicated complete disappearance of **7** and the formation of a single new material at lower R_f. After 0.2 g of $Ca(OH)_2$ was added the mixture was stirred for 5 min and filtered and the filtrate was concentrated under vacuum to give 0.615 g of nearly pure **8**: nmr ($CDCl_3$) δ 1.10, 1.30 (s, 6, methyls), 4.66 (d, 1, J = 4 Hz, C-2 H), and 5.93 ppm (d, 1.5, J = 4 Hz, C-1 H).

Bromine Oxidation of 8.—A solution of Br_2 (4.14 mmol) in 10 ml of ice-cold pyridine was treated dropwise with a solution of **8** (0.576 g, 2.07 mmol) in 5 ml of pyridine in an apparatus arranged for collection of evolved gases over water. In 15 min 33.4 ml of gas was collected at 23° (749 mm). The reaction mixture was concentrated under vacuum at 60° to remove pyridine and organic products were isolated by washing the residue with EtOAc. Evaporation of EtOAc gave 0.239 g of whitish solid whose tlc (EtOAc, silica gel) showed two closely moving spots (H_2SO_4) at R_f ~0.8. Recrystallization from EtOH gave colorless needles of **9**, mp 228.5–231° dec, identical by comparison of ir, nmr, and melting point with those of an authentic specimen.[19]

1,2-*O*-Isopropylidene-6-*O*-carbobenzyloxy-α-D-glucofuranose-3,5-carbonate (13).—To a stirred solution of monoacetone glucose[20] (5.00 g, 0.0227 mol) in 50 ml of dry pyridine was added 17.64 g (0.103 mol) of benzyl chloroformate dropwise over 15 min. The exothermic reaction was moderated at 27–35° with intermittent cooling during the addition. After *ca.* 1 hr pyridine was removed under vacuum and the residue was treated with water and extracted with ether three times. The ether was washed with 1 N HCl twice, saturated $NaHCO_3$ solution, and brine and finally dried over anhydrous $MgSO_4$. Concentration of the filtered ether solution gave a white solid which after benzene recrystallization gave 5.08 g (63%) of **11**: mp 118–120°; ir ($CHCl_3$) 5.72 μ (C=O); nmr ($CDCl_3$) δ 1.30, 1.47 (both s, 6, methyls), 4.51 (d, 1, J = 4 Hz, C-2 H), 5.21 (s, 2, benzylic CH_2), 5.93 (d, 1, J = 4 Hz, C-1 H), and 7.38 ppm (s, 5, benzene ring H); $[\alpha]^{30}D$ −7.7° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.69; H, 5.97.

Compound **11** (3.54 g, 0.010 mol) was dissolved in 50 ml of dry

(14) B. Helferich and W. Klein, *Justus Liebigs Ann. Chem.*, **450**, 219 (1926).

(15) R. M. Acheson, *Accounts Chem. Progr.*, **4**, 177 (1971); S. Hanessian and P. Dextraze, *Chem. Ind. (London)*, 958 (1971), and references cited therein.

(16) Norwich Pharmical Co., British Patent 944,594 (1963); *Chem. Abstr.*, **60**, 14510 (1964).

(17) L. v. Vargha, *Chem. Ber.*, **67B**, 1223 (1934).

(18) Spectral assignments of ring protons closely paralleled those made by A. Rosenthal and K. Shudo, *J. Org. Chem.*, **37**, 1608 (1972), for similar α-D-furanosides.

(19) Early workers (*cf.* ref 13) reported mp 223–224° dec for **9**, while Doane, *et al.*, *Carbohyd. Res.*, **5**, 346 (1967), reported 228–230°. Our material prepared by the method of ref 13 had mp 225–228° dec after several recrystallizations from EtOH.

(20) F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," Circular of The National Bureau of Standards C440, U. S. Government Printing Office, Washington, D. C., 1942, p 483.

pyridine, diluted with CH_2Cl_2 (20 ml), and cooled to −60° in a Dry Ice–acetone bath. While stirring at −60° a mixture of 12.5% phosgene in benzene (9.1 ml, 0.010 mol) and CH_2Cl_2 (25 ml) was added dropwise over 16 min. After slow equilibration to 25° the reaction mixture was evaporated to dryness under vacuum and the residue was broken up with water, filtered, and dried to give 3.48 g of crude **13**. Recrystallization from EtOH gave 3.24 g (85%) of pure **13** as colorless, thin, lathe-like crystals: mp 145–146°; ir ($CHCl_3$) 5.69 μ (C=O); nmr ($CDCl_3$) δ 1.32, 1.48 (s, 6, methyls), 4.88 (d, 1, J = 4 Hz, C-2 H), 5.17 (s, 2, benzylic CH_2), 5.93 (d, 1, J = 4 Hz, C-1 H), and 7.39 ppm (s, 5, benzene ring H); $[\alpha]^{30}D$ +59.8 (c 1, $CHCl_3$); mass spectrum molecular ion m/e 380 (calcd mol wt, 380).

Anal. Calcd for $C_{18}H_{20}O_9$: C, 56.84; H, 5.30. Found: C, 56.83; H, 5.11.

Conversion of 11 to 12.—A solution of **11** (0.532 g) in pyridine (10 ml) was treated with Ac_2O (0.5 ml) and stirred for 1 hr at 25° and 1 hr at 100–120°. Removal of pyridine and Ac_2O under vacuum gave **11** diacetate quantitatively: nmr ($CDCl_3$) δ 1.30, 1.50 (s, 6, isopropylidene methyls), 1.97, 2.05 (s, 6, acetyl methyls), 5.17 (s, 2, benzylic CH_2), 5.36 (d, 1, J = 4 Hz, C-2 H), 5.90 (d, 1, J = 4 Hz, C-1 H), and 7.35 ppm (s, 5, benzene ring H). The crude diacetate was hydrogenolyzed with 10% Pd/C catalyst under 50 psig of H_2 for 4 hr at 25° after which time tlc analysis (Et_2O, silica gel) indicated complete removal of the CBZ group (R_f change of 0.90 to 0.55). Concentration of the filtered solution gave 0.462 g of yellow oil which was dissolved in pyridine (15 ml), cooled to 0°, and treated with 0.2 ml of methanesulfonyl chloride in $CHCl_3$ (6 ml). The mixture was kept at 4° for 16 hr, and concentrated to dryness under vacuum. After water was added the product was extracted with EtOAc, and the EtOAc solution was washed with 2% H_2SO_4, saturated $NaHCO_3$ solution, and water and dried over anhydrous $MgSO_4$. Concentration of the filtered EtOAc solution followed by recrystallization of the residue from MeOH gave 0.299 g (52% overall from **11**) of **12**: mp 141–143° (lit.[21] mp 143°); nmr ($CDCl_3$) δ 1.30, 1.52 (s, 6, isopropylidene methyls), 2.07 (s, 6, acetyl methyls), 3.03 (s, 3, methanesulfonyl methyl), 5.37 (d, 1, J = 4 Hz, C-2 H), 5.91 (d, 1, J = 4 Hz, C-1 H).

Anal. Calcd for $C_{14}H_{22}O_{10}S$: C, 43.97; H, 5.80; S, 8.38. Found: C, 43.81; H, 5.68; S, 8.13.

Acid-Catalyzed Hydrolysis of 13.—Pure **13** (0.328 g) was refluxed in 5 ml of 1:1 v/v HOAc–water for 50 min. Cooling to 4° followed by filtration gave 0.064 g of recovered **13**, mp 144–145.5°. The filtrate was concentrated to dryness under vacuum and the residue was crystallized from water to give 0.026 g of **11**. Recrystallization from benzene gave prisms, mp 118–119.5°. The balance of **13** apparently underwent more extensive hydrolysis to water-soluble products.

Hydrogenolysis of 13.—Compound **13** (0.180 g) in 25 ml of THF was treated with 0.050 g of PtO_2 and hydrogenated under 50 psig H_2 at 25° for 2 hr. Filtration of catalyst followed by removal of THF under vacuum gave 0.098 g (84%) of **9**, mp 207–209° dec, whose ir (KBr) was identical with the ir of authentic **9**. One recrystallization from EtOH gave colorless needles, mp 229–231.5° dec. Similar reduction (1 hr) with EtOH in place of THF gave 82% of **9**, mp 204–205° dec, which on recrystallization from EtOH had mp 227.5–230° dec.

Methanolysis of 13.—Compound **13** (0.105 g) was refluxed in dry methanol (5 ml) for 19 hr and subsequently solvent was removed under vacuum. Nmr ($CDCl_3$) showed a new singlet at δ 3.80 ppm corresponding to 2.5 H (methyl carbonates from ring opening). Tlc indicated complete disappearance of **13** and formation of three reaction products. No evidence was found for methanolysis of the CBZ group in that peaks corresponding to benzyl alcohol were not observed.

Registry No.—**7**, 37056-03-4; **7** mono-*p*-nitrobenzyl derivative, 37056-04-5; **8**, 37056-05-6; **9**, 2875-90-3; **11**, 37056-07-8; **11** diacetate, 37056-08-9; **12**, 37056-09-0; **13**, 37056-10-3.

Acknowledgments.—The author is indebted to Dr. Richard S. Treptow for optical rotation measurements and to Mr. John D. Wendel for his able technical assistance with synthetic aspects of the work.

(21) K. Freudenberg and K. v. Oertzen, *Justus Liebigs Ann. Chem.*, **574**, 37 (1951).

Use of L-1,4-Cyclohexadiene-1-alanine in Peptide Synthesis as a Phenylalanine Analog

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In constructing analogs of biologically active peptides with potential inhibitory activity, a residue to replace phenylalanine has been needed. For this purpose, L-1,4-cyclohexadiene-1-alanine (L-2,5-dihydrophenylalanine, L-DiHPhe, **1**), a new and effective antagonist of phenylalanine,[2-5] appeared to be a likely candidate. It is readily available by Birch reduction of commercial phenylalanine and it also occurs naturally in several bacterial sources.[6] The present note examines attempts to incorporate L-DiHPhe into peptides and into a variety of derivatives suitable for peptide synthesis. Dehydrogenation to the phenylalanine compound and spirolactonization were considered to be the major likely side reactions.[2] When this study was essentially complete, incorporation of D-1,4-cyclohexadienylglycine into semisynthetic penicillins and cephalosporins came to our attention.[7] This diene was N-protected as an enamine or *t*-BOC derivative, and coupling was effected by a mixed anhydride procedure. No information, however, was given concerning dehydrogenation.

It was recently established that dehydrogenation of L-DiHPhe in the solid state is associated with a hydrated form of the amino acid which is unstable if stored and if an attempt is made to desiccate it.[2,8] Precautions were thus taken to store the solid as a stable salt or in aqueous solution and to avoid subjecting it to a high vacuum;[8] acylations were done under nitrogen. To confirm structure and determine the content of the corresponding phenylalanine compound all products were examined carefully by nmr, column chromatography, or uv absorption.

L-1,4-Cyclohexadiene-1-alanine methyl ester hydrochloride (**2**) was obtained in high yield by application of the Brenner–Huber method[9] to DiHPhe hydrate and was purified by crystallization.[10] Nmr evidence

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(10) Compound **2** could also be prepared by starting from the Cu complex of L-DiHPhe. This was converted directly with $COCl_2$ to the *N*-carboanhydride by the general method of R. D. Hamilton and D. J. Lyman, *J. Org. Chem.*, **34**, 243 (1969). Without isolation the *N*-carboanhydride was then treated with MeOH–HCl.