Methyl 17β-Hydroxyalloyohimban-16β-carboxylate (8h), (±)-Alloyohimbine (8m) and (±)-α-Yohimbine (8n) from 7d.—A solution of 0.12 g (0.34 mmol) of **7d** in 10 ml of methanol was reduced with 0.2 g (5.3 mmol) of sodium borohydride over a 5-hr period at 0° [tlc, chloroform–methanol (10:1.5), R_f **7d** > **8n** > **8m** > **8h**]. After neutralization with acetic acid, most of the solvent was removed *in vacuo* and the product was extracted with chloroform (5 × 50 ml). The extracts were combined, washed with water (2 × 10 ml), dried, and evaporated and the resulting mixture of isomers (96 mg, 90%) was separated by (1) preparative tlc [Al_2O_3 G (type E), hexane–ethyl methyl ketone (60:40), R_f **8h** > **8n** ~ **8m**, and then silica gel $PF_{254+366}$, chloroform–methanol (100:15), R_f **8n** > **8m**]; (2) column chromatography over alumina (Brockmann, activity II–III), elution with hexane–ethyl methyl ketone (90:10) and with increasing amount of ethyl methyl ketone (12–20%) as eluents. In another reduction run exactly as above, starting from 0.16 g of **7c**, 32 mg (20%) of **8h**, 10 mg (6%) of **8n**, and 14 mg (9%) of **8m** were obtained.

8h was identical in all respects (ir, mass spectrum, tlc spot) with an authentic sample obtained from **8f**.

8m had mp 136–137° (from ethyl acetate following ether); by mixture melting point, ir, nmr, and tlc spot, **8m** was identical with an authentic sample of (±)-alloyohimbine obtained from **9b**.[1]

8n had ir ($CHCl_3$) identical with that of natural α-yohimbine, 3570 (OH), 3480 (NH), 2805, 2765 (Bohlmann bands), 1730 (CO_2CH_3), 1055 cm^{-1} (COH); nmr ($CDCl_3$ at 300 M-z) δ 7.75 (s, 1, NH), 7.44 (d, 1, C_9 H),[11] 7.28 (d, 1, C_{12} H), 7.15–7.02 (m, 2, C_{10}, C_{11} H), 3.99 (d of t, 1, C_{17} H, J = 26 Hz), 3.84 (s, 3, CO_2CH_3), 3.15 (m, 1, C_3 H);[12] mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (88), 339 (4.8), 337 (1.6), 335 (1.8), 323 (4.8), 321 (2.9), 320 (2), 295 (5.1), 293 (3.1), 226 (8), 224 (13), 223 (5.6), 221 (5.8), 184 (9.7), 170 (11), 169 (12), 156 (8).

Epimerization of Alloyohimine Isomers. Preparation of 8i (and 10c) from 8h.—**8h** (28 mg, 7.9 × 10^{-1} mmol) in 1 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen for 3–4 days. Separation of the mixture by preparative tlc [Al_2O_3 G (type E), hexane–ethyl methyl ketone (60:40), R_f **10c** > **8h** > **8i**] gave 5.5 mg (20%) of **10c**, 5.0 mg (18%) of **8h**, and 11.8 mg (42%) of **8i**.

10c had mp 195–197°, ir (KBr) 3350 (NH), 1700 (CO_2CH_3 conj), 1640 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 336 (100, M^+), 335 (99), 321 (23), 206 (15), 197 (11), 191 (12), 184 (17), 169 (14), 165 (26).[12]

8i was identical in all respects with an authentic sample obtained from **8g**.

Preparation of (±)-α-Yohimbine (8n) from (±)-Alloyohimbine (8m).—**8m** (30 mg, 8.1 × 10^{-2} mmol) in 1 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen. The progress of the epimerization was followed by tlc [chloroform–methanol (10:1.5), R_f **8n** > **8m**]. After 3–4 days the solution was neutralized with acetic acid, evaporated to dryness, and triturated with chloroform (3 × 2 ml). After the solvent was evaporated, 17.3 mg (58%) of **8n** was obtained, identical with the sample obtained from **7d**.

Thin Layer Chromatographic Behavior of Hydroxy Esters with Alloyohimbane Skeleton.—Al_2O_3 G (Type E), hexane–ethyl methyl ketone (6:4), showed R_f **8h** > **8j** > **8n** > **8i** > **8m** > **8k**; silica gel G, hexane–ethyl methyl ketone–methanol (6:3:1) showed R_f **8n** > **8m** > **8h** > **8i** > **8j** > **8k**.

Registry No.—**1**, 40087-90-9; **2**, 2107-58-6; 2 free base, 2107-57-5; **3a**, 40087-94-3; **3b**, 40087-91-0; **3b** oxalate, 40087-92-1; **4**, 40087-93-2; (*Z*)-**5a**, 40087-95-4; (*E*)-**5a**, 40087-96-5; **5b**, 40087-97-6; **6a**, 39032-75-2; **6b**, 39032-72-9; **6c**, 39032-73-0; **6d**, 39032-74-1; **6e**, 39032-76-3; **6e** HCl, 40037-02-3; **6f** HCl, 40037-03-4; **6g**, 40088-02-6; **6h**, 40088-03-7; **6i**, 40088-04-8; **6j**, 40085-19-6; **6k**, 40088-06-0; **6k** HCl, 40088-07-1; **7a**, 40088-08-2; **7b**, 40088-09-3; **7c**, 40088-10-6; **7d**, 40088-11-7; **8a**, 40088-12-8; **8b**, 40088-13-9; **8c**, 40088-14-0; **8d**, 40088-15-1; **8e**, 40088-16-2; **8f**, 40088-17-3; **8g**, 40088-18-4; **8h**, 40088-19-5; **8i**, 40088-20-8; **8j**, 40088-21-9; **8k**, 40088-22-0; **8l**, 40088-23-1; **8m**, 40085-32-3; **8n**, 40088-25-3; **9a**, 40085-22-1; **9b**, 40085-21-0; **10a**, 40088-28-6; **10b**, 40088-29-7; **10c**, 40088-30-0; diethyl α-acetylglutarate, 1501-06-0; diethylamine hydrochloride, 660-68-4; methyl iodide, 74-88-4; ammonium acetate, 631-61-8; acetic acid, 64-19-7; triethylamine, 121-44-8; phosphorus pentoxide, 1314-56-3; methyl cyanoacetate, 105-34-0; malononitrile, 109-77-3; sodium borohydride, 16940-66-2; sodium methoxide, 124-41-4; potassium *tert*-butoxide, 865-47-4.

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Heterocyclic Amino Sugar Derivatives. VI. Stabilization of a Reactive Intermediate by Steric Hindrance. Mechanism of 3,6-Anhydro Sugar Formation[1]

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Circumstantial evidence was obtained that 3,6-anhydro-2-benzamido-2-deoxy-β-D-glucopyranosides are formed from 2-benzamido-2-deoxy-3-*O*-mesyl-β-D-glucopyranosides *via* the 3,4 epoxide, and *not via* an oxazoline intermediate. For the synthesis of benzyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside from benzyl 2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside the order of ring closures of the carbonyl and anhydro rings was determined. An intermediate with the 3,6-anhydro structure was isolated. This intermediate was then changed to the 2-*N*,4-*O*-carbonyl compound.

Two procedures are currently available for the synthesis of 3,6-anhydro derivatives of 2-amino-2-deoxy-β-D-glucopyranosides.

Foster, Stacey, and Vardheim[2] used methyl 2-benzyloxycarbonylamino-2-deoxy-6-*O*-tosyl-β-D-glucopyranoside (I) in reaction with base to form methyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside (II).[2] Under these conditions no inversion occurred at C_3. The tosyl group at C_6 was readily displaced and the 3,6-anhydro ring was unequivocally formed, the formation of other rings being sterically impossible. In the second procedure, Reckendorf and Bonner used methyl 2-benzamido-2-

(1) A preliminary communication was presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract Carb 000. Taken from the doctoral thesis of C. A. Johnson, University of the Pacific, 1971. This work was partially supported by Grant No. GP 12222 of the National Science Foundation. Part V: F. R. Seymour and P. H. Gross, *J. Org. Chem.*, **36**, 1085 (1971).

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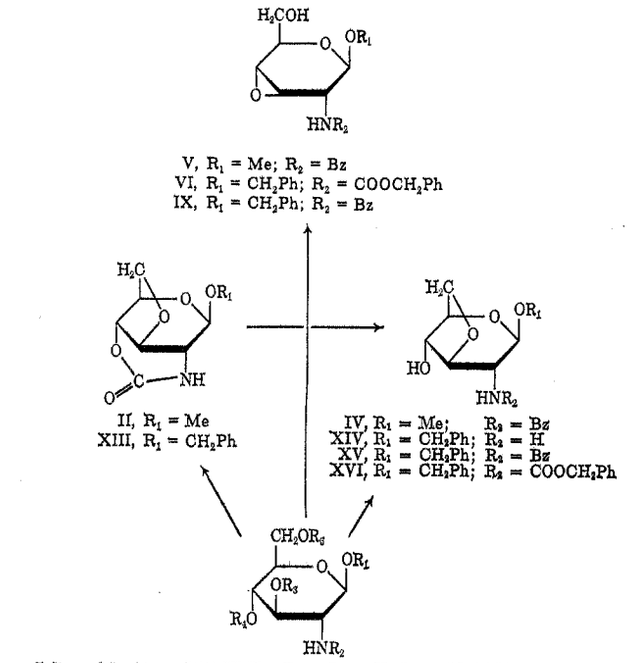

I, R_1 = Me; R_2 = $COOCH_2Ph$; R_3 = R_4 = H; R_5 = $SO_2C_6H_4Me$
III, R_1 = Me; R_2 = Bz; R_3 = SO_2Me; R_4 = R_5 = H
VII, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = SO_2Me; R_4 = R_5 = H
VIII, R_1 = CH_2Ph; R_2 = Bz; R_3 = SO_2Me; R_4 = R_5 = H
X, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = Ac; R_4 = R_5 = H
XI, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = Ac; R_4 = H; R_5 = $SO_2C_6H_4Me$
XII, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = Ac; R_4 = R_5 = $SO_2C_6H_4Me$
XVII, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = R_4 = H; R_5 = $SO_2C_6H_4Me$

deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (III) as starting material for the preparation of a 3,6-anhydro derivative (IV).[3] In this case there are other possible products. The benzamido group at C_2 could attack at C_3 to form either an oxazoline or an epimine derivative of the allo configuration. The 3,6-anhydro derivative IV which Reckendorf and Bonner obtained in fact was assumed to result from a second inversion at C_3 by attack of the C_6 hydroxyl on an intermediate oxazoline.[3] Also, the OH group at C_4 could attack with inversion at C_3 to form a 3,4-anhydro derivative (V) of the allo configuration. The similar 3,4-anhydro sugar VI was formed[4] when benzyl 2-benzyloxycarbonylamino-2-deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (VII)[5] or its 4,6-di-*O*-acetyl derivative[5] were treated with base. At the time when these experiments were carried out, it was already considered possible that such 3,4-anhydro sugars may rearrange to 3,6-anhydro sugars.[6] Similarly, the 3,4-anhydro sugar V, instead of an oxazoline, could have been[7] the actual intermediate in the 3,6-anhydro sugar synthesis by Reckendorf and Bonner.[3]

Two explanations appear possible for the difference in results obtained by Reckendorf and Bonner with the methanesulfonate III and by this laboratory with the methanesulfonate VII. First, benzamido groups are known to give better anchimeric assistance as compared to benzyloxycarbonylamino groups, and this may explain 3,6-anhydro sugar formation *via* the oxazoline.[3]

Secondly, there exists recent evidence[8] that arrangements of large syn-diaxial groups are thermodynamically unfavorable structures. The bulky benzyl glycoside in VI may have prevented or slowed down the rearrangement of the 3,4-anhydro to the 3,6-anhydro sugar.

If the second explanation is true, it should be possible to ascertain the nature of the intermediate in the reaction of III to give IV with alkali, by replacing only the methyl glycoside by the bulkier benzyl glycoside (VIII). The formation of either the 3,4-anhydro sugar IX or an oxazoline intermediate should then still be possible in the C1 conformation.[9] However, the bulkier benzyl glycoside in VIII would make attainment of the 1C conformation in the transition state leading to XV less favorable, and whatever would be the "intermediate," 3,4-anhydro sugar or oxazoline, could be isolated as end product.

Following the procedures of Reckendorf and Bonner,[3] benzyl 2-benzamido-2-deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (VIII)[9] was treated with $NaOCH_3$ to give benzyl 3,4-anhydro-2-benzamido-2-deoxy-β-D-allopyranoside (IX). Compound IX decomposed in methanolic aqueous KOH at room temperature. The 3,6-anhydro derivative XV, prepared by the unequivocal procedure to be described below, was stable under these conditions. The ir spectra of IX and XV differed. The ir spectrum of IX had absorptions at 1638 and 1536 cm^{-1}, ascribed to an amide group. This indicated that IX was not an epimine or an oxazoline derivative.

It is thus found here that the formation of 3,6-anhydro sugars from a cis configuration of methanesulfonyl and hydroxymethyl groups follows a similar mechanistic pattern as the formation of 1,6-anhydro sugars from a cis configuration of negative leaving group at the glycosidic carbon and the hydroxymethyl group at C-5, where the intermediate was shown to be a 1,2 epoxide.[10] Studies with molecular models show that, more so than the normal C1 conformation of an oxazoline intermediate, the C1 half chair of epoxides lends itself to an easy switch into the 1C half-chair conformation, and an axial back-side attack of the hydroxymethyl group in accordance with the Fürst–Plattner rule.[11] Also, the anomeric effect[12] should favor half-chair inversion for a β-glycoside. By contrast, axial back-side attack in a normal 1C conformation is seen to be sterically hindered by axial hydrogen. For nonnitrogenous sugars, conversion of 3,4-anhydroglucopyranoside into 3,6-anhydroglucopyranoside was first suggested by Ohle and Wilcke.[13] The technique of stabilization by steric hindrance of a reactive intermediate that precedes a reaction step involving conformational change may be applied to other investigations of complex neighboring group reactions in the cyclohexane or carbohydrate series.

Following the experimental procedure of Foster, *et al.*,[2] the tosylation of benzyl 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside[5] (X) gave benzyl 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XI). Some

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of the 4,6-di-*O*-tosyl derivative (XII) was also formed. The reaction of XI with methanolic aqueous KOH gave the carbonyl compound benzyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside (XIII). Especially characteristic for this structure was the ir absorption for the ring carbonyl amide at 3322 (NH) and 1722 cm^{-1} (C=O) and the absence of the amide II band.

Compound XIII was heated in aqueous methanolic KOH to give benzyl 2-amino-3,6-anhydro-2-deoxy-β-D-glucopyranoside (XIV). Treatment of XIV with benzoyl chloride gave the *N*-benzoyl derivative XV. Similarly, treatment of XIV with carbobenzoxy chloride gave XVI.

A more direct route for the preparation of XVI was also developed. This route led to the resolution of a mechanistic question in the preparation of the carbonyl compound XIII. For the synthesis of the methyl glycoside II by Foster, *et al.*,[2] it was assumed that the 3,6-anhydro ring was closed before the formation of the 2,4-carbonyl ring. For compound XIII this was proven as follows. Benzyl 2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XVII) was obtained from the 3-*O*-acetyl derivative XI and methanolic aqueous KOH at room temperature. Deacetylation occurs easily under these conditions and XVII crystallized immediately before the 3,6-anhydro ring could be formed. Compound XVII left for 3 days in methanolic aqueous KOH at room temperature gave the benzyloxycarbonylamino-3,6-anhydro derivative XVI. When XVI was kept longer in the methanolic aqueous KOH, compound XIII was formed.

Experimental Section

Melting points were taken in a Thomas-Hoover melting point apparatus Model No. 6404H. All melting points reported herein are uncorrected. Optical rotations were measured at the sodium D line with an O. C. Rudolph and Sons Inc., Model No. 956 polarimeter. Ir spectra were recorded with a Perkin-Elmer spectrophotometer (Model 337) using the KBr pellet technique. The homogeneity of all compounds synthesized was determined by thin layer chromatography using a mixture of two parts Merck silica gel G with one part Merck silica gel GF_{254}, the plates being activated by heating at 120° for 2 hr. The plates were developed with chloroform containing sufficient ethanol to produce R_f values between 0.2 and 0.7. The compounds were detected by extinction of the ultraviolet fluorescence of a zinc–silicate indicator and also by subsequent spraying with sulfuric acid (10%)–methanol and heating for about 15 min at 120°. The preparative tlc separations were made on Merck precoated silica gel plates, F_{254}, 2 mm thick. The microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Engelskirchen, West Germany.

Benzyl 3,4-Anhydro-2-benzamido-2-deoxy-β-D-allopyranoside (IX).—Benzyl 2-benzamido-2-deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (VIII)[9] (0.5 g, 0.0011 mol) was dissolved in methanol (10 ml) containing sodium methoxide (0.0013 mol) and left overnight at room temperature. The solution was poured into water. The precipitate was filtered, washed with water, and recrystallized from methanol–water to give 0.29 g (74%): mp 183–185°; $[\alpha]^{25}D$ 142.8° (*c* 1, $CHCl_3$); $\bar{\nu}_{max}$ 3261 (NH), 1638, 1536 (amide C=O), 746, 695 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.59; H, 5.96; N, 3.95. Found: C, 67.44; H, 592; N, 3.89.

Benzyl 3-*O*-Acetyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XI).—Benzyl 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (X)[5] (5 g, 0.011 mol) was dissolved in pyridine (25 ml) and the solution was cooled to 0° in an ice bath. *p*-Toluenesulfonyl chloride (4 g) in pyridine (12 ml) was added over a 20-min period. The solution was left at room temperature for 36 hr and poured into ice water (100 ml). The resulting oil was separated and dissolved in hot ethanol. At 0° the 4,6-di-*O*-tosyl derivative XII precipitated and was filtered off. The filtrate was concentrated, and the resulting precipitate was recrystallized from chloroform and diisopropyl ether to give 3.25 g (49%): mp 117–118°; $[\alpha]^{25}D$ 25° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3300 (NH), 1736 (ester C=O), 1682, 1555, 1512 (amide (C=O), 1350 (SO_2), 744, 696 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{30}H_{33}NO_{10}S$ (599.63): C, 60.09; H, 5.54; N, 2.33; S, 5.35. Found: C, 60.43; H, 5.54; N, 2.39; S, 5.29.

Benzyl 3-*O*-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-di-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XII).—The 4,6-di-*O*-tosyl derivative XII, which was separated in the preparation of XI, was recrystallized from ethanol to give 0.97 g (11%): mp 158–159°; $[\alpha]^{25}D$ −8.5° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3397 (NH), 1755 (ester C=O), 1695, 1522 (amide C=O), 1265 (SO_2), 737, 697 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{37}H_{39}NO_{12}S_2$ (753.82): C, 58.96; H, 5.22; N, 1.86; S, 8.51. Found: C, 59.24; H, 5.03; N, 1.88; S, 8.52.

Benzyl 2-Amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside (XIII). Following the procedures of Foster, *et al.*,[2] for the preparation of methyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside, compound XI (2 g, 0.0033 mol) was dissolved in ethanol (20 ml), and 1 *N* potassium hydroxide (10 ml) was added. The solution was refluxed for 30 min and then cooled. The precipitate was filtered off and washed in ethanol to give 0.53 g (58%): mp 235–236°; $[\alpha]^{25}D$ −172° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3322 (NH), 1722 (C=O), 754, 704 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{14}H_{15}O_5N$ (277.27): C, 60.63; H, 5.45; N, 5.05. Found: C, 60.83; H, 5.24; N, 5.07.

Benzyl 2-Amino-3,6-anhydro-2-deoxy-β-D-glucopyranoside (XIV).—Compound XIII (0.4 g, 0.0014 mol) was dissolved in methanol (10 ml), and potassium hydroxide (2.17 g) in water (3 ml) was added. The solution was heated at 70° for 15 hr and evaporated *in vacuo*. The residue was crystallized from water to give 0.16 g (49%): mp 172–173°; $[\alpha]^{25}D$ −149.5° (*c* 1, CH_3OH); $\bar{\nu}_{max}$ 3301 (NH), 737, 692 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{13}H_{17}NO_4$ (251.28): C, 62.12; H, 6.82; N, 5.59. Found: C, 62.22; H, 6.82; N, 5.61.

Benzyl 3,6-Anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XV).—Compound XIV (0.2 g, 0.0008 mol) was dissolved in ethylene dichloride (10 ml) and added to 2.5% aqueous sodium bicarbonate (4 ml). Benzoyl chloride (0.1 ml) was added and the mixture was vibrated overnight. The ethylene dichloride layer was evaporated *in vacuo* and the product was recrystallized from ethanol and chloroform to give 0.18 g (63%): mp 184–185°; $[\alpha]^{25}D$ −156° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3238 (NH), 1633, 1522 (amide C=O), 740, 690 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.58; H, 5.96; N, 3.95. Found: C, 67.71; H, 5.96; N, 3.84.

Benzyl 3,6-Anhydro-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (XVI).—Compound XIV (0.05 g, 0.0002 mol) was dissolved in ethylene dichloride (10 ml) and added to 2.5% aqueous sodium bicarbonate (3 ml). Carbobenzoxy chloride (0.036 g) was added and the mixture was vibrated overnight. The ethylene dichloride layer was separated and evaporated *in vacuo* at room temperature, and the resulting oil solidified with addition of diisopropyl ether to give 0.04 g (52%): mp 147–148°; $[\alpha]^{25}D$ −98° (*c* 1, $CHCl_3$); $\bar{\nu}_{max}$ 3360 (NH), 1677, 1511 (amide C=O), 744, 696 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.42): C, 65.44; H, 6.02; N, 3.64. Found: C, 65.11; H, 6.02; N, 3.56.

Benzyl 2-Benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XVII).—Compound XI (3.5 g, 0.0058 mol) was dissolved in methanol (30 ml) at room temperature, and potassium hydroxide (1 g) in water (20 ml) was added. Precipitation occurred almost immediately and the precipitate was filtered off and washed with a mixture of water and methanol (1:1). The product was recrystallized from 2-propanol to give 2.2 g (63%): mp 149–150°; $[\alpha]^{25}D$ −16° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3416 (NH) 1688, 1525 (amide C=O), 1360 (SO_2), 737, 693 cm^{-1} (C_6H)$_5$.

Anal. Calcd for $C_{28}H_{31}NO_9S$ (577.60); C, 60.21; H, 5.60; N, 2.51; S, 5.76. Found: C, 59.86; H, 5.22; N, 2.70; S, 5.81.

The filtrate from the above reaction was left at room temperature for 3 days and precipitation occurred. The precipitate

was filtered and recrystallized from toluene to give 0.16 g, mp 147–148°. It was homogenous on tlc and had physical constants and an ir spectrum identical with those of compound XVI.

Further precipitation from the filtrate from the above reaction gave mixtures of XVI and XIV as shown by tlc.

Registry No.—VIII, 24718-05-6; IX, 39533-58-9; X, 10512-69-3; XI, 39533-60-3; XII, 39533-61-4; XIII, 39599-19-4; XIV, 39533-62-5; XV, 39533-63-6; XVI, 39533-64-7; XVII, 39533-65-8; *p*-toluenesulfonyl chloride, 98-59-9.

A Condensed Methyl Reductic Acid from Hydrolysis of Amino-hexose-reductones

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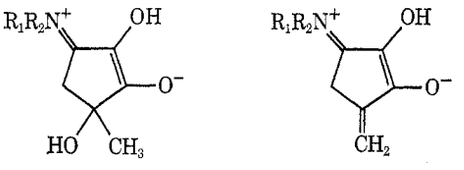
Dilute mineral acid hydrolyzes the amino group of hexose-reductones to yield 26% of a new yellow reductone, 2-hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione. The structure is assigned from ultraviolet, infrared, mass spectral, and proton magnetic resonance data. Chemical evidence supporting the condensed methyl reductic acid structure was obtained from periodate and hydrogen peroxide oxidations; 2-methyl-(*Z*)-butenedioic acid and 2-carboxy-2-methylbutanedioic acids were identified. Reduction of the yellow reductone and acetylation of the mixture produce the diacetate of methyl reductic acid, the di- and triacetates of unreacted yellow reductone, and the mixed acetates of the partially reduced parent material. These products were also identified by spectral techniques and confirmed by comparisons with data from authentic compounds whenever possible.

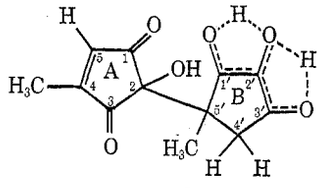
The hydroxy- and amino-substituted methyl reductic acids (**1**), trivially named amino-hexose-reductones, have been prepared from aldo- and ketohexoses in reactions with various secondary amine salts.[2–5] Dehydration of **1** by dehydrohalogenation yields **2**.[3,4] The mechanism of formation of piperidino-hexose-reductone has been determined.[6,7] Although both **1** and **2** are excellent antioxidants in animal fats and vegetable oils,[8] most of the different amino derivatives of **1** and **2** are toxic to small animals.[9,10]

To eliminate the toxicity and retain the antioxidant properties, removal of the amino group by acid hydrolysis was tried; however, no simple hexose-reductone was isolated. Instead, hydrolysis condensed the C_6 methyl reductic acid radicals to C_{12}, C_{22}, and higher compounds. The major product after hydrolysis of either **1** or **2** (R_1, R_2 = C_5H_{10} or $C_2H_4OC_2H_4$; $R_1 = R_2 = C_6H_5CH_2$) in 2 or 4 *N* hydrochloric acid at 25° was a new, yellow, crystalline, nonnitrogenous reductone, 2-hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione (**3**). This reductone did not induce the neurological effects that were observed for various amino derivatives of **1**, and lethal dosages were much higher than those of amino derivatives of **2**.[11]

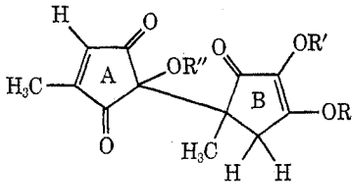
Elemental analysis of **3** furnished the formula $C_{12}H_{12}O_6 \cdot H_2O$, and this composition was confirmed by mass spectrometry (*m/e* 252.0660, M·+). Ir analysis



1 **2**



3



4a, R = OAc; R′ = R″ = H
b, R = R′ = OAc; R″ = H
c, R, R′, R″ = OAc
5, R = CH_3; R′ = R″ = H

(KBr disk) of **3** indicated several H-bonded hydroxyl groups (3500–3250 cm^{-1}). The yellow reductone **3** forms a monoacetate **4a** and, since the diacetate **4b** still exhibited a broad absorption at 3410 cm^{-1}, a third hydroxyl group was evident. Isolation of the triacetate **4c** confirmed the number of free hydroxyls. The important absorptions at 1748, 1706, and 1607 cm^{-1} were difficult to assign with certainty. The weaker 1748-cm^{-1} absorption is not congruent with an ene-1,3-dione, other reductone systems, an overtone, or a Fermi resonance assignment. Hesse, *et al.*,[12,13] presented solid-state ir spectra for methyl reductic acid and a tetramethyl, six-membered ring reductone, which

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