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CONFIRMATION OF THE STRUCTURES OF THE PRODUCTS OBTAINED ON ACYLATION OF 2-AMINO-2-DEOXY-D-GLUCONIC ACID

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ABSTRACT

Acetylation of 2-amino-2-deoxy-D-gluconic acid (**1**) with acetyl chloride–pyridine gave 2,3-unsaturated six- and five-membered lactones (**2** and **3**). Their benzoylated analogs (**4** and **5**) were obtained by benzoylation of **1** with benzoyl chloride–pyridine. Reaction of **1** with hot acetic anhydride–sodium acetate gave a ~1:2 mixture of (*E*)- and (*Z*)-2-acetamido-6-acetoxyhexa-2,4-dien-4-olide (**6**-*E* and **6**-*Z*). Treatment of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene also gave as the main product **6**-Z, which was isolated crystalline from the reaction mixture. The same reaction applied to compound **5** gave selectively the *Z*-isomer of the benzoylated furanone **7**. Partial and total hydrogenation (H_2–Pd-C) of the mixture **6**-*E,Z* gave, respectively, a racemic monounsaturated lactone (**8**) and a dideoxy lactone (**9**), for which the *threo*-configuration for the chiral centers at C-2 and C-4 was determined. Acidic removal of the acetyl groups from **9** afforded the 2-amino-6-hydroxy-1,4-lactone hydrochloride **10**. On the other hand, acetylation at high temperature of the 4,6-*O*-benzylidene derivative of **1** (**11**) gave the 2,3-unsaturated, six-membered lactone (**12**), precursor of 2-acetamido-6-acetoxyhexa-2,4-dien-5-olide (**14**).

INTRODUCTION

2-Amino-2-deoxyhexonic acids and their derivatives undergo β-elimination during acylation reactions to give enamine compounds[1]. It had long ago been reported[2] that acetylation of 2-amino-2-deoxy-D-gluconic acid (**1**) with hot acetic anhydride–sodium acetate gave a product (m.p. 125°) of empirical formula $C_{10}H_{15}NO_5$. Bergmann *et al.*[3] repeated the reaction and performed an extensive series of transformations in order to establish the structure of the product, which was formulated as 2-acetamido-6-acetoxyhexa-2,4-dien-5-olide (**14**). Later, Inoue[4] employed the supposed 6-membered lactone (**14**) in what was claimed to be a new route to 5-hydroxylysine. However, we have found[5], and it was later confirmed[6],

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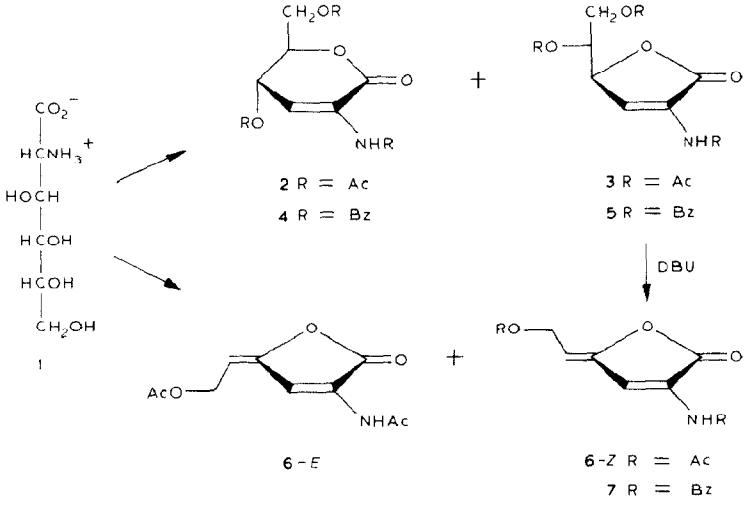
that the structure assigned to the product having m.p. 125° was erroneous, and it was definitively established as an isomeric mixture (*E* and *Z*) of 2-acetamido-6-acetoxyhexa-2,4-dien-4-olide (**6**-*E and* **6**-*Z*). We have found other structures described by Bergmann that required revision. The chemical transformations performed and the spectral evidence for the reassignment of the structure of the m.p. 125° product are now reported. Furthermore, we present in this work a detailed study of the products obtained on acetylation and benzoylation of 2-amino-2-deoxy-D-gluconic acid (**1**) under various conditions.

RESULTS AND DISCUSSION

Acetylation of 2-amino-2-deoxy-D-gluconic acid (**1**) with acetyl chloride–pyridine gave a mixture of two products which were separated by column chromatography. The main product had the same physical constants as the compound synthesized by Pravdić and Fletcher[7] through a different route, and characterized by them as 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**2**). The ^{13}C-n.m.r. spectrum of **2** (Table II) confirmed its structure, showing the signals for the vinyl carbons at δ 126.7 (C-2) and 117.6 (C-3). The signal for C-5 (77.9 p.p.m.) appeared at lower field than that for C-4 (63.6 p.p.m.), as observed for other hex-2-enono-1,5-lactones[8]. The minor product obtained by acetylation of **1** was identified as 2-acetamido-5,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,4-lactone (**3**), as it had the same properties as the product prepared[9] by treatment of 2-acetamido-2-deoxy-D-mannono-1,4-lactone with methanolic potassium hydroxide, followed by acetylation. The ^{13}C-n.m.r. spectrum of **3** showed the signals for the carbons of the double bond at δ 126.6 (C-2) and 124.9 (C-3). The signal for C-4 (79.0 p.p.m.) in compound **3**, in contrast with its behavior in **2**, appeared at lower field than that of C-5 (70.6 p.p.m.), confirming the presence of a five-membered enonolactone ring[8].



As with the acetylation results, the benzoylation of **1** with benzoyl chloride–pyridine, gave a mixture of two compounds, obtained crystalline after chromatographic separation. The structure of the main product was established as **4** on the basis of its ^{1}H-n.m.r. spectrum, which resembles that of **2**, although H-3 was not detected because of its overlapping with the aromatic protons. The structure assigned to **4** was confirmed by its ^{13}C-n.m.r. spectrum. It showed the vinyl carbons at δ 127.4 (C-2) and 117.3 (C-3); and C-5, as observed for the acetylated analog **2**, at lower field (78.6 p.p.m.) than C-4 (64.8 p.p.m.). The ^{1}H-n.m.r. spectrum of the minor product exhibited relative chemical shifts for H-4 and H-5 comparable with those shown by the acetylated derivative **3**, and a 2-enono-1,4-lactone structure (**5**) was proposed. As for compound **3**, the resonance for C-4 (79.7 p.p.m.) in the ^{13}C-n.m.r. spectrum of **5** appeared at lower field than that for C-5 (71.2 p.p.m.).

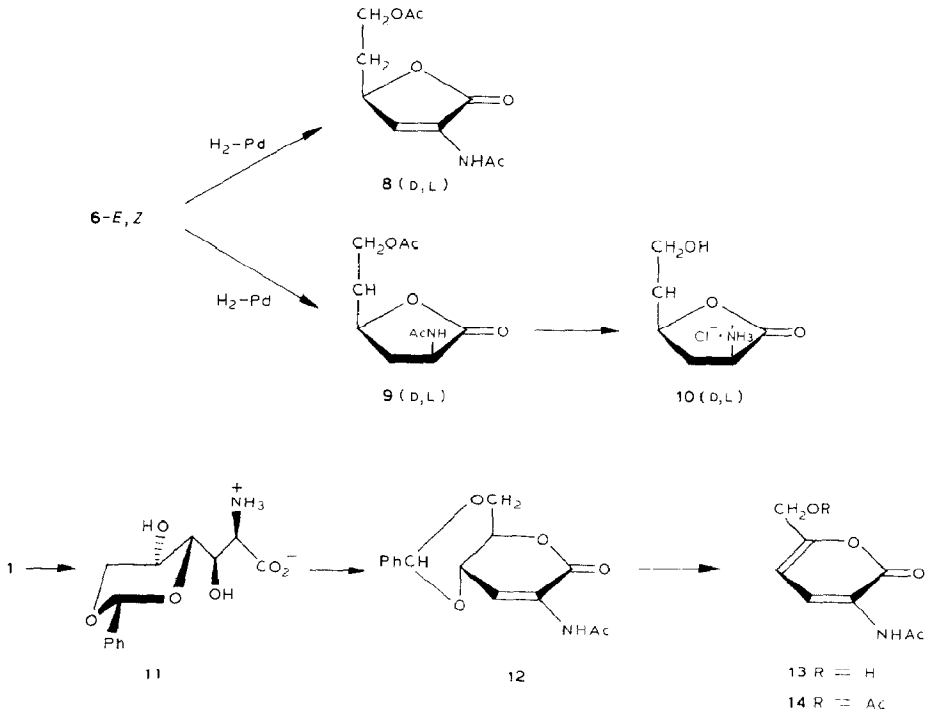
Acetylation of 2-amino-2-deoxy-D-gluconic acid (**1**), following the procedure of Bergmann *et al.*[3], led to the product earlier formulated[3] as 2-acetamido-6-acetoxyhexa-2,4-dien-5-olide (**14**). However, it was demonstrated[5,6] that the product was actually a mixture of (*E*)- and (*Z*)-2-acetamido-6-acetoxyhexa-2,4-dien-4-olide (**6**-*E,Z*). We now could isolate the pure *E* and *Z* isomers by recrystallization of the mixture (see Experimental). The structures **6**-*E* and **6**-*Z* were assigned by comparison with the spectral data reported in the literature[6].

Isomer **6**-*Z* crystallized in high yield on treatment of furanone **3** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). The same reaction, when applied to compound **5**, afforded also a single crystalline product, which was characterized as (*Z*)-2-benzamido-6-benzoyloxyhexa-2,4-dien-4-olide (**7**). The ^{1}H-n.m.r. spectrum of **7** showed the signal for H-5 at 5.57 p.p.m., H-3 was overlapped with the aromatic hydrogens, and the methylene-proton resonance appeared as a doublet at 5.17 p.p.m. These chemical shifts values are similar to those found for the furanone **6**-*Z*, although somewhat deshielded because of the change of benzoyl for acetyl substituents. The ^{13}C-n.m.r. spectrum of **7** also resembles that of **6**-*Z*, indicating a *Z* configuration for the exocyclic double bond.

An ElcB mechanism has been proposed[10] for β-elimination reactions in acylated aldono-1,4-lactones. Also an ElcB mechanism would operate in the elimination of acetic acid from **3** or benzoic acid from **5**. Removal of the proton at C-4 by a base would produce a resonance-stabilized carbanion, which gives **6** or **7**, respectively. Since *Z* isomers were mainly obtained, *syn*-elimination of the acyloxy group at C-5 should take place.

Controlled hydrogenation of the mixture **6**-*E,Z* gave compound **8**, to which Bergmann *et al.*[3] wrongly assigned a pyranoid structure. The chemical shift for C-4 (79.0 p.p.m.) confirms[8] the presence of a furanoid ring in **8**. The vinyl carbons appeared at δ 125.6 (C-2) and 128.8 (C-3), and the deoxy carbon (C-5) at 33.0 p.p.m. Complete hydrogenation of **6**-*E,Z* gave the dideoxy-1,4-lactone **9**, which was also proposed to have a six-membered ring lactone structure[3]. However, a furanoid structure is now established for **9**. Its ^{1}H-n.m.r. spectrum showed a multiplet (δ 4.63) for H-4, and H-2 gave a double doublet because of its coupling

with H-3 and H-3′. In the ^{13}C-n.m.r. spectrum of **9** the signal for C-4 appeared at 75.0 p.p.m., and the methylene carbons (C-3,5) at 35.6 and 34.1 p.p.m. Although compound **9** could not be crystallized, the spectral data of the syrup indicated that we were dealing with only one pair of enantiomers of the two theoretically possible from **6**. We have already reported[11] high stereoselectivity on hydrogenation of diunsaturated aldono-1,4-lactone derivatives. Hydrogenation of the exocyclic double-bond should occur first, to give the racemic furanone **8**. The orientation of the lateral chain would induce the addition of hydrogen to the endocyclic double-bond from the opposite side, to afford a single pair of enantiomers, in which the two chiral centers bear a *threo* relationship. Furthermore, in accordance with the proposed configuration, the coupling-constant values from the ^{1}H-n.m.r. spectrum of **9** showed a close resemblance[11] to those for 1,4-lactones having a *threo* relationship at C-2 and C-4.



Treatment of **9** with hydrochloric acid, at the reflux temperature, afforded compound **10** in crystalline form (m.p. 173–174°). The ^{13}C-n.m.r. spectrum of **10** showed only six signals, as expected for a single diasteroisomer. The deshielding of the signal for C-4 (79.4 p.p.m.) with respect to the chemical shift for C-4 in aldonic acids (for example **1**) indicates a 1,4-lactone structure for **10**, which can be formulated as 2-amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone hydrochloride.

Bergmann *et al.*[3] have reported the separation by crystallization of two stereoisomers of "2-amino-5,6-dihydroxy-caproic acid hydrochloride". However, the melting points of both products were similar, and close to the melting point of the product now characterized as **10**.

As the products of acetylation of **1** were firmly determined to have the structures of the furanones **6**-*E,Z*, and their properties differ from those of the compound prepared[3] by a different route but formulated as **6**, we decided to determine the correct structure of this latter substance. We first noted that the starting material, thought to be the 5,6-*O*-benzylidene derivative of **1**, was later shown to be[12] 2-amino-4,6-*O*-benzylidene-2-deoxy-D-gluconic acid hydrochloride ethanol solvate (**11**). Compound **11** prepared by us showed the ^{1}H-n.m.r. signals expected for the solvate [δ 3.65 (q) and 1.17 (t)]; however the molecule of ethanol could be removed by prolonged drying in vacuum. The presence of a 1,3-dioxane system in **11** was confirmed by the ^{13}C resonance of the acetal carbon (100.2 p.p.m.), similar to the value reported for 2-phenyl-1,3-dioxanes[13] but at higher field than that found for normal 1,3-dioxolanes. Furthermore, according to the shifts that usually accompany the formation of a 4,6-*O*-benzylidene ring[14], signals at 81.8 and 70.8 p.p.m., were attributed to C-4 and C-6, respectively, considering a deshielding of ~10 and ~7 p.p.m. for those carbons. The signal for C-5 usually shifted upfield about 11 p.p.m. by 4,6-*O*-benzylidenation is, in this case, difficult to identify.

Acetylation of **11** with acetic anhydride and sodium acetate, at the reflux temperature, gave a crystalline product. Its ^{1}H-n.m.r. spectrum showed the presence of the acetal proton (δ 5.64) and the large value for the coupling constants $J_{4,5}$ (9.6 Hz) and $J_{5,6'}$ (11.2 Hz) indicates a *trans*-diaxial disposition for H-4,5 and H-5,6', suggesting a benzylidene acetal fused with a six-membered ring (1,5-lactone). A 2-enono-1,5-lactone structure (**12**) was deduced from the ^{13}C-n.m.r. spectrum, which showed two vinyl carbons at 124.4 (C-2) and 124.0 p.p.m. (C-3). When compared with **11**, the signal for C-1 (lactone carbonyl group) appeared shifted upfield, as occurred in analogous compounds, for example **2** and **4** with respect to **1**. On the other hand, C-5 was shifted downfield because of lactonization, and C-4 upfield, due[8] to the introduction of an unsaturation at C-2–C-3. Compound **12** had the same m.p. and optical rotation as reported for the product erroneously formulated[3] as 2-acetamido-5,6-*O*-benzylidene-2,3-dideoxyhex-2-enono-1,4-lactone.

Treatment of **12** with concentrated hydrochloric acid caused hydrolysis of the benzylidene acetal and the elimination of a molecule of water to give a product (**13**) which on acetylation afforded 2-acetamido-6-acetoxyhexa-2,4-dien-5-olide (**14**). We have previously observed[15] acidic catalysis in the elimination of benzoic acid from benzoylated 2-enono-1,5-lactones to give the corresponding pyran-2-one derivatives. Compound **14** had been isolated[6] by liquid chromatography as a by-product in the reaction of **1** with hot acetic anhydride–sodium acetate. The ^{13}C-n.m.r. spectrum of **14** showed the pattern of signals found for pyran-2-one deriva-

tives[8], evidencing a six membered-ring instead of a furanoid system, as proposed[3].

The reassigned structures and their physical constants are summarized in Table III.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. ^{1}H- And ^{13}C-n.m.r. spectra were recorded at 100.1 and 25.2 MHz respectively, with a Varian XL-100 spectrometer. Unless otherwise noted chloroform-*d* was used as solvent and tetramethylsilane as internal reference (δ 0.00). Data are shown in Tables I and II. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; w, weak; v, very. The strongest lines are numbered (1, strongest), and double numbers indicate approximately equal intensities. Ultraviolet spectra were recorded with a Bausch and Lomb "Spectronic 505" recording spectrometer. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. T.l.c. was performed on 0.25 mm 60F-254 (Merck) aluminium supported plates with *A*, 1:1 hexane–ethyl acetate and *B*, 3:1 hexane–ethyl acetate as irrigants. Detection was effected by spraying the plates with 5% H_2SO_4 in ethanol and subsequent heating. Silica gel 60 (230–400 mesh, Merck) was used for column chromatography.

*2-Acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-*D-erythro-*hex-2-enono-1,5-lactone* (**2**) *and 2-acetamido-5,6-di-*O*-acetyl-2,3-dideoxy-*D-erythro-*hex-2-enono-1,4-lactone* (**3**). — To a suspension of 2-amino-2-deoxy-D-gluconic acid (**1**, 1.0 g, 5.12 mmol) in dry pyridine, 0.3 mL portions of acetyl chloride (total: 1.8 mL) were added with vigorous stirring. The mixture was heated in a boiling-water bath for 1 h, and then poured into ice–water. After 1 h the mixture was extracted with CH_2Cl_2 (30 mL, twice) and the extracts were washed first with 5% aqueous HCl, then aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue showed, on t.l.c. in solvent *A*, two spots, having R_F 0.39 and 0.33. The components of the mixture were separated by column chromatography, using 2:1 hexane–ethyl acetate as eluent. Fractions containing the faster-moving compound were pooled and evaporated, affording syrupy compound **2** (0.42 g); it had $[\alpha]_D^{25}$ +137° (*c* 1, chloroform), similar to the reported[7] $[\alpha]_D^{25}$ of +144.5°. The more polar component was isolated as a syrup (0.12 g), and characterized as the furanone **3**; it had $[\alpha]_D^{25}$ +58° (*c* 1, chloroform), lit.[9] $[\alpha]_D^{25}$ +58.1°. The intermediate fractions consisted of a mixture of **2** and **3** (0.40 g). The overall yield from the reaction was 0.92 g (63%).

*2-Benzamido-4,6-di-*O*-benzoyl-2,3-dideoxy-*D-erythro-*hex-2-enono-1,5-lactone* (**4**) *and 2-benzamido-5,6-di-*O*-benzoyl-2,3-dideoxy-*D-erythro-*hex-2-enono-1,4-lactone* (**5**). — To a suspension of compound **1** (1.0 g, 5.12 mmol) in pyridine (20 mL), benzoyl chloride (5 mL) was added dropwise with stirring, at room

TABLE I

^{1}H-N.M.R. DATA FOR COMPOUNDS **2–7, 8, 9, 12** AND **14**

Compound	*Chemical shift (δ, p.p.m.)*						*Coupling constant (Hz)*			
	H-3	*H-4*	*H-5*	*H-6,6′*	*NH*	*CH_3CON*	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$
2	7.45(d)	5.66(t)	4.75(m)	4.44(dd), 4.21(dd)	7.84	2.20	5.0	5.2	5.8	5.0
3	7.45(d)	←5.30(m)→		4.55(dd), 4.14(dd)	7.72	2.22	1.5	n.d.[d]	3.5	5.0
4	[a]	6.07(dd)	5.12(m)	4.78(dd), 4.63(dd)	8.62		5.0	4.3	5.4	4.5
5	[a]	5.56(dd)	5.67(m)	4.80(dd), 4.61(dd)	8.20		2.0	6.0	5.5	4.5
6-*E*	7.80(d)		5.77(dt)	4.79(d)	8.00	2.25	($J_{3,5}$ ~1.0)		←7.3→	
6-*Z*	7.49(bs)		5.36(t)	4.88(d)	8.01	2.24			←7.4→	
7	[a]		5.57(t)	5.17(d)	8.24				←6.7→	
8	7.45(d)	5.17(m)	2.0(m)	4.24(m)	7.60	~2.20	2.0	5.1 ($J_{4,5'}$ 7.4)		
9[b]	2.87(m)	4.63(m)	2.0(m)	4.23(t)	6.80	~2.06	5.3		←6.4→	
12[c]	[a]	4.70(dd)	4.41(m)	4.47(dd), 4.00(t)	7.70	2.15	1.2	9.6	7.0	11.2
14	8.22(d)	6.33(d)		4.84(s)	8.00	2.21	7.2			

[a]Overlapped with aromatic protons. [b]H-2 δ 4.63 (dd, $J_{2,3}$ 8.5 Hz, $J_{2,3'}$ 12.0 Hz), H-3′ δ ~2.0 ($J_{3',4}$ ~10 Hz). [c]PhC*H* δ 5.64. [d]Not determined.

TABLE II

^{13}C-N.M.R. DATA FOR COMPOUNDS **1–7**, **8–12**, AND **14**

Compound	*Chemical shift (δ, p.p.m.)*					
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
1[a]	173.5	59.3	73.7*[b]	71.7*	68.2*	63.7
2	159.7	126.7	117.6	63.6	77.9	62.0
3	168.6[c]	126.6	124.9	79.0	70.6	61.3
4	160.3	127.4	117.3	64.8	78.6	63.2
5	168.8	126.8	125.1	79.7	71.2	61.9
6-*E*	165.7	127.7	114.9	151.7	106.4	58.6
6-*Z*	165.5	127.2	118.6	149.8	106.6	58.2
7	165.7	[d]	118.6	145.2	107.4	58.8
8	169.3[c]	125.6	128.8	79.0	33.0	60.0
9	170.6[c]	50.1	35.6*	75.0	34.1*	60.2
10[e]	175.3	51.4	38.3*	79.4	34.7*	59.5
11[e]	169.1	55.7*	66.4*	81.8	60.2*	70.8*
12[f]	161.0	124.4	124.0	73.5*	73.1*	67.6*
14	159.0*	125.1	122.5	106.4	150.4*	61.5

[a]Recorded in 1:1 D_2O-H_2O. [b]* indicates signals may be interchanged. [c]C-1 is overlapped with the acyl-carbonyl carbons. [d]Overlapped with the aromatic carbons. [e]Recorded in $(CD_3)_2SO$, Ph*C*H δ 100.2. [f]Ph*C*H δ 102.1.

temperature. After 2 h the mixture was poured into ice–water and processed as described for the acetylation of **1**. The syrup was chromatographed with 5:1 hexane–ethyl acetate as eluent. Evaporation of the fractions containing the product of R_F 0.40 (solvent *B*) afforded a syrup (1.08 g), which crystallized from ethanol. Compound **4** had m.p. 130–131°, $[\alpha]_D^{25}$ +87° (*c* 1, acetone).

Anal. Calc. for $C_{27}H_{21}NO_7$: C, 68.78; H, 4.49; N, 2.97. Found: C, 69.13; H, 4.76; N, 3.17.

The slower-moving component of the mixture (R_F 0.30, solvent *B*), compound **5**, crystallized on evaporation of the solvent (0.42 g); recrystallized from ethanol, it had m.p. 138–141°, $[\alpha]_D^{25}$ −15° (*c* 1, chloroform).

Anal. Calc. for $C_{27}H_{21}NO_7$: C, 68.78; H, 4.49; N, 2.97. Found: C, 68.48; H, 4.47; N, 2.89.

From the intermediate fractions a mixture of **4** and **5** was obtained (0.81 g). The overall yield from the reaction was 2.31 g (96%).

(E)- *And* (Z)-*2-acetamido-6-acetoxyhexa-2,4-dien-4-olide* [(E)- *and* (Z)-*3-acetamido-5-(2-acetoxyethylidene)-(5*H*)-furan-2-one*] (**6**-E *and* **6**-Z). — The procedure described by Bergmann *et al.*[3] was followed, starting from 2-amino-2-deoxy-D-gluconic acid (3.0 g, 15.4 mmol). A crystalline product (3.3 g, 95%) was obtained. Its ^{1}H-n.m.r. spectrum indicated that it contained 63% of one isomer (**6**-*Z*) and 37% of a second isomer (**6**-*E*). Three recrystallizations of the product from water gave long, white needles, m.p. 126–148° that gave acceptable microanalytical values for $C_{10}H_{11}NO_5$ but whose ^{1}H-n.m.r. spectrum showed that both isomers (**6**-*E* and

TABLE III

REASSIGNED STRUCTURES FOR COMPOUNDS **6**-*E,Z*; **8**, **10–12**, AND **14**

Reassigned structure	*M.p.*	$[\alpha]_D$	*Original structure assignment*	*Reference*
(*E,Z*)-2-Acetamido-6-acetoxyhexa-2,4-dien-4-olide (**6**-*E,Z*)	126–148°		2-Acetamido-6-acetoxyhexa-2,4-dien-5-olide (**14**)	3,4
2-Acetamido-6-acetoxyhexa-2,4-dien-5-olide (**14**)	117–118°		2-Acetamido-6-acetoxyhexa-2,4-dien-4-olide (**6**)	3
2-Acetamido-6-*O*-acetyl-2,3,5-trideoxy-D,L-*glycero*-hex-2-enono-1,4-lactone (**8**)	109–111°		2-Acetamido-6-*O*-acetyl-2,3,4-trideoxy-hex-2-enono-1,5-lactone	3
2-Amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone hydrochloride (**10**)	173–174°		2-Amino-5,6-dihydroxyhexanoic acid hydrochloride	3,4
2-Amino-4,6-*O*-benzylidene-2-deoxy-D-gluconic acid hydrochloride ethanol solvate[a] (**11**)	133–134°	−29.2°	Ethyl 2-amino-5,6-*O*-benzylidene-2-deoxy-D-gluconate hydrochloride	3,17
2-Acetamido-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**12**)	193–194°	−32°	2-Acetamido-5,6-*O*-benzylidene-2,3-dideoxy-hex-2-enono-1,4-lactone	3

[a]The correct structure was first given by Karrer and Mayer[16].

6-*Z*) were still present. Partial separation was achieved by stirring the crude mixture (3.3 g) in hot carbon tetrachloride (100 mL). After standing for 18 h at room temperature, the suspension was filtered. Three subsequent recrystallizations from water afforded the pure major isomer (**6**-*Z*); yield 0.3 g, m.p. 149–150°, R_F 0.52 (solvent *A*); $\lambda_{max}^{CH_3CN}$ 295 (ε 31000) and 307 nm (ε 28000); X-ray powder diffraction data: 13.80 vw, 12.06 s (3), 10.25 m, 9.11 w, 6.69 vw, 6.03 w, 5.47 m, 4.86 vw, 4.63 w, 4.37 m, 4.13 m, 3.98 s (4), 3.71 vs (1), 3.18 s (2), 3.05 vw, 2.73 vw, 2.52 vvw, and 2.32 m.

Anal. Calc. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.00; H, 4.88; N, 6.48.

The carbon tetrachloride filtrate was evaporated and the residue was recrystallized three times from 50% aqueous ethanol to give the pure, minor isomer (**6**-*E*); yield 0.2 g, R_F 0.52 (solvent *A*); it had m.p. 150–152°; $\lambda_{max}^{CH_3CN}$ 295 (ε 30000) and 307 nm (26000); X-ray powder diffraction data: 8.97 s (2), 8.05 vvw, 7.46 m, 5.60 vw, 5.22 s (1), 4.35 s (3), 4.11 m, 3.95 m, 3.79 s (4), 3.62 m, 3.49 m, 3.37 m, 3.27 w, 3.18 w, 2.79 m, 2.72 w, 2.61 w, 2.53 vw, 2.44 vw, 2.36 vw, 2.31 vw, 2.22 vvw, 2.13 w, 1.95 vw, 1.90 m.

Anal. Calc. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.36; H, 4.85; N, 6.27.

(Z)-*2-Acetamido-6-acetoxyhexa-2,4-dien-4-olide* (**6**-*Z*). — To a solution of compound **3** (0.15 g, 0.53 mmol) in dry CH_2Cl_2 (20 mL), cooled at 0°, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2 mL) was added. The mixture was stirred for 0.5 h at 0°, in the dark, then diluted with CH_2Cl_2 (100 mL). The solution was

extracted with 5% aqueous HCl, and water (twice), dried ($MgSO_4$), and evaporated. The residue crystallized from benzene to yield 90 mg (71%) of compound **6**-*Z*, which had the same physical constants and spectral properties as the product just described.

(Z)-2-Benzamido-6-benzoyloxyhexa-2,4-dien-4-olide [*(Z)-3-benzamido-5-(2-benzoyloxyethylidene)-(5H)-furan-2-one*] (**7**). — To a solution of compound **5** (0.10 g, 0.21 mmol) in dry CH_2Cl_2 (5 mL), cooled at 0°, DBU (0.1 mL) was added. The mixture was stirred for 0.5 h at 0°, in the dark, then treated as described for the preparation of **6**-*Z*. Compound **7** crystallized upon addition of ethanol; yield 46 mg (62%). Recrystallized from the same solvent it had m.p. 189–190°.

Anal. Calc. for $C_{20}H_{15}O_5N$: C, 68.76; H, 4.33. Found: C, 69.01; H, 4.54.

*2-Acetamido-6-O-acetyl-2,3,5-trideoxy-*D,L-glycero-*hex-2-enono-1,4-lactone* (**8**). — A solution of **6**-*E,Z* (0.29 g, 1.20 mmol) in ethyl acetate (15 mL) was hydrogenated over 10% Pd on charcoal for 2 h, when the theoretical volume of 1.20 mmol of H_2 had been consumed. The catalyst was filtered and the filtrate evaporated. The residue, compound **8**, R_F 0.34 (solvent *A*), crystallized from benzene (0.18 g, 62%); m.p. 109–111°; lit.[6] 111–112°.

*2-Acetamido-6-O-acetyl-2,3,5-trideoxy-*D,L-threo-*hexono-1,4-lactone* (**9**). — Compound **6**-*E,Z* (0.29 g, 1.20 mmol) was hydrogenated as just described, until the consumption of hydrogen ceased (6 h). A single spot of R_F 0.1 (solvent *A*) was observed by t.l.c. Compound **9** could not be crystallized, but it gave a good elemental analysis.

Anal. Calc. for $C_{10}H_{15}NO_6$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.17; H, 6.77; N, 5.91.

*2-Amino-2,3,5-trideoxy-*D,L-threo-*hexono-1,4-lactone hydrochloride* (**10**). — Compound **9** (0.15 g, 0.65 mmol) was heated with 5M HCl (10 mL) at reflux temperature for 1.5 h. The solution was evaporated several times with the addition of water, and the residue was dried overnight in vacuum. Compound **10** crystallized from ethanol; yield 62 mg (52%), m.p. 173–174°.

For a compound similarly obtained, and formulated as 2-amino-4,6-dihydroxyhexanoic acid hydrochloride, Bergmann *et al.*[3] reported m.p. 175°.

*2-Amino-4,6-benzylidene-2-deoxy-*D-*gluconic acid hydrochloride ethanol solvate*[12] (**11**). — To a mixture of benzaldehyde (3 mL) and anhydrous ethanol (15 mL) was added 2-amino-2-deoxy-D-gluconic acid (**1**; 2.0 g, 10 mmol) and the suspension was cooled in an ice–water bath. Anhydrous HCl was passed in until saturation. The mixture formed a clear solution and then solidified after 1 min. Ether (25 mL) was added, and the solid formed was filtered off, washed with ether (200 mL), and dried; yield 3.13 g (88%); m.p. 133–134°, $[\alpha]_D^{24}$ −29.2° (*c* 0.9, water); lit.[12] m.p. 129°, $[\alpha]_D^{25}$ −30.2°; X-ray powder diffraction data: 13.48 s, 9.82 m, 8.04 s (3), 7.44 w, 5.55 w, 4.24 s (3), 4.81 m, 4.54 w, 4.31 s (1), 3.83 m, 3.71 w, 3.61 s (2), 3.52 w, 3.41 m, 3.25 s, 3.13 m, 2.95 s, 2.73 w, and 2.61 s.

Anal. Calc. for $C_{15}H_{24}ClNO_7$: C, 49.27; H, 6.59; Cl, 9.70; N, 3.83. Found: C, 49.37; H, 6.83; Cl, 9.99; N, 4.10.

Drying for 3 days in a vacuum over P_2O_5 at room temperature removed most of the ethanol of solvation. The product had m.p. 148–151°.

2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-D-erythro-*hex-2-enono-1,5-lactone* (**12**). — A mixture of compound **11** (0.50 g, 1.37 mmol), anhydrous sodium acetate (0.5 g), and acetic anhydride (10 mL) was boiled for 10 min under reflux. The solution was poured over ice and the mixture was extracted with two 40-mL portions of chloroform. The extract was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to a syrup. Crystallization from ether gave the lactone **12**; yield 0.32 g (71%); m.p. 193–194°, $[\alpha]_D^{21}$ −32° (*c* 0.9, chloroform); X-ray powder diffraction data: 12.27 w, 9.93 w, 7.67 m, 7.65 vw, 6.85 s (2), 5.58 m, 5.41 vw, 4.85 s (3), 4.74 w, 4.59 w, 4.46 w, 4.05 w, 3.69 s (1), 3.55 w, and 3.37 w.

Anal. Calc. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.38; H, 5.40; N, 4.71.

For a compound formulated as 2-acetamido-5,6-*O*-benzylidene-2,3-dideoxy-D-hex-2-enono-1,4-lactone, Bergmann *et al.*[3] reported m.p. 198°, $[\alpha]_D^{30}$ −30.1° (chloroform).

2-Acetamido-6-hydroxyhexa-2,4-dien-5-olide [*3-acetamido-6-(hydroxymethyl)pyran-2-one*] (**13**). — Concentrated hydrochloric acid (2 mL) was added to compound **12** (0.65 g, 0.22 mmol) and the solution was stirred for 0.5 h at room temperature, diluted with water (20 mL), extracted twice with 30-mL portions of ether, and the aqueous solution was concentrated at 35° until crystallization began. The solution was cooled and the lactone **13** was filtered off; yield 0.12 g (29%), it had m.p. 157–158°.

For a compound formulated as 3-acetamido-5-(2-hydroxyethylidene)-2-(5*H*)-furanone, Bergmann *et al.*[3] reported m.p. 158.5°.

2-Acetamido-6-acetoxyhexa-2,4-dien-5-olide [*3-acetamido-6-(acetoxymethyl)-pyran-2-one*] (**14**). — A mixture of acetic anhydride (5 mL), anhydrous sodium acetate (0.5 g), and lactone **13** (90 mg) was heated for 30 min at 95–100°. The solution was stirred with ice–water for 30 min then extracted with three 20 mL-portions of chloroform, and the extract was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to a syrup. Crystallization from absolute ethanol gave **14** as needles; yield 104 mg (95%); m.p. 117–118°; R_F 0.42 (solvent *A*); $\lambda_{max}^{CH_3CN}$ 246 (ε 10000) and 311 nm (ε 18000); X-ray powder diffraction data: 16.05 w, 13.38 vs (1), 11.40 m, 9.35 vw, 7.95 s, 6.62 m, 5.48 w, 4.92 vs (2), 4.42 w, 4.05 s, 3.69 s, 3.51 s, 3.27 s, and 3.14 s.

Anal. Calc. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 52.99; H, 5.03; N, 6.31.

For a compound formulated as 3-acetamido-5-(2-acetoxyethylidene)-2-(5*H*)-furanone, Bergmann *et al.*[3] reported m.p. 115°.

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REFERENCES

1 R. J. FERRIER, *Adv. Carbohydr. Chem. Biochem.*, 20 (1965) 67–137 (see pp. 106–108).
2 C. NEUBERG, *Ber.*, 35 (1902) 4009–4023.
3 M. BERGMANN, L. ZERVAS, AND E. SILBERKWEIT, *Ber.*, 64 (1931) 2428–2436.
4 Y. INOUE, Jap. Pat. 6511/1962, *Chem. Absir.*, 59 (1963) 760e.
5 D. HORTON AND J. K. THOMSON, *Abstr. Pap. Am. Chem. Soc. Meeting*, 157th, CARB-15 (1969); J. K. THOMSON, M. S. Thesis, The Ohio State University, 1969.
6 C. T. CLARKE, J. H. JONES, AND R. WALKER, *J. Chem. Soc., Perkin Trans. 1*, (1976) 1001–1003.
7 N. PRAVDIĆ AND H. G. FLETCHER, JR., *Carbohydr. Res.*, 19 (1971) 353–364.
8 A. FERNANDEZ CIRELLI, M. SZNAIDMAN, O. VARELA, AND M. DE LEDERKREMER, *Tetrahedron*, 39 (1983) 313–316.
9 N. PRAVDIĆ AND H. G. FLETCHER, JR., *Carbohydr. Res.*, 19 (1971) 339–352.
10 L. O. JERONIC, O. VARELA, A. FERNANDEZ CIRELLI, AND R. M. DE LEDERKREMER, *Tetrahedron*, 40 (1984) 1425–1430; M. I. LITTER AND R. M. DE LEDERKREMER, *Carbohydr. Res.*, 26 (1973) 431–434.
11 O. VARELA, A. FERNANDEZ CIRELLI, AND R. M. DE LEDERKREMER, *Carbohydr. Res.*, 100 (1982) 424–430.
12 D. B. HOPE AND P. W. KENT, *J. Chem. Soc.*, (1955) 1831–1833.
13 T. B. GRINDLEY AND V. GULASEKHARAM, *Carbohydr. Res.*, 74 (1979) 7–30.
14 A. S. PERLIN, in G. O. ASPINALL (Ed.), *M. T. P. Internat. Rev. Sci., Org. Chem., Ser. Two*, 7 (1976) 1–34.
15 O. VARELA, A. FERNANDEZ CIRELLI, AND R. M. DE LEDERKREMER, *Carbohydr. Res.*, 79 (1980) 219–224.
16 P. KARRER AND J. MAYER, *Helv. Chim. Acta*, 20 (1937) 407–417.
17 P. A. LEVENE AND F. B. LA FORGE, *J. Biol. Chem.*, 21 (1915) 345–348.