Neighboring-Group Participation in Carbohydrates. The Synthesis of 2,3-Diamino-2,3-dideoxy-L-ribose[1]

ELMER J. REIST AND SANDRA H. CRUSE

Stanford Research Institute, Menlo Park, California 94025

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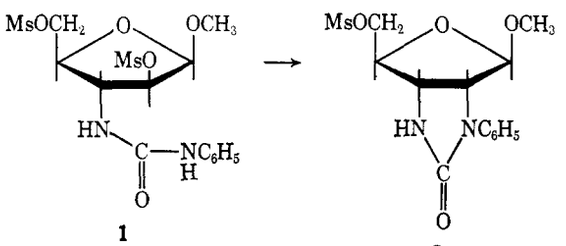
Treatment of methyl 3-deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside with sodium fluoride in DMF effected the elimination of the mesylate at C-4 to give methyl 3-amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-cyclic urethan (**7**). An SN2 displacement on **7** using sodium azide yielded methyl 3-amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (**8**). Hydrogenation of **8** and subsequent deblocking gave 2,3-diamino-2,3-dideoxy-L-ribose (**11**) as its crystalline dihydrochloride.

In recent years, there has been considerable interest in the preparation and chemistry of diaminodideoxy sugars, *e.g.*, derivatives of 2,3-diamino-2,3-dideoxy-D-mannose,[2] 2,3-diamino-2,3-dideoxy-D-allose,[3] 2,3-diamino-2,3-dideoxy-D-altrose,[2a] 4,5-diamino-4,5-dideoxy-D-arabinose,[4] and many others. The widespread occurrence in nature of derivatives of D-ribose made the preparation of diamino analogs an interesting challenge, both from the standpoint of the synthetic problems connected with the preparation of a 2,3-*cis*-diamine and also from the possibility of obtaining compounds which may have interesting biological activity. Baker and Hullar[5] described the preparation of a material which was believed to be a derivative (**2**) of 2,3-diamino-2,3-dideoxy-D-ribose by the displacement of the 2-O-mesylate by the neighboring ureido group of **1**. The de-



1 **2**

blocking of **2**, however, must give an N-phenyl derivative of 2,3-diamino-2,3-dideoxy-D-ribose. To avoid removal of the N-phenyl group of **2**, an alternative method was sought for the preparation of the unsubstituted 2,3-diamino sugar. The preparation of cyclic carbonates of sugars as intermediates for the synthesis of sugars which contain *cis* related functional groups has been described.[6] It seemed possible to adapt this approach to the synthesis of *cis*-diamino sugars. The synthesis of 2,3-diamino-2,3-dideoxy-L-ribose dihydrochloride from D-arabinose by this approach is described here. The D-ribose analog can be prepared from L-arabinose.

Methyl 3-amino-3-deoxy-β-D-xylopyranoside (**3**),[7] prepared from D-arabinose, was treated with methyl chloroformate in pyridine to give crystalline methyl 3-deoxy-2,4-di-O-methoxycarbonyl-3-methoxycarbonylamino-β-D-xylopyranoside (**4**). Treatment of **4** with methanolic sodium methoxide effected O-deacylation to give methyl 3-deoxy-3-methoxycarbonylamino-β-D-xylopyranoside (**5**). Mesylation of **5** using methanesulfonyl chloride in pyridine gave a good yield of methyl 3-deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside (**6**). When this compound was treated with anhydrous sodium fluoride in DMF, a 58% yield of a crystalline product was obtained which had analytical data that was satisfactory for methyl 3-amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-cyclic urethan (**7**), the product to be expected from the displacement of the O-mesylate at C-4 from **6**. Alternatively, the product of this reaction could be methyl 3-amino-3-deoxy-4-O-methylsulfonyl-β-D-lyxopyranoside 2,3-cyclic urethan (**15**) by displacement of the O-mesylate at C-2 from **6**. That the correct structure was **7** rather than **15** was determined by nmr spectroscopy, which is described later.

Treatment of **7** with sodium azide in DMF effected the displacement of the remaining mesylate to give a quantitative yield of crystalline methyl 3-amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (**8**). Catalytic hydrogenation of **8** using 5% palladium on carbon yielded 90% of crystalline methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (**9**). Removal of the cyclic urethan was carried out using refluxing aqueous barium hydroxide to give a 94% yield of crystalline methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside (**10**). Hydrolysis of **10** with 6 *N* hydrochloric acid gave 2,3-diamino-2,3-dideoxy-L-ribose (**11**), isolated as its crystalline dihydrochloride.

It is interesting to note that the infrared spectra of **7** and all subsequent compounds in which the cyclic urethan is intact failed to show amide II absorption at 6.5 μ. A similar observation was reported by Gross, *et al.*,[8] for cyclic urethans derived from benzyl 2-amino-2-deoxy-α-D-gulopyranoside.

The nmr spectra of the dimesylate **6** and the subsequent reaction products **7**–**9** were examined (Table I); band assignments were made by means of spin decoupling. The formation of the cyclic urethan in **7** to create a fused ring system had little effect on the position of the nmr bands. The displacement of the second mesylate by azide to give **8** and subsequent hydrogenation of the azide to give the free amine **9** caused a pronounced shift upfield in the position of H-2. Thus, the free amine must be on C-2 and the sodium fluoride cyclization product must be **7** rather than the isomeric 4-mesylate **15**.

Efforts to prepare a phenylosazone of **11** by the pro-

(1) This investigation was supported by the U. S. Public Health Service, Research Grants GM 11438 from the General Medical Sciences Institute and NB 07776 from the National Institute of Neurological Diseases and Blindness.

(2) (a) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963). (b) B. R. Baker and T. L. Hullar, *ibid.*, **30**, 4038 (1965).

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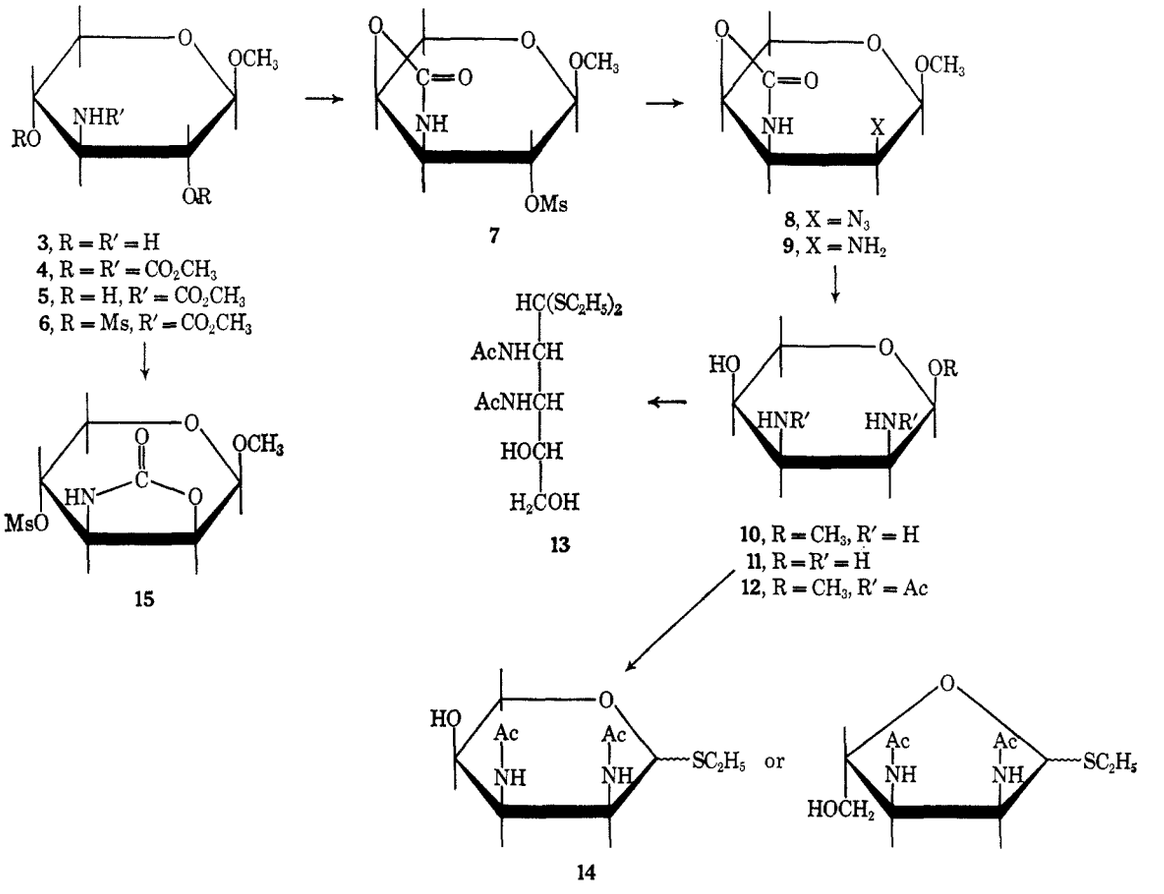


cedure reported[9] for the preparation of such a derivative from D-glucosamine failed and decomposition resulted. The preparation of a dithioacetal by the procedure developed for the preparation of the diethylthioacetal of glucosamine hydrochloride[10] also failed and starting material was recovered. As an alternative route for the preparation of a thioacetal of **11**, the methyl glycoside **10** was N-acetylated to give crystalline methyl 2,3-diacetamido-2,3-dideoxy-α-L-ribopyranoside (**12**). When **12** was treated with ethanethiol in concentrated hydrochloric acid, a low yield of a crystalline derivative was obtained, which analyzed for a thioglycoside (**14**) rather than the thioacetal (**13**) expected from such a procedure.[11] A similar result was observed by Hough and Taha[12] when they treated 2-acetamido-2-deoxy-D-glucose under similar conditions. The isolation of a thioglycoside under these conditions is consistent with the 2,3 diamino structure arising from **7** rather than the isomeric 3,4-diamine derived from **15**.

No evidence could be obtained for the formation of the 2-O-mesylate **15**. The apparently exclusive cyclization of the carbonate of **6** to give **7** is in agreement with the observation of Baker and Schaub,[13] who reported that the reaction of methyl 3-acetamido-3-deoxy-2,4-di-O-methylsulfonyl-β-L-xylopyranoside (**16**) with sodium acetate in ethanol gave a 66% yield of a monomesylate to which they gave the 4-O-mesylate structure **18**. Their tentative assignment was based on the analogous reactivity of the 3-acetamido-2-mesylate

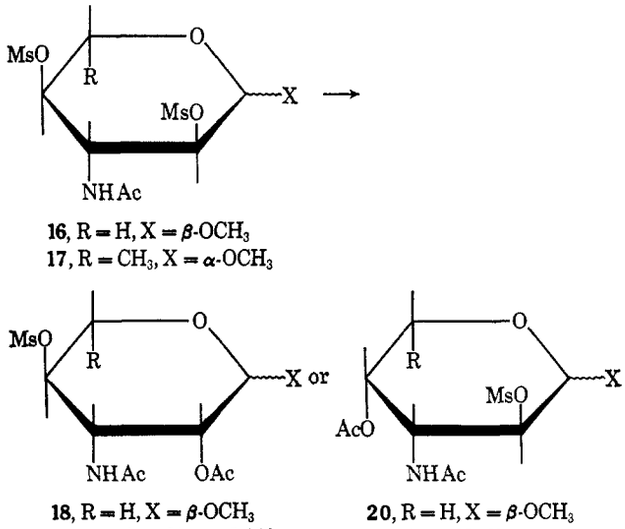
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

Compd	H-1[a]	H-2	H-3	H-4	H-5e	H-5a
6	5.5 (d)	5.5 (q)	6.0 (m)	5.3 (m)	5.8 (q)	6.4 (q)
7	5.6 (d)	5.6 (q)	6.1 (m)	5.3 (m)	6.1 (q)	6.2 (q)
8	5.7 (d)	6.5 (t)	6.5 (q)	5.4 (m)	5.9 (q)	6.2 (q)
9	5.9 (d)	7.2 (q)	6.5 (q)	5.4 (m)	5.9 (q)	6.2 (q)

[a] Band positions are expressed in τ units.

of methyl 3-acetamido-4,6-benzylidene-3-deoxy-2-O-methylsulfonyl-α-D-altropyranoside toward sodium acetate in ethanol. A subsequent report by Richardson and McLauchlan[14] described a similar treatment of



(9) F. Tiemann, *Ber.*, **19**, 49 (1886).
(10) L. Hough and M. I. Taha, *J. Chem. Soc.*, 3564 (1957).
(11) M. L. Wolfrom, R. U. Lemieux, and S. M. Olin, *J. Amer. Chem. Soc.*, **71**, 2870 (1949).
(12) L. Hough and M. I. Taha, *J. Chem. Soc.*, 2042 (1959).
(13) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).
(14) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).

methyl 3-acetamido-3,6-dideoxy-2,4-di-O-methylsulfonyl-α-L-glucoside (17) with sodium acetate in 2-methoxyethanol. They presented convincing evidence that the initial displacement occurred at C-4 to give methyl 3-acetamido-3,6-dideoxy-2-O-methylsulfonyl-α-L-galactopyranoside (21). From these results the suggestion was made[15] that the monosulfonate isolated from 16 was indeed the 2-sulfonate, 20, rather than the 4-sulfonate, 18.

The results reported in this paper on the participation of the N-methoxycarbonyl neighboring group are consistent with the results of Richardson and McLauchlan[14] and support the suggestion[15] that the monomesylate of Baker and Schaub[13] is probably the 2-mesylate 20.

Experimental Section[16]

Methyl 3-Deoxy-2,4-di-O-methoxycarbonyl-3-methoxycarbonylamino-β-D-xylopyranoside (4).—A solution of 10.34 g (62.5 mmol) of methyl-3-amino-3-deoxy-β-D-xylopyranoside[7] (3) in 100 ml of dry pyridine was cooled to 0° under a nitrogen atmosphere, and 25 ml (30.7 g, 327 mmol) of methyl chloroformate was added dropwise with stirring and continued cooling. The reaction was stirred at room temperature for 20 hr, and then stirred for 1 hr with 2 ml of water to decompose the excess methyl chloroformate.

The mixture was diluted with 100 ml of water and extracted with three 80-ml portions of chloroform. The chloroform layers were washed with 50 ml of saturated aqueous sodium bicarbonate and 50 ml of water, combined, dried, and evaporated to dryness *in vacuo* to give 22.3 g of an oil which crystallized on standing. The product was recrystallized from 95% ethanol to give 12.25 g of crystals, mp 118.5–120.0°.

The analytical sample was recrystallized from cyclohexane–benzene (5:3) to give material with mp 126–127.5°; $[\alpha]^{23}D$ −65° (*c* 0.30, chloroform); λ_{max}^{Nujol} 3.0 (NH), 5.70, 5.80, 5.90 (C=O), 7.75, 8.10 μ (C—O—C).

Anal. Calcd for $C_{12}H_{19}NO_{10}$: C, 42.7; H, 5.63; N, 4.15. Found: C, 42.6; H, 5.60; N, 4.25.

Methyl 3-Deoxy-3-methoxycarbonylamino-β-D-xylopyranoside (5).—To a solution of 10.5 g of methyl 3-deoxy-2,4-di-O-methoxycarbonyl-3-methoxycarbonylamino-β-D-xylopyranoside (4) in 200 ml of methanol was added 10 ml of 0.1 *N* methanolic sodium methoxide. The mixture was stored at room temperature for 3 hr and neutralized to pH 7 with IRC 50 (H). The neutralized solution was filtered and evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to give 6.4 g (93%) of product, mp 159–161°.

The analytical sample, obtained by recrystallization from ethyl acetate, had mp 158–160°; $[\alpha]^{23}D$ −60° (*c* 0.50, water); λ_{max}^{Nujol} 2.90 (OH, NH), 5.75, 5.95 (C=O), 6.45 μ (secondary amide).

Anal. Calcd for $C_8H_{15}NO_6$: C, 43.5; H, 6.78; N, 6.34. Found: C, 43.5; H, 6.95; N, 6.33.

Methyl 3-Deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside (6).—A solution of 7.35 g (33.3 mmol) of methyl 3-deoxy-3-methoxycarbonylamino-β-D-xylopyranoside (5) in 250 ml of dry pyridine was cooled to 0° in an ice bath, and 12 ml (17.8 g, 155 mmol) of methanesulfonyl chloride was added dropwise with stirring and continued cooling. After the exothermic reaction had ceased, the mixture was stirred at room temperature for 18 hr, and the excess methanesulfonyl chloride was decomposed by stirring with 2 ml of water for 0.5 hr.

The reaction mixture was partitioned between 100 ml each of chloroform and water. The chloroform layer was washed with saturated aqueous sodium bicarbonate and water, dried, and evaporated to dryness *in vacuo* to give 11.4 g of product as a yellow solid. Recrystallization from methanol gave 8.25 g (72%) of product as white crystals, mp 139–141°. The analytical sample was recrystallized from methanol: mp 142.5–143.5°; $[\alpha]^{23}D$ −55° (*c* 0.50, chloroform); λ_{max}^{Nujol} 3.0 (NH), 5.95 (C=O), 6.50 μ (secondary amide).

Anal. Calcd for $C_{10}H_{19}NO_{10}S_2$: C, 31.8; H, 5.03; N, 3.72. Found: C, 31.9; H, 5.04; N, 3.47.

Methyl 3-Amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-Cyclic Urethan (7).—A mixture of 6.75 g of methyl 3-deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside (6) and 6.75 g of sodium fluoride was dried *in vacuo* at 63°, heated with stirring under nitrogen in 125 ml of dry DMF at 130° for 24 hr, and evaporated to dryness *in vacuo*. The residue was partitioned between chloroform and water. The chloroform layer was dried and evaporated to dryness to give 4.0 g of product as an oil. Trituration with 10 ml of ethyl acetate gave 1.10 g of crystalline product, mp 122–125°. Chromatography of the mother liquors on silica gel using ethyl acetate as the eluant gave an additional 1.65 g of crystalline product, mp 125–126°, for a total yield of 58%. The analytical sample was recrystallized from ethyl acetate: mp 128.5–129.5°; $[\alpha]^{23}D$ −12° (*c* 0.36, water); λ_{max}^{Nujol} 3.0 (NH), 5.70 μ (C=O).

Anal. Calcd for $C_8H_{13}NO_7S$: C, 36.0; H, 4.87; N, 5.25. Found: C, 36.1; H, 5.03; N, 5.38.

Methyl 3-Amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-Cyclic Urethan (8).—A mixture of 1.08 g of methyl 3-amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-cyclic urethan (7) and 1.10 g of sodium azide were suspended in 50 ml of benzene, the benzene was distilled to dryness, 50 ml of dry DMF was added, and the reaction was heated at 140° for 18 hr under nitrogen. The reaction mixture was evaporated to dryness *in vacuo* and the residue was triturated several times with boiling ether. The ether was filtered and evaporated to dryness to give 0.870 g (100%) of white solid which was satisfactory for the next reaction. The analytical sample was obtained by recrystallization from water: mp 108–109°; $[\alpha]^{23}D$ 14° (*c* 0.48, water); λ_{max}^{Nujol} 3.05, 3.15 (NH), 4.70 (N_3), 5.60, 5.80 μ (C=O).

Anal. Calcd for $C_7H_{10}N_4O_4$: C, 39.3; H, 4.68; N, 26.2. Found: C, 39.2; H, 4.71; N, 25.9.

Methyl 2,3-Diamino-2,3-dideoxy-α-L-ribopyranoside 3,4-Cyclic Urethan (9).—A solution of 230 mg of methyl 3-amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (8) which contained a suspension of 55 mg of 5% palladium on carbon was hydrogenated at atmospheric pressure and room temperature for 6 hr, and the catalyst was removed by filtration through a Celite pad. The filtrate was evaporated to dryness *in vacuo* to give 180 mg of solid which was free of azide in the infrared. The analytical sample was recrystallized from methanol: mp 143–144°; $[\alpha]^{22}D$ −39° (*c* 0.50, water); λ_{max}^{Nujol} 2.95–3.15 (NH, OH), 5.70 (C=O), 6.30 μ (NH_2).

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.6; H, 6.38; N, 14.9. Found: C, 44.6; H, 6.26; N, 15.1.

Methyl 2,3-Diamino-2,3-dideoxy-α-L-ribopyranoside (10).—To a solution of 57 mg of methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (9) in 2 ml of water was added 140 mg of barium hydroxide octahydrate. The mixture was heated at reflux for 2 hr, and a heavy white precipitate of barium carbonate began to separate after 0.5 hr. The reaction was cooled, the precipitate was removed by filtration, and carbon dioxide was bubbled through the filtrate to remove the excess barium ions. The precipitated barium carbonate was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was extracted with 20 ml of boiling chloroform. The chloroform was evaporated to dryness to give 46 mg of white solid, mp 148–150°. The analytical sample was recrystallized from chloroform: mp 145–151°; $[\alpha]^{22}D$ −3° (*c* 0.49, water); λ_{max}^{Nujol} 2.95–3.20 (OH, NH), 6.25 μ (NH_2).

Anal. Calcd for $C_6H_{14}N_2O_3$: C, 44.4; H, 8.66; N, 17.3. Found: C, 44.1; H, 8.94; N, 17.3.

2,3-Diamino-2,3-dideoxy-α-L-ribose (11) Dihydrochloride.—A solution of 100 mg of methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside (11) in 4 ml of 6 *N* hydrochloric acid was heated at 110° for 3 hr and evaporated to dryness *in vacuo* at 20°. Two small portions of water were added and lyophilized, and the residue was triturated with 2 ml of absolute ethanol to effect crystallization. The analytical sample was prepared by recrystallization from aqueous acetic acid to give white crystals with mp 175° (gas evolution); $[\alpha]^{17}D$ 113° → 70° (*c* 0.49, water).

Anal. Calcd for $C_5H_{12}N_2O_3 \cdot 2HCl$: C, 27.1; H, 6.33; N, 12.7; Cl^-, 32.1. Found: C, 27.0; H, 6.60; N, 12.6; Cl^-, 31.8.

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(16) Melting points are corrected. Thin layer chromatograms were run on silica gel HF (E. Merck AG, Darmstadt). Spots were detected by iodine vapor. Organic solutions were dried using anhydrous magnesium sulfate. Nmr spectra were recorded with either a Varian A-60 or HA-100 spectrometer, for solutions in chloroform-*d*, with tetramethylsilane (*c* 1.00) as the internal standard unless otherwise indicated.

Methyl 2,3-Diacetamido-2,3-dideoxy-α-L-ribopyranoside (12).—To a solution of 108 mg of methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside (**10**) in 1 ml of water was added 0.5 ml of acetic anhydride. The mixture was stirred for 5 min and evaporated to dryness *in vacuo* to give 148 mg of crude product as a white solid. Purification was carried out by trituration with two 1-ml portions of methanol to give 109 mg of white solid, mp >275°, which was homogeneous on tlc with R_f 0.2 using ethyl acetate–methanol (9:1); λ_{max}^{Nujol} 2.83–3.2 (NH), 6.05, 6.15 (C=O), 6.35–6.45 μ (secondary amide).

Anal. Calcd for $C_{10}H_{18}N_2O_5 \cdot 1/3\ H_2O$: C, 47.7; H, 7.40; N, 11.1. Found: C, 47.5; H, 7.23; N, 10.9.

Ethylthio 2,3-Diacetamido-2,3-dideoxy-L-riboside (14).—A solution of 100 mg of 12 in 1.5 ml of concentrated hydrochloric acid and 1.5 ml of ethanethiol was stirred at 0–5° for 20 hr and neutralized with ammonia. The aqueous solution was extracted with chloroform and the aqueous phase was evaporated to dryness *in vacuo*. The dry residue was extracted with several 2–3 ml portions of chloroform. The chloroform extracts were evaporated to dryness *in vacuo* and the solid residue was recrystallized from methanol–ether to give 12 mg of product as a white solid: mp 275° dec; λ_{max}^{Nujol} 3.0 (NH), 6.05 (C=O), 6.5 μ (secondary amide). The nmr spectrum in D_2O showed one ethyl group and two N-acetates.

Anal. Calcd for $C_{11}H_{20}N_2O_4S \cdot {}^3/_4H_2O$: C, 45.6; H, 7.43; N, 9.70. Found: C, 45.9; H, 7.20; N, 9.52.

Registry No.—**4**, 20453-03-6; **5**, 20452-98-6; **6**, 20452-99-7; **7**, 20453-00-3; **8**, 20453-04-7; **9**, 20453-05-8; **10**, 20452-95-3; **11** (2HCl), 20452-96-4; **12**, 20452-97-5; **14**, 20453-06-9.

The Condensation of Glyoxylic Acid with 5α-Androstanolone

MANUEL DEBONO, R. MICHAEL MOLLOY, AND L. E. PATTERSON

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

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The condensation of 5α-androstanolone with glyoxylic acid gave steroids with an α-hydroxyacetic acid side chain at C-2. This side chain then reacts further with the C-3 carbonyl group to give ring-A-fused lactols. The chemistry of these lactols was studied, and the lactols were used to synthesize the novel ring-A-fused pyridazone **6**. When the condensation reaction was carried out in refluxing methanol, the C-2 *trans*-ylidene acetic acid derivative was isolated. The chemistry of these acids was studied, and their derivatives were used for synthesis of ring-A-fused γ-lactones.

Recent interest in the synthesis of ring-A-fused heterocyclic steroids has been prompted by the discovery of the unique biological properties of the steroidal pyrazoles.[1]

The goal of the present study was the synthesis of a 3-keto steroidal intermediate bearing a two-carbon side chain at C-2. This could be subsequently converted to fused steroidal heterocyclic systems possessing six-membered rings bearing two heteroatoms or five-membered rings bearing one heteroatom. This synthesis was accomplished by a modification of the procedure outlined by Newman, *et al.*, and also by Kurath and Cole, for the synthesis of 17-keto-16-*trans*-ylidene acetic acid steroids.[2] Condensation of 5α-androstanolone with glyoxylic acid in aqueous methanol and sodium hydroxide at room temperature gave hydroxyketo acid **1**, which could readily be lactolized to give the methoxylactol **2** when treated with methanolic HCl (Scheme I). An analogous condensation has recently been employed by Pettit[3] for synthesis of the isocardenolide side chain from 20-keto steroids.

The structure of **2** was deduced from its infrared spectrum[4] (1760 cm^{-1}) and from the properties of its diacetoxy derivative (**3**) obtained by refluxing **2** with acetic anhydride containing sodium acetate. The infrared spectrum showed that the lactol carbonyl group was unaltered by these acetylation conditions. Since no enol lactonization was observed under these conditions, it was concluded that the methoxyl group was at C-3 rather than on the side chain.[5] The position of the C-2′ hydroxyl group was confirmed by the observation that the doublet in the nmr of **2** at δ 4.85 shifted to δ 5.85 upon acetylation. The nmr spectrum of **3** (see Figure 1) showed two acetoxy groups as singlets at δ 2.06 and 2.16; the C-2 proton was observed as a quintet at δ 2.74 (J = 5 Hz). The proton at C-2′ was observed as a doublet at δ 5.83 (J = 5 Hz), and the methoxyl group and 17α proton gave signals at δ 3.37 and 4.62, respectively.

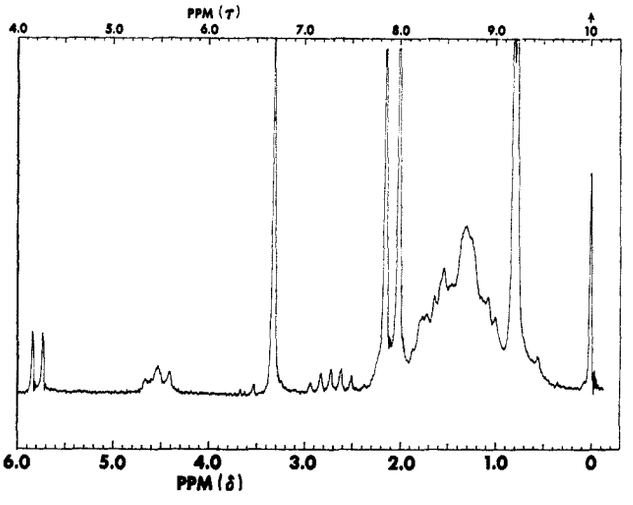

Figure 1.—Nuclear magnetic resonance spectrum of lactol diacetate **3**.

The stereochemistry of ring fusion of the lactol to ring A and its orientation can be deduced from the nmr spectrum of **3** and through the use of conformational analysis. It is well established that γ-lactones prefer a

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