Anal. Calcd. for $C_{20}H_{26}O$: C, 85.1; H, 9.3. Found: C, 85.4; H, 9.1.

2-(2,6-Diisopropylphenoxy)ethyl chloride. A solution of 53.5 g. (0.3 mole) of 2,6-diisopropylphenol in 300 ml. of toluene was added dropwise to a stirred suspension of 7.1 g. (0.3 mole) of sodium hydride in 150 ml. of toluene. The mixture was then stirred at reflux for one hour. To this thick suspension was added in five portions 70.7 g. (0.31 mole) of β-chloroethyl-*p*-toluenesulfonate. After refluxing overnight, the reaction mixture was treated while hot with 25 ml. of 20% sodium hydroxide, and when cool, with 200 ml. of water. The toluene layer was separated, dried, and distilled. A fraction boiling at 130–140° at 8 mm. appeared to be essentially the desired product: 18.7 g. (26% yield) was obtained, n_D^{25} 1.5070. A considerable amount of DIP was recovered as forerun.

Anal. Calcd. for $C_{14}H_{21}ClO$: C, 69.8; H, 8.8. Found: C, 70.1; H, 8.8.

3,3',5,5'-Tetraisopropyldiphenoquinone (II). To a stirred solution of 220 g. (1.23 moles) of 2,6-diisopropylphenol in 450 ml. of benzene and 320 ml. of glacial acetic acid, held at 0–5°, was added dropwise 90 ml. of concentrated nitric acid. Some brown fumes were evolved during the addition and appeared to have ceased at the end. After standing overnight at room temperature, the reaction mixture was poured into one liter of water, shaken well, and the aqueous layer discarded. The benzene layer was extracted in turn with 10% urea solution and saturated sodium bicarbonate solution. Evaporation of the solvent from the dried benzene solution left a semisolid residue, which on trituration with 250 ml. of cold methanol gave 55.1 g. of purplish red solid, m.p. 185–198°. Three recrystallizations from isopropyl alcohol gave material melting at 199–203°: red plates with a purple luster (lit.[1] m.p. 196–198°).

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SYRACUSE 1, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Synthesis of Amino Compounds in the Sugar Series by Phenylhydrazone Reduction[1,2]

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It has been shown that the reduction of the phenylhydrazone function provides a convenient method for the synthesis of a variety of amino compounds in the sugar series. These include: the 1-amino-1-deoxy derivatives of D-arabinitol, D-galactitol, D-glucitol, D-gulitol, and D-xylitol; the diaminodideoxyalditols 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol, 1,4-diamino-1,4-dideoxy-D-threitol, 1,2-diamino-1,2-dideoxy-D-glucitol, and 1,2-diamino-1,2-dideoxy-D-mannitol; and 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose. All of these compounds have been isolated as crystalline salicylaldehyde Schiff bases and some of them have been further characterized as their hydrobromide and *N*-(2,4-dinitrophenyl) derivatives.

Reduction of the condensation products of carbohydrates with nitrogen bases provides a general route for the synthesis of a variety of amino sugars. Thus, many of the 1-amino-1-deoxyalditols have been prepared through the sodium amalgam reduction of the corresponding oximes.[3] These compounds can also be prepared by the reduction of the aldoses in the presence of ammonia[4,5] or by the hydrogenation of glycosylamines[6] and of 1-deoxy-1-benzylaminoalditols.[5] Other methods are based on the reduction of the aldonamides with lithium aluminum hydride[7] and the reduction of hydrazine derivatives. The latter method was employed by Fischer and Groh[8] for converting the phenylhydrazones of certain keto acids to the corresponding amino acids, a process which has been employed for the identification and estimation of the keto acids in plant products.[9] Emil Fischer also prepared (as the acetate salt) 1-amino-1-deoxy-D-fructose, "isoglucosamine," by the reduction of D-glucose phenylosazone with zinc and acetic acid.[10] Maurer and Schiedt[11] increased the yield in this reaction to 60% through employment of catalytic

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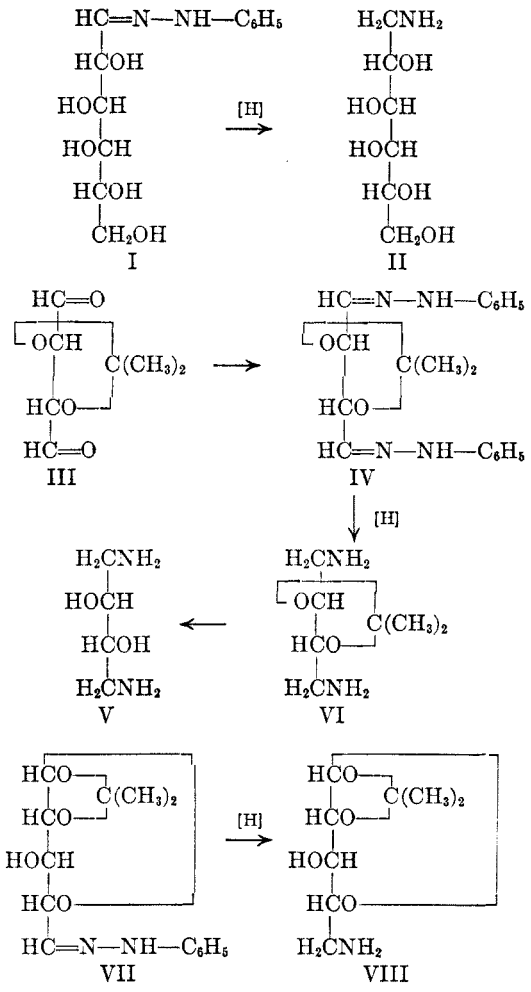
hydrogenation with a palladium catalyst in acetic acid.

The carbohydrate hydrazone derivatives provide a class of readily available and often highly crystalline compounds. Thus, their reduction should be of interest. Despite this, applications in carbohydrate chemistry[12,13] have been sporadic. We have found that this reaction provides a convenient method for the synthesis of a variety of amino sugar derivatives, some of which have been prepared for the first time.

The catalytic reduction of the aldose hydrazone derivatives with Raney nickel proceeds under mild conditions and provides a good yield of the expected 1-amino-1-deoxyalditol. Thus, the reduction of a hot concentrated solution of D-galactose phenylhydrazone, which is known to exist in the acyclic form (I)[14,15] in the Parr hydrogenation apparatus provides 1-amino-1-deoxy-D-galactitol (II) and presumably aniline, which can be extracted from the aqueous solution with benzene. We have isolated the product, 1-amino-1-deoxy-D-galactitol, as a crystalline hydrobromide salt, salicylaldehyde Schiff base, and *N*-(2,4-dinitrophenyl) derivative. 1-Deoxy-1-salicylideneamino-D-galactitol[2] is a useful intermediate for the isolation of the amino alditol. This compound has recently been recorded by Kagan and associates.[5] The amino alditol can also be isolated from the reaction mixture as the hydrochloride or hydrobromide salt. However, the salt obtained through this method is contaminated with an unknown impurity which can be separated by fractional crystallization. The physical constants and properties of this material are in agreement with those reported for the substance designated "didulcitylamine" by Kagan and co-workers.[5]

Derivatives of 1-amino-1-deoxy-D-arabinitol, 1-amino-1-deoxy-D-gulitol, (6-amino-6-deoxy-L-glucitol), 1-amino-1-deoxy-D-glucitol, and 1-amino-1-deoxy-D-xylitol have been similarly prepared through the catalytic reduction of the corresponding phenylhydrazones. The above reaction has been extended to the phenylhydrazone derivatives prepared from the product of glycol cleavage of some carbohydrate acetals. Thus, 2,3-*O*-isopropylidene-*dialdehydo*-D-*threo*-tetrodiose (III), first prepared by the lead tetraacetate oxidation of 3,4-*O*-isopropylidene-D-mannitol[16] and later by the periodate oxidation of 3,4-*O*-isopropylidene-D-glucitol,[17] has been converted to the bis(phenylhydrazone) derivative[16] (IV) and subsequently hydrogenated. The product, 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol (VI) has been isolated as a crystalline dipicrate salt and bis(salicylaldehyde Schiff base). Acid hydrolysis of the isopropylidene group gave 1,4-diamino-1,4-dideoxy-D-threitol (V), isolated as the crystalline bis(salicylaldehyde Schiff base). In similar manner, the phenylhydrazone derivative of 1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodiofuranose (VII), produced by lead tetraacetate[18] or periodate[19,20] oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose, was converted to 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (VIII). This product was isolated as the crystalline hydrobromide salt and salicylaldehyde Schiff base. Since our first report on this subject,[2] the isolation of the above compound, as the free base and *p*-toluenesulfonate salt, has been recorded by other investigators.[21] The hydrobromide and hydrochloride salts of the above compound are unstable and grad-



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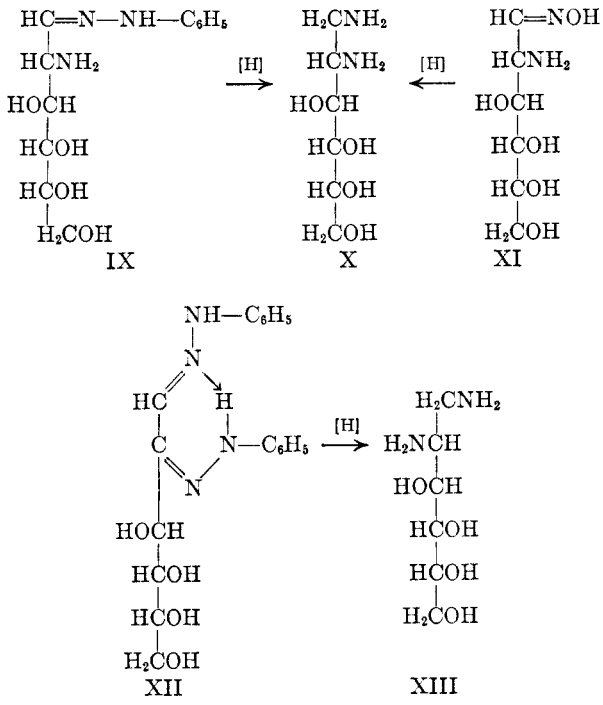
ually decompose with the evolution of acetone. Attempts to prepare the free 5-amino-5-deoxy-D-xylose by the acid hydrolysis of the above compound led to the extensive decomposition with the formation of a product resembling the "browning" polymers formed in the Maillard reaction.[22]

The reduction of the phenylhydrazine derivatives of carbohydrates has been herein extended to the synthesis of 1,2-diamino-1,2-dideoxyalditols which constitute a unique class of carbohydrate derivatives. Thus, 2-amino-2-deoxy-D-glucose hydrochloride was treated with phenylhydrazine and the reaction mixture, containing 2-amino-2-deoxy-D-glucose phenylhydrazone (IX), was hydrogenated with Raney nickel catalyst. The reduction product was isolated, in low yield, as the crystalline bis-(salicylaldehyde Schiff base), identical with the product (X) obtained by the hydrogenation of 2-amino-2-deoxy-D-glucose oxime (hydrochloride)[23] (XI) with palladium-charcoal catalyst. This demonstrates that X bears the D-glucose structure. An isomeric substance (XIII) was obtained, in low yield, by the reduction of D-*arabino*-hexose phenylosazone ("glucosazone"; XII) with palladium-charcoal catalyst, in the presence of hydrochloric acid. This compound must therefore possess the D-mannose configuration.

It has been noted that the reduction of D-*arabino*-hexose phenylosazone, in the presence of acetic acid according to Emil Fischer[10] and Maurer and Schiedt,[11] results in the formation of 1-amino-1-deoxy-D-fructose. This is in contrast with the properties of acetophenone ketazine, $C_6H_5(CH_3)C{=}N{-}N{=}C(CH_3)C_6H_5$, which on catalytic hydrogenation gives 1,2-bis(α-methylbenzyl)hydrazine, $C_6H_5(CH_3)CHNHNHCH(CH_3)C_6H_5$, without cleavage, and with benzil phenylosazone which remains unchanged.[13] Kuhn and Kirschenlohr[24] have isolated the *N*-acetyl derivatives of 2-amino-2-deoxylactose and 1-amino-1-deoxylactulose by chromatographic separation of the mixture obtained from the catalytic reduction of lactose phenylosazone in the presence of acetic acid. According to these authors,[24] the acidic conditions cause one of the phenylhydrazone functions to be hydrolyzed and subsequent reduction gives a mixture of 2-amino-2-deoxyaldose and 1-amino-1-deoxyketose, in which the latter product predominates. These considerations reflect the complexity of the reduction products of D-*arabino*-hexose phenylosazone (XII) which is stabilized in the acyclic structure[25,26] by the formation of a chelate ring,[26,27] and may provide an explanation for the low yield of 1,2-diamino-1,2-dideoxy-D-mannitol.



EXPERIMENTAL

*1-Deoxy-1-salicylideneamino-*D*-galactitol.* D-Galactose phenylhydrazone[28] (15 g.) was dissolved in 150 ml. of hot water and hydrogenated in the Parr apparatus at 3-atm. pressure for 17 hr., using Raney nickel catalyst. The reaction mixture was filtered and extracted with five 100-ml. portions of benzene. The aqueous solution containing 1-amino-1-deoxy-D-galactitol was then treated with 7 g. of salicylaldehyde and 5 g. of sodium bicarbonate. After shaking for 2 hr., the product, 1-deoxy-1-salicylideneamino-D-galactitol, was filtered and recrystallized from 50% aqueous ethanol; yield 12.1 g., m.p. 202°; no suitable solvent was found for the determination of optical rotation.

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.58; H, 6.86; N, 4.91.

*1-Amino-1-deoxy-*D*-galactitol hydrobromide.* A suspension of 1-deoxy-1-salicylideneamino-D-galactitol (10 g.) in 200 ml. of abs. ethanol was treated with 6 g. of 48% aqueous hydrogen bromide. The resulting colorless precipitate of 1-amino-1-deoxy-D-galactitol hydrobromide was filtered and recrystallized from hot aqueous methanol; yield 6.8 g., m.p. 136°, $[\alpha]_D^{20}$ −10.5° (*c* 4.59, water).

Anal. Calcd. for $C_6H_{16}BrNO_5$: C, 27.49; H, 6.15; Br, 30.49; N, 5.34. Found: C, 27.66; H, 6.25; Br, 30.21; N, 5.50.

This compound, as well as the hydrochloride salt, could be isolated directly from the benzene-extracted hydrogenation mixture described above, by concentration to a sirup and addition of methanolic hydrogen bromide or hydrogen chloride and repeated fractional crystallization from aqueous methanol. The less soluble fraction, which crystallized first, is a by-product which was obtained as the hydrochloride salt, after two more recrystallizations from the same solvent; m.p. 241–242° (the reported[5] m.p. of "didulcitylamine hydrochloride" is 240–241°).

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Anal. Calcd. for $C_{12}H_{28}ClNO_{10}$: C, 37.75; H, 7.39; N, 3.67. Found: C, 36.92; H, 7.04; N, 3.67.

1-Deoxy-1-(2,4-dinitroanilino)-D-galactitol. A solution of 150 mg. of 1-amino-1-deoxy-D-galactitol hydrobromide in 3 ml. of water was treated with 140 mg. of 2,4-dinitrofluorobenzene and 300 mg. of sodium bicarbonate. The reaction mixture was heated briefly at 100° with continuous stirring. After cooling, the orange colored precipitate of 1-deoxy-1-(2,4-dinitroanilino)-D-galactitol was filtered and recrystallized from aqueous methanol; yield 138 mg., m.p. 195–196°.

Anal. Calcd. for $C_{12}H_{17}N_3O_9$: C, 41.49; H, 4.89; N, 12.1. Found: C, 41.43; H, 4.85; N, 11.98.

1-Deoxy-1-salicylideneamino-D-gulitol. D-Gulose phenylhydrazone[29] (3 g.) was dissolved in 90 ml. of water and hydrogenated as described above for D-galactose phenylhydrazone. The resultant aqueous solution of 1-amino-1-deoxy-D-gulitol was treated with 1.3 g. of salicylaldehyde and 3 g. of sodium bicarbonate. Evaporation of the reaction mixture gave 1-amino-1-deoxy-D-gulitol salicylaldehyde Schiff base as a sirup which crystallized on standing. The product was filtered, washed with small amounts of water and ether, and recrystallized from ethanol; yield 1.58 g., m.p. 157.5–158°, $[\alpha]_D^{20}$ −11.5° (*c* 2.24, *N,N*-dimethylformamide).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.69; H, 6.74; N, 4.88.

1-Amino-1-deoxy-D-arabinitol hydrobromide, salicylaldehyde Schiff base and N-2,4-dinitrophenyl derivative. D-Arabinose phenylhydrazone[30] (10 g.) was hydrogenated as described above and the product was converted to 1-amino-1-deoxy-D-arabinitol salicylaldehyde Schiff base; yield 5.5 g., m.p. 184–185°, $[\alpha]_D^{20}$ +25° (*c* 2.24, *N,N*-dimethylformamide).

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.26; H, 6.52; N, 5.56.

A suspension of 2 g. of 1-amino-1-deoxy-D-arabinitol salicylaldehyde Schiff base in 50 ml. of methanol, on treatment with 1.6 g. of 48% aqueous hydrogen bromide, gave a colorless solution containing 1-amino-1-deoxy-D-arabinitol hydrobromide. This product was precipitated by the gradual addition of ether and was recrystallized from 95% ethanol; yield 0.75 g., m.p. 166–167°, $[\alpha]_D^{20}$ +11° (*c* 4.14, water).

Anal. Calcd. for $C_5H_{14}BrNO_4$: C, 25.58; H, 6.08; Br, 34.43; N, 6.03. Found: C, 26.12; H, 5.84; Br, 34.56; N, 5.80.

The above product was converted to 1-deoxy-1-(2,4-dinitroanilino)-D-arabinitol, m.p. 174–175°.

Anal. Calcd. for $C_{11}H_{15}N_3O_8$: C, 41.64; H, 4.77; N, 13.25. Found: C, 41.52; H, 5.35; N, 13.07.

1-Deoxy-1-salicylideneamino-D-glucitol. This compound (3.8 g.) was prepared from the reduction product of 8 g. of D-glucose phenylhydrazone (α-form),[28] m.p. 177–177.5°, $[\alpha]_D^{23}$ −20° (*c* 2.58, *N,N*-dimethylformamide).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.86; H, 6.55; N, 4.86.

1-Amino-1-deoxy-D-xylitol salicylaldehyde Schiff base and hydrobromide. The Schiff base (14.5 g.) was prepared from the reduction product of 20 g. of D-xylose phenylhydrazone;[31] m.p. 128–129°, $[\alpha]_D^{23}$ −20° (*c* 2.79, *N,N*-dimethylformamide) Kagan and co-workers,[5] quote the m.p. 131–133°.

The above compound (12 g.) was converted to 1-amino-1-deoxy-D-xylitol hydrobromide (9.2 g.), m.p. 167–168°, $[\alpha]_D^{23}$ −13° (*c* 4.33, water).

Anal. Calcd. for $C_5H_{14}BrNO_4$: C, 25.58; H, 6.08; N, 6.03. Found: C, 25.85; H, 5.93; N, 6.14.

1,4-Diamino-1,4-dideoxy-2,3-O-isopropylidene-D-threitol dipicrate. 2,3-*O*-Isopropylidene-*dialdehydo*-D-*threo*-tetrodiose bis(phenylhydrazone)[16,17] (664 mg.) was dissolved in 67% aqueous ethanol and hydrogenated with freshly prepared Raney nickel catalyst at atmospheric pressure for 18 hr. The reaction mixture was then filtered and the filtrate was evaporated under reduced pressure. Treatment of the residue with a hot concentrated solution of 910 mg. of picric acid in ethanol gave 870 mg. of 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol dipicrate, which was purified by several recrystallizations from aqueous ethanol and from water; m.p. 217–218° (dec.).

Anal. Calcd. for $C_{19}H_{22}N_8O_{16}$: C, 36.90; H, 3.58; N, 18.12. Found: C, 36.99; H, 3.54; N, 18.72.

1,4-Dideoxy-2,3-O-isopropylidene-1,4-bis(salicylideneamino)-D-threitol. 1,4-Diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol dipicrate (100 mg.) was dissolved in 2 ml. of saturated sodium bicarbonate solution and sufficient water was added to keep the resulting sodium picrate in solution. The warmed reaction mixture was treated with 0.04 ml. of salicylaldehyde and the resulting precipitate of 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol bis(salicylaldehyde Schiff base) (55 mg.) was isolated after standing at 0° for 15 hr. The product was purified by several recrystallizations from aqueous methanol; m.p. 111°.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.61. Found: C, 68.48; H, 6.43; N, 8.11.

1,4-Dideoxy-1,4-bis(salicylideneamino)-D-threitol. 1,4-Diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol dipicrate (200 mg.) was suspended in 10 ml. of water containing one drop of concentrated hydrochloric acid and the mixture was heated for 2 hr. over the steam bath. It was then neutralized to *p*H 8 with sodium bicarbonate and sufficient water was added to keep the resulting sodium picrate in solution. The reaction mixture was then treated with 0.11 ml. of salicylaldehyde, heated briefly, and allowed to stand at 0° for 18 hr. The resulting precipitate of 1,4-diamino-1,4-dideoxy-D-threitol bis(salicylaldehyde Schiff base) (100 mg.) was recrystallized from 18 ml. of methanol; m.p. 228–231° (dec.). This compound was poorly soluble in most of the organic solvents and in water.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.70; H, 6.18; N, 8.46.

5-Amino-5-deoxy-O-isopropylidene-α-D-xylofuranose hydrobromide, hydrochloride, and salicylaldehyde Schiff base. 1,2-*O*-Isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodiofuranose phenylhydrazone[18] (4.5 g.) was suspended in 200 ml. of water and hydrogenated in the Parr apparatus at 3-atm. pressure, using Raney nickel as catalyst. After 17 hr., the reaction mixture was filtered and extracted with benzene as before. Evaporation of the aqueous layer furnished 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose as a thick sirup. This was dissolved in ethanol and neutralized with hydrogen chloride to *p*H 4.5. The resultant hydrochloride was precipitated by the addition of ether and was recrystallized from aqueous ethanol; yield 1.68 g., m.p. 130° dec., $[\alpha]_D^{20}$ −12° (*c* 3.2, water).

Anal. Calcd. for $C_8H_{16}ClNO_5$: C, 42.6; H, 7.09; N, 6.2. Found: C, 42.07; H, 7.71; N, 6.33.

The hydrobromide salt was prepared in like manner; m.p. 170° (dec.).

Anal. Calcd. for $C_8H_{16}BrNO_4$: C, 35.55; H, 5.90; N, 5.2. Found: C, 35.60; H, 5.54; N, 5.09.

Both of the above salts were unstable and decomposed gradually with the evolution of acetone.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose on treatment with salicylaldehyde furnished a crystalline Schiff base; m.p. 155°.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.48; N, 4.77. Found: C, 61.40; H, 6.45; N, 4.78.

Attempted isolation of the free 5-amino-5-deoxy-D-xylose through the acid hydrolysis of the isopropylidene group was unsuccessful and resulted in rapid browning of the reaction mixture and the formation of a gummy dark brown product.

1,2-Dideoxy-1,2-bis(salicylideneamino)-D-glucitol. A solution of 5 g. of 2-amino-2-deoxy-α-D-glucose (α-D-glucosamine) hydrochloride, 2.5 g. of phenylhydrazine, and 0.5 ml. of acetic acid in 2.0 ml. of water was heated with stirring until the initial formation of D-glucose phenylosazone. The reaction mixture was then cooled and filtered from the small precipitate of D-glucose phenylosazone, and the filtrate was

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hydrogenated in the Parr apparatus at 3-atm. pressure, using Raney nickel as catalyst. After 18 hr., the reaction mixture was filtered and extracted with benzene in the manner described above. The aqueous solution containing the 1,2-diamino-1,2-dideoxy-D-glucitol was treated with 2 g. of sodium bicarbonate and 4.68 g. of salicylaldehyde and the mixture was heated over the steam bath, with stirring, for 3 hr. The product, 1,2-diamino-1,2-dideoxy-D-glucitol bis(salicylaldehyde Schiff base), was recrystallized from 95% ethanol; yield 2.34 g., m.p. 208–208.5°, $[\alpha]_D^{20}$ −83° (*c* 4.04, *N*,*N*-dimethylformamide), x-ray powder diffraction data:[32] 15.17w, 11.87m, 8.04w, 5.93m, 5.55vw, 5.15s(3), 4.90vs(1,1), 4.62s, 4.47s, 4.14vs(1,1), 3.85vw, 3.71vw, 3.53vw, 2.72 vw.

Anal. Calcd. for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.65; H, 6.01; N, 7.00.

2-Amino-2-deoxy-D-glucose oxime hydrochloride[23] (11.5 g.) was dissolved in 200 ml. of 75% ethanol and the solution was hydrogenated as in the above experiment, but with palladium-charcoal catalyst. The reaction mixture was then evaporated under reduced pressure and a portion of the product (10%) was converted to 1,2-dideoxy-1,2-bis(salicylideneamino)-D-glucitol. This compound had the same x-ray powder diffraction pattern and physical properties as the product synthesized above from 2-amino-2-deoxy-D-glucose phenylhydrazone.

1,2-Dideoxy-1,2-bis(salicylideneamino)-D-mannitol. D-*arabino*-Hexose phenylosazone (3.6 g., 10 millimoles) was dissolved in 100 ml. of 95% ethanol containing 40 millimoles of hydrogen chloride and the solution was hydrogenated in the Parr apparatus at 3-atm. pressure, using palladium-charcoal as catalyst. The reaction mixture was filtered and the filtrate was concentrated to 25 ml., diluted with 100 ml. of water, neutralized with sodium bicarbonate, and extracted with four 100-ml. portions of benzene. The aqueous solution of the reduction product was treated with 4 g. of sodium bicarbonate and 1 ml. of salicylaldehyde and heated over the steam bath with stirring for 2 hr. The resulting yellow precipitate of 1,2-diamino-1,2-dideoxy-D-mannitol bis(salicylaldehyde Schiff base) was purified by three recrystallizations from 95% ethanol; yield 0.15 g., m.p. 223–224°, $[\alpha]_D^{23}$ +54.2° (*c* 2.15, *N*,*N*-dimethylformamide), x-ray powder diffraction data:[32] 14.98w, 11.33m, 8.67m, 6.71w, 5.40m, 5.10vs(1), 4.80m, 4.60vs(2), 4.31vw, 4.00s(3), 3.73vw, 3.48vw, 3.29vw, 3.14w.

Anal. Calcd. for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 62.02; H, 6.46; N, 7.17.

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(32) Interplanar spacing, Å, CuK_α radiation. Relative intensity, estimated visually; s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

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Synthesis of β-(4-Pyridyl)-DL-alanine and of β-(4-Pyridyl-1-oxide)-DL-, D-, and L-alanine[1]

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A practical synthesis of β-(4-pyridyl)-DL-alanine, suitable for application on a gram scale, has been developed. β-(4-Pyridyl-1-oxide)-DL-alanine has been prepared in good yield, by a procedure capable of being employed on a much larger scale, and a satisfactory resolution of *N*-benzoyl-β-(4-pyridyl-1-oxide)-DL-alanine has been achieved.

Two methods have been reported for the synthesis of β-(4-pyridyl)-DL-alanine. The first[3] was based upon the sequence, 4-pyridylcarbinol→4-pyridylmethyl bromide→diethyl benzamido-(4-pyridylmethyl)malonate→β-(4-pyridyl)-DL-alanine and the second[4] upon the sequence, 4-picoline→ethyl α-oximino-β-(4-pyridyl)propionate→α-oximino-β-(4-pyridyl)propionic acid→β-(4-pyridyl)-DL-alanine. Both syntheses involved a step in which poor yields were obtained. The malonic ester condensation gave but a 4% yield, and the Claisen condensation a 12% yield. It was decided to study the malonic ester condensation with the aim of improving the yield.

The starting material for the malonic ester condensation, 4-pyridylmethyl bromide hydrobromide, was obtained in 85% yield from 4-pyridylcarbinol. This hydrobromide, and its parent amine, are severe vesicants.

The principal competing side reaction in the malonic ester condensation is the polymeric quaternization of 4-pyridylmethyl bromide. This quaternization has been studied by Sorm and Sedivy,[5] who also observed that 2-pyridylmethyl bromide quaternized at a slower rate. The quaternization of 4-bromopyridine is much faster than that of 2-bromopyridine,[6] the difference in rate being attributed to steric effects.[7] Presumably the same effects are operative in the case of 2- and 4-pyridylmethyl bromide. Examination of various modifi-

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