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The Preparation of Glycamines[1]

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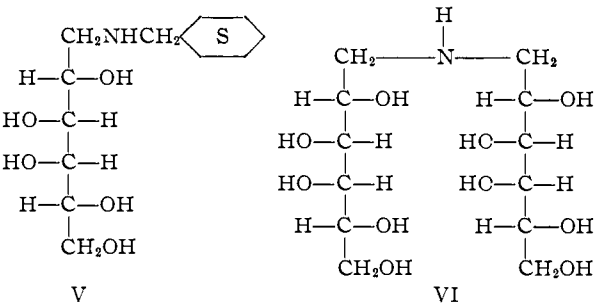
Large quantities of pure glycamines were conveniently prepared by the reductive alkylation of ammonia or by the hydrogenolysis of N-benzylglycamines. To ensure high quality products, purification of the glycamines from either process should be carried out through their Schiff bases.

Although 1-amino-1-deoxy sugars, the glycamines, have been known for over fifty years, a good preparative method which is practical for the synthesis of large quantities of high purity material is not available. The need for large quantities of galactamine of greater than 95% purity as a resolving agent in a synthesis of pantothenic acid[2] prompted us to reinvestigate the preparation of this class of compounds.

Glycamines previously have been prepared by the chemical reduction of sugar oximes,[3-5] by electrolytic, chemical and catalytic reduction of glycosylamines[6] and by the reductive alkylation of ammonia with a sugar.[6-8] The chemical and electrolytic reduction methods were of little interest because they were not readily adaptable to large-scale operations. The Flint and Salzburg[7] method yielded impure sirups unsuitable for our purposes. Wayne and Adkins[8] prepared glucamine in low yield by the reduction of glucose in methanolic ammonia. Holly and co-workers[9] synthesized glycamines of approximately 80% purity by the reductive alkylation of liquid ammonia with sugars. None of these methods was suitable for the large-scale production of pure sugar amines.

One route to glycamines which we investigated involved the hydrogenolysis of an N-benzylglycamine. For example, N-benzylgalactamine (III), prepared in 64% yield by the reductive alkylation of benzylamine with galactose, gave galactamine (IV) in 77% yield when hydrogenolyzed in the presence of palladium-on-charcoal. An attempt to simplify the process by carrying out the two hydrogenations consecutively in the same vessel without isolating the intermediate N-benzylgalactamine yielded an impure product, a major constituent of which proved to be cyclohexylmethylgalactamine (V). Structure assignment was made on the basis of elementary analysis (6 more hydrogens than N-benzylgalactamine), the absence of characteristic phenyl absorption in the ultraviolet and by the neutral equivalent. One attempt to carry out the reductive alkylation and hydrogenolysis steps simultaneously in the presence of a mixed catalyst (platinum and palladium-on-charcoal) yielded another new sugar amine, didulcitylamine (VI). The structure VI has been assigned tentatively to the product on the basis of the elementary analyses of both the free base and the hydrochloride and on the basis of the neutral equivalent.



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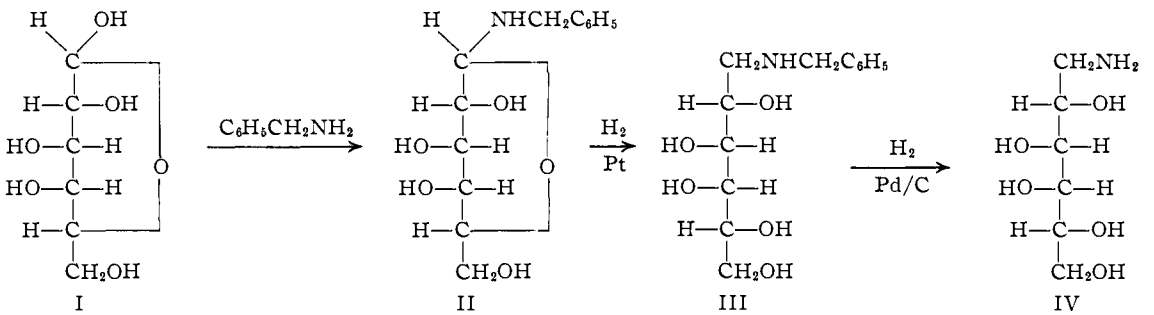

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In several experiments, the glycamines obtained by the hydrogenolysis procedure were difficult to purify. It seems likely that didulcitylamine and cyclohexylmethylgalactamine, were the main contaminants. To ensure a high quality product, it is recommended that the crude hydrogenolysis mixture be purified through either the benzylidene or salicylidene derivative as described below.

Although the hydrogenolysis of an N-benzylglycamine was a satisfactory low pressure laboratory procedure for the preparation of glycamines, cata-

(1) Presented in part before the 129th Meeting of The American Chemical Society, Dallas, Texas, April, 1956.

(2) F. Kagan, R. V. Heinzelman, D. I. Weisblat and W. Greiner, THIS JOURNAL, **79**, 3545 (1957).

(3) L. Maquenne and E. Roux, *Compt. rend.*, **132**, 980 (1901).

(4) E. Roux, *ibid.*, **135**, 691 (1902).

(5) C. Neuberg and F. Marx, *Biochem. Z.*, **3**, 539 (1907).

(6) A. R. Ling and D. R. Nanji, *J. Chem. Soc.*, 1682 (1922).

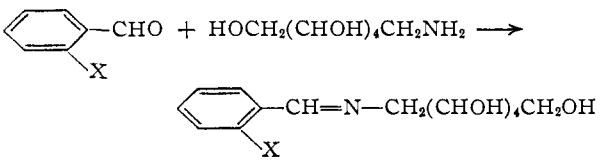
(7) R. B. Flint and P. L. Salzburg, U. S. Patent 2,016,962, Oct. 8, 1935; *C. A.*, **29**, 8007 (1935).

(8) W. Wayne and H. Adkins, THIS JOURNAL, **62**, 3314 (1940).

(9) F. W. Holly, E. W. Peel, R. Mozingo and K. Folkers, *ibid.*, **72**, 5416 (1950).

lyst costs and the multiplicity of steps made it unattractive for large-scale preparative work.

Roux[2] has reported the preparation of benzylideneglucamine and its hydrolysis by steam distillation. He suggested that this procedure could be used for the purification of glucamine; however, no experimental details were given. Wayne and Adkins[3] prepared benzylideneglucamine by heating glucamine with benzaldehyde at 180–190° They obtained a dark reaction mixture from which the benzylidene derivative was isolated by fractional crystallization. The low over-all yield of glucamine in this case may have been due in part to the vigorous conditions used in the isolation of the product. These investigators stated that in their opinion the difficulty in obtaining glucamine was not in the hydrogenation stage but in the isolation of the compound. We found that crude glycamines could be converted to aromatic Schiff bases easily at room temperature in aqueous solution. The Schiff bases separated in excellent yield leaving water-soluble sugar derivatives in solution. A variety of aldehydes were used for Schiff base formation, the best



being salicylaldehyde, benzaldehyde, cinnamaldehyde, furfural, 2-hydroxy-3-methoxybenzaldehyde and anisaldehyde. Vanillin and 2,4-dihydroxybenzaldehyde condensed sluggishly with galactamine and yielded only small amounts of Schiff bases. The ease of hydrolysis of the Schiff bases depended to a great extent upon the nature of the substituent X. When X was hydrogen, the benzylidene derivative was hydrolyzed easily by steam distillation; however, when X was hydroxyl, mineral acid was required to effect hydrolysis. Therefore, it was necessary to include an ion exchange step in the salicylidene method of purification to convert galactamine salts to the free base.

The utilization of the Schiff-base purification procedure to isolate the product from the complex reaction mixture obtained from the reductive alkylation of ammonia by a sugar enabled us to isolate good yields of high purity galactamine. In addition to galactamine, dulcitol (VIII) was isolated in up to 12% yield by ion exchange treatment of crude reaction mixtures. It is of interest that even in the presence of a large excess of liquid ammonia a significant portion of the original sugar remained in the aldehyde form and was reduced to dulcitol during the hydrogenation. Didulcitylamine (VI) was also isolated; however, the yields were generally less than 10% when liquid ammonia was used as solvent during the hydrogenation. When concentrated aqueous ammonia was used as solvent, the yield of VI was variable, being as high as 20% in one case. Compound VII, 1,2-dideoxydiaminodulcitol was not isolated as such; however, its presence in some of our products was inferred from potentiometric titration data. In addition to the inflections for galactamine (pK_a' in water, 9.4) and didulcitylamine (pK_a' in water, 8.9), a basic group (in small amounts) with a pK_a' of 5.9 was identified. The pK_a' of this group is typical of what one would expect from the neutralization of the second amino group in VIII; however, in addition to the titration behavior, we have further justification for assigning the vicinal diamine structure to VII. Careful purification of the salicylidenegalactamine obtained from crude hydrogenation mixtures yielded a salicylidene derivative, m.p. 126–128°, in very low yield (<3%). This material was hydrolyzed to an amine hydrochloride whose infrared spectrum was identical to that of ethylenediamine dihydrochloride. This material could have formed by cleavage of the carbon chain after the formation of a vicinal diamine or by cleavage to ethanolamine followed by conversion to ethylenediamine. In view of the titration data, which indicated the presence of a diamine, we prefer the former hypothesis.

We investigated many sets of conditions for the reductive alkylation of ammonia with a sugar. Since most of our work was done with galactamine, the data obtained with this sugar are summarized in Table II (*cf.* Experimental). It should be noted that we were able to obtain reasonably good yields (54–57%) of salicylidenegalactamine using concentrated ammonium hydroxide as the solvent and source of ammonia along with very mild hydrogenation conditions (55° at 200 p.s.i.) and a long reaction time (16 hr.). Although the reaction proceeded well at pressures as low as 50 p.s.i. (48–52% yields), our best yields (66–77%) were obtained using conditions similar to those of Holly, *et al.*[3] (85° at 2000 p.s.i. for 3 hr.).

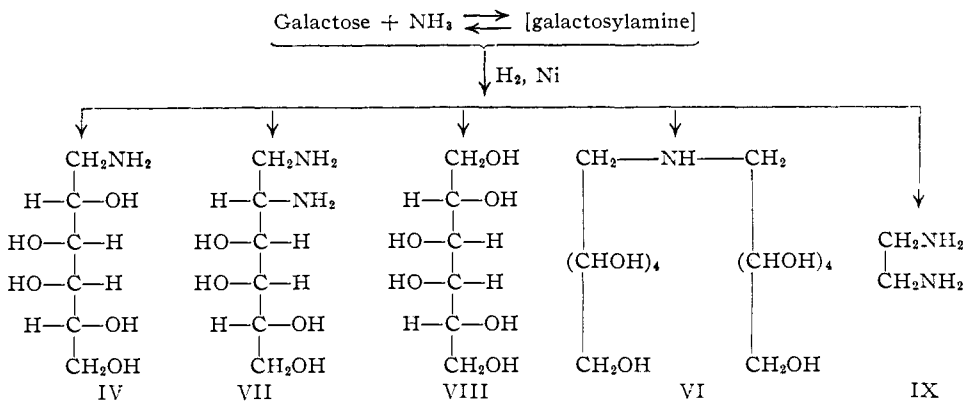


TABLE I[a]

SALICYLIDENE GLYCAMINES OBTAINED BY THE HYDROGENOLYSIS OF N-BENZYLGLYCAMINES

$$\text{Sugar} \xrightarrow[(2)\ H_2,\ Pt]{(1)\ C_6H_5CH_2NH_2} \text{N-Benzylglycamine} \xrightarrow[(2)\ \text{Salicylaldehyde}]{(1)\ \text{Hydrogenolysis}} \text{Salicylideneglycamine}$$

Sugar	N-benzylglycamine Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Salicylidene glycamine Overall yd., %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
L-Arabinose	64	122–123	$C_{12}H_{19}NO_4$	59.73	59.74	7.94	8.11	5.81	5.77	60	187–188	$C_{12}H_{17}NO_5$	56.46	56.35	6.71	6.47	5.49	5.76
D-Galactose	64[b]	157–159	$C_{13}H_{21}NO_5$	57.55	57.23	7.80	7.59	5.16	5.05		200–202	$C_{13}H_{19}NO_6$	54.73	54.94	6.71	7.09	4.91	4.75
D-Glucose	68[c]	138–139	$C_{13}H_{21}NO_5$	57.55	57.59	7.80	8.03	5.16	5.00									
D-Ribose	46	102–103	$C_{12}H_{19}NO_4$	59.73	59.58	7.94	8.21	5.81	5.71	25	126–128	$C_{12}H_{17}NO_5$	56.46	56.18	6.71	6.30	5.49	5.56
D-Xylose	Oil									26	131–133	$C_{12}H_{17}NO_5$	56.46	56.57	6.71	6.65	5.49	5.63

[a] The experiments on L-arabinose, D-ribose and D-xylose were carried out by R. D. Birkenmeyer of these laboratories. [b] Crude yield, m.p. 151–157°. [c] Crude yield, m.p. 132–135°.

TABLE II

CONDITIONS USED FOR THE ALKYLATION OF AMMONIA WITH GALACTOSE

No.	Catalyst	Time, hr.	Temp., °C.	Pressure, p.s.i.	Product[e] and yield, %
1	Ni (R)[a]	3	85	1500–2000	S, 66–77
2	Ni (R)[a]	1	100	2000	S, 43
3	Co (R)[a]	3	85	1500	B, 65
4	Ni (R)[a]	4	50	500[d]	B, 28
5	Ni (R)[a]	16	50	500[d]	B, 59
6	Ni (R)[b]	16	55	200[d]	B, 54–57
7	Ni (R)[b]	16	55	50[d]	B, 48–52
8	Ni (R)[b]	7	55	50[d]	B, 43

Solvent: [a] Liquid ammonia containing 3% by weight of water. [b] 28–30% ammonium hydroxide. [c] S = salicylidenegalactamine; B = benzylidenegalactamine. Under comparable conditions, the yield of benzylidenegalactamine was consistently about 5% less than that of the salicylidene derivative. [d] Constant.

Experimental[10]

N-Benzylgalactamine (III).—Galactose (50 g., 278 millimoles), benzylamine (30 g., 280 millimoles) and 15 ml. of water were heated on a steam-bath at 60° until solution was complete. Methanol (50 ml.) was added and the reaction mixture was set aside to cool. Platinum oxide (3.2 g.) was added, the volume of the solution was adjusted to 500 ml. with methanol and the mixture was hydrogenated at 40–50° at 50–20 p.s.i. for 15 hr. The reaction mixture was diluted with 1.5 l. of methanol and heated on a steam-bath with stirring until all of the product appeared to be in solution. The catalyst was removed by filtration and the filtrate was allowed to cool slowly to room temperature as the product separated from solution. N-Benzylgalactamine (48 g., 64%, m.p. 151–157°) was obtained in three crops. An analytical sample was prepared by recrystallization from methanol, m.p. 157–159°, $[\alpha]D$ −6°.

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.23; H, 7,59; N, 5.05.

N-Benzylglucamine.—The procedure for the preparation of N-benzylglucamine was similar to that for N-benzylgalactamine. The yield of crude product, m.p. 132–135°, was 67.5%. Recrystallization from ethanol to a constant melting point, 138–139°, produced an analytical sample.

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.59; H, 8.03; N, 5.00.

Preparation of Galactamine (IV). (a) Hydrogenolysis of N-Benzylgalactamine.—N-Benzylgalactamine (30 g., 111 millimoles) was suspended in 250 ml. of 95% ethanol and 5.0 g. of 10% palladium-on-charcoal was added. The mixture was hydrogenated at 50° and 50–30 p.s.i. for 1.5 hr. The reaction mixture was diluted to 500 ml. with methanol and heated on a steam-bath until the supernatant liquid was clear. The catalyst was removed by filtration and the filtrate was allowed to cool overnight in a refrigerator at approximately 3°. The product (14.1 g., 77% yield) was removed by filtration, m.p. 143–145°, $[\alpha]D$ −1°.

(b) Liquid Ammonia Process.—D(−)-Galactose (150 g., 833 millimoles), 400 ml. of liquid ammonia and 4 teaspoonfuls of Raney nickel were hydrogenated in a stainless steel autoclave equipped with a mechanical stirrer at 1800 p.s.i. at 85° for 4 hr. The contents of the reactor were removed with hot water and the purple reaction mixture was filtered to remove the catalyst The filtrate was concentrated under reduced pressure until the odor of ammonia was no longer apparent. The concentrate was diluted to 750 ml. with water, transferred to a 3-necked, creased flask equipped with a mechanical stirrer and a nitrogen inlet. Salicylaldehyde (103 g., 833 millimoles) was added with stirring and the mixture was stirred vigorously for 10 minutes while being cooled in an ice-bath. The yellow solid which precipitated was removed by filtration, washed on the filter by slurrying with water and dried in a vacuum oven at 50° to yield 192 g. of salicylidenegalactamine (81% yield), m.p. 189–195°.

The crude salicylidene derivative (159 g.) was suspended

(10) All melting points were taken in capillaries and are uncorrected. Rotations were measured in water at 23° at a concentration of 1–4% in a 2-decimeter tube.

in 400 ml. of ether, and the mixture was stirred vigorously for 5 minutes. The salicylidene derivative was washed onto a filter with an additional 250 ml. of ether and air-dried under a heat lamp to yield 146 g. (74% over-all) of purified material, m.p. 196–198°. A nicely crystalline solid (2.5 g.), m.p. 123–125.5°, was isolated from the ether solution by concentrating and cooling. This material proved to be N,N′-bis-salicylideneethylenediamine (*cf.* below for proof of structure).

An analytical sample of salicylidenegalactamine was prepared by recrystallization from methanol, m.p. 200–202°.

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.94; H, 7.09; N, 4.75.

The purified salicylidenegalactamine (145.5 g., 0.51 mole), m.p. 196–198°, was suspended in a solution of 1 l. of water and 90 ml. of concentrated hydrochloric acid, and the mixture was heated on a steam-bath for 15 minutes with vigorous stirring. After being cooled to room temperature the reaction mixture was extracted three times with 125-ml. portions of methylene chloride to remove salicylaldehyde. The aqueous phase was concentrated to dryness, the residual galactamine hydrochloride was dissolved in 2 l. of water and the solution was passed through a bed of IR-410 anion exchange resin ($1^5/_8'' \times 31''$) (OH^- cycle). The column was rinsed with water until the *p*H of the effluent was 7–8. The effluent was concentrated under reduced pressure (20 mm.) to a volume of 200 ml., 800 ml. of ethanol was added and the solution was cooled at 3° overnight. The galactamine which crystallized was removed by filtration (78 g., 85% over-all from salicylidenegalactamine), m.p. 145–148°, $[\alpha]D$ −1°. The over-all yield of galactamine from galactose was 63%.

Anal. Calcd. for $C_6H_{15}NO_5$: C, 39.77; H, 8.34; N, 7.73; Van Slyke N, 7.73; neut. equiv., 181. Found: C, 39.43; H, 8.65; N, 7.29; Van Slyke N, 8.0; neut. equiv., 183.

The Isolation of Galactamine through the Benzylidene Derivative.—The procedure for the preparation of benzylidenegalactamine was similar to that used for the salicylidene derivative. From a hydrogenation mixture which yielded 66% of pure salicylidenegalactamine, we obtained a 61% yield of benzylidenegalactamine, m.p. 192–193° (analytical sample, m.p. 191.5–193°). The benzylidenegalactamine was hydrolyzed by steam distillation in a nitrogen atmosphere to yield galactamine in 91% yield (based on the benzylidene derivative), m.p. 146–148°, $[\alpha]D$ −1°.

Anal. Calcd. for $C_6H_{15}NO_5$: Van Slyke N, 7.7; neut. equiv., 181. Found: Van Slyke N, 7.72; neut. equiv., 182.

Hydrogenolysis of N-Benzylglucamine. The Preparation of Glucamine.—The procedure in this preparation was similar to that employed for the hydrogenolysis of N-benzylgalactamine. The yield was 62% of material melting at 124.5–130°. Recrystallization of the crude product from absolute ethanol showed that a considerable amount of a high melting impurity was present which proved very difficult to separate by fractional crystallization. The Schiff base procedure was not developed at the time this experiment was done.

Proof of Structure of N,N′-Bis-salicylidenegalactamine.—The ether-soluble salicylidene derivative isolated above had a melting point after recrystallization from ethanol of 126–128°. The literature melting point of N,N′-bis-salicylidenegalactamine is 125–126°.[11]

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.10; H, 6.42; N, 10.94; ash, 0.24.

A sample of the salicylidene derivative was hydrolyzed with dilute hydrochloric acid to yield salicylaldehyde and an amine hydrochloride melting over 250°. The infrared spectrum of the latter was identical to that of an authentic sample of ethylenediamine dihydrochloride.

Isolation of Cyclohexylmethylgalactamine (V) from a Preparation of Galactamine by Hydrogenolysis of N-Benzylgalactamine.—Galactose (54 g., 300 millimoles), benzylamine (32.1 g., 300 millimoles) and 16.5 ml. of water were heated at 60° for 20 minutes, and the reaction mixture was stored at room temperature overnight. The resulting viscous solution was diluted with 360 ml. of methanol and hydrogenated in a stainless steel autoclave in the presence of 3.5 g. of platinum oxide for 5 hr. at 50° and 30 p.s.i. The hydrogen in the reactor was displaced with nitrogen, the head was removed and 15 g. of 10% palladium-on-charcoal, slurried in 150 ml. of 95% ethanol, was added. Hydrogenation was continued at 50° and 30 p.s.i. for 3 hr. The product was washed from the autoclave with 250 ml. of water and the resulting suspension was heated to 60°, filtered, and the filtrate was concentrated under reduced pressure until a solid began to separate. After cooling to 3°, a white solid was isolated (6.1 g., 11.3%), m.p. 148–152°. The mother liquor was concentrated to an oil which crystallized when triturated with methanol yielding 35 g. (65%) of a white solid, m.p. 120–127°, $[\alpha]D$ +2°, neut. equiv., 244.

The first crop of crystals was recrystallized from water yielding a 38% recovery of a new sugar amine, m.p. 132–135°. Recrystallization of this material four times from water yielded an analytical sample of N-cyclohexylmethylgalactamine, m.p. 135–136°, $[\alpha]D$ −6°. The ultraviolet spectrum showed no evidence for the presence of a phenyl group.

Anal. Calcd. for $C_{13}H_{27}NO_5$: C, 56.29; H, 9.81; N, 5.05; neut. equiv., 277. Found: C, 56.45; H, 9.68; N, 4.95; neut. equiv., 279.

D(−)-Didulcitylamine (VI).—A mixture of galactose (54 g., 300 millimoles), benzylamine (33 g., 308 millimoles) and water (16.5 ml.) was heated on a steam-bath at 60° with occasional swirling until homogeneous. The reaction mixture was diluted with alcohol (54 ml.) and set aside for 17 hr. Further dilution with 500 ml. of alcohol was followed by the addition of 3.5 g. of platinum oxide and 15 g. of 10% palladium-on-charcoal. The mixture was then hydrogenated at 50° and 10 p.s.i for 6 hr. The reaction mixture was heated to 65°, filtered and diluted to 1 l. with water. The white solid that separated was removed by filtration (10.3 g., 20%), m.p. 195–197°. A second crop was obtained by concentrating under reduced pressure to a white paste-like mass which was diluted to 500 ml. with methanol and filtered. The solid which was obtained (21.0 g., 40%) melted at 169–173°. A third crop of solid was obtained after storage of the filtrate at 3° for 5 days (8.6 g., 16.7%), m.p. 93–100°.

Recrystallization of the first crop of solid three times from water yielded an analytical sample of D-(−)-didulcitylamine, m.p. 202–204°, $[\alpha]D$ −9°.

Anal. Calcd. for $C_{12}H_{27}NO_{10}$: C, 41.73; H, 7.88; N, 4.06; neut. equiv., 345. Found: C, 42.00; H, 7.71; N, 4.08; neut. equiv., 352.

A crystalline hydrochloride salt of this amine melted at 240–241°.

Anal. Calcd. for $C_{12}H_{28}ClNO_{10}$: C, 37.75: H, 7.39; N, 3.67; Cl, 9.29. Found: C, 38.05; H, 7.34; N, 3.95; Cl, 9.24.

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(11) A. T. Mason, *Ber.*, **20**, 271 (1887).