[CONTRIBUTION FROM THE DIVISION OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

A New Synthesis of Glycosides[1,a]

BY J. E. CADOTTE, F. SMITH AND D. SPRIESTERSBACH

Cation exchange resins have been shown to be effective catalysts for promoting the formation of glycosides from pentoses, hexoses, uronic acids and methylated sugars. These resins also catalyze the formation of acetone derivatives of sugars and methyl glycosides.

In 1893 Fischer showed that when D-glucose was heated in a sealed tube with methanolic hydrogen chloride crystalline methyl α-D-glucopyranoside was produced.[2,3] The inconvenience and limitation of using the sealed tube method was later surmounted by carrying out the reaction under reflux[4] and also increasing the concentration of the acid catalyst.[5] This reaction, and that in which the acetohalogen sugar is condensed with an alcohol in the presence of an acid acceptor[6,7] have played a major role in the preparation of sugar glycosides for structural studies. Such investigations have indeed enabled ring structures to be assigned to the glycosides themselves and also to the parent sugars.[8,9]

Although the modification of Hudson and his associates has often proved to be a decided improvement on the Fischer sealed tube method especially when relatively large quantities of glycosides are required, it is usually necessary to neutralize the acid catalyst (HCl, H_2SO_4, sulfonic acid,[10] etc.) before isolation of the glycoside can safely be brought about unless the rather limited and somewhat extravagant method of Patterson and Robertson is adopted.[11]

The work reported in this paper has shown that certain cation exchange resins, especially those possessing sulfonic acid groups, can be used to catalyze the formation of glycosides. This reaction is analogous to those in which cation exchange resins have been employed to promote esterification, alcoholysis and acetal formation.[12] The glycoside reaction can be carried out either in an autoclave in which case the time required is about two hours, or more conveniently perhaps, in spite of the increase in time required, by allowing a hot alcoholic solution of the sugar to percolate through the resin in an apparatus such as the one represented diagrammatically in Fig. 1. The reaction proceeded smoothly to completion and the various glycosides were obtained by concentrating the alcoholic solution (see Table I). The yields were further increased by recycling the mother liquors through the resin. Polarimetric observation and determination of the reducing power of the reaction mixture in the case of glucose revealed that in the early stages there is a preponderance of alkyl furanoside which is subsequently transformed into a pyranoside. With regard to the nature of the reaction and the final products formed, it is apparent that this new method of synthesizing glycosides using an insoluble acid catalyst is very similar to that in which glycoside formation is catalyzed by dissolved acids.

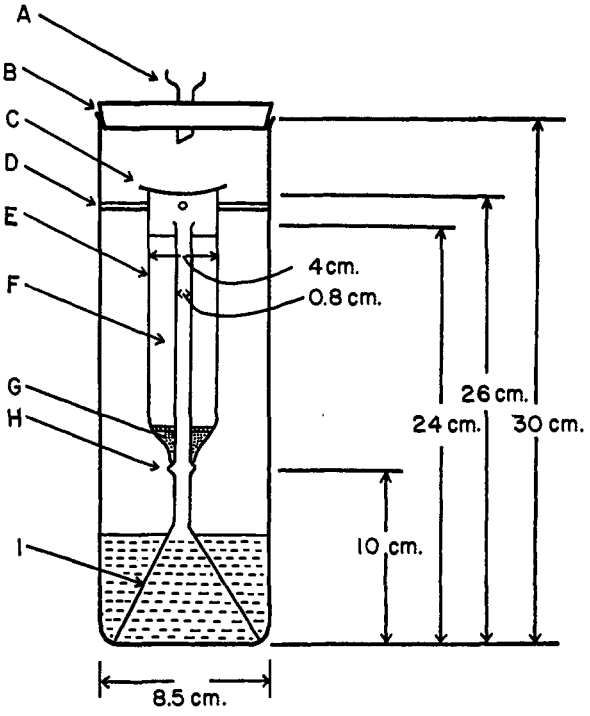

Fig. 1.—A, condenser; B, stopper; C, cover glass; D, centering rods attached to resin column E; F, cation exchange resin; G, glass wool held in place with filter disk; H, projections on elongated stem of funnel I to support the resin column E.

The reaction is not confined to simple hexoses and pentoses for the uronic acids were likewise transformed into the corresponding uronosides. Thus when D-galacturonic acid was boiled with methanol in the presence of a cation exchange resin it gave the methyl ester of methyl-α-D-galactopyruronoside.[13] It is of interest to note that if instead of boiling the reaction mixture it is

(1) This work which was presented in part at the 117th Meeting of the American Chemical Society in Detroit in 1950 constitutes part of a thesis submitted by John E. Cadotte to the Graduate School of the University of Minnesota in partial fulfillment for the degree of M.S.

(a) Paper No. 2695, Scientific Journal Series, Minnesota Agricultural Experiment Station, University of Minnesota, St. Paul, Minnesota.

(2) E. Fischer, *Ber.*, **26**, 2400 (1893); *ibid.*, **28**, 1145 (1895).

(3) *Cf.* W. A. van Ekenstein, *Rec. trav. chim.*, **13**, 183 (1894).

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shaken at room temperature methyl-D-galacturonate is formed.[14]

Similarly D-glucurone which has been shown to possess two interlocking five atom rings[15,16] yielded a crystalline mixture of the α- and β-forms of methyl-α-D-glucofurunonoside 3,6-lactone. The β-anomer proved to be identical with the compound prepared by the action of methanolic hydrogen chloride upon glucurone[17] and its structure was confirmed by methylation whereby the characteristic crystalline methyl 2,5-dimethyl β-D-glucofurunonoside 3,6-lactone[15,16] was obtained. The α-isomer, unknown at the time when this work was completed, was characterized by its conversion into methyl-2,5-dimethyl α-D-glucofurunonoside 3,6-lactone.[15,16] Following the initial report[1] of the use of cation exchange resins as catalysts for glycoside formation similar results with D-glucurone have since been obtained by other workers.[18]

D-Mannurone likewise furnished a methyl glycoside when it was boiled with methanol in the presence of a sulfonic acid cation exchange resin.

Preliminary attempts to prepare the methyl glycosides of disaccharides met with no success since cleavage of the biose link occurred.[19-22] This observation appears to indicate that acid exchange resins might be useful in the graded hydrolysis of polysaccharides.

The general usefulness of these cation exchange resins in carbohydrate studies was further demonstrated by the fact that they are capable of catalyzing the formation of the glycosides of methylated sugars and the formation of isopropylidene derivatives of sugars and sugar glycosides.

Experimental

A. The Synthesis of Glycosides Promoted by Cation Exchange Resins.—Four typical experiments are given below to illustrate the methods used.

(1) A mixture of glucose (10.0 g.), "Amberlite, IR 120" cation exchange resin (20 g.) and methanol (150 ml.) was boiled for 12 hours. Filtration of the almost colorless solution and isolation of the product in the usual manner gave methyl α-D-glucopyranoside (4 g. or 44%), m.p. 165° (after crystallization from ethanol).

Anal. Calcd. for $C_7H_{14}O_6$: OCH_3, 16.0. Found: OCH_3, 16.1.

(2) A solution of glucose (50 g.) (complete solution is not essential at the outset since the glucose dissolves in one-half hour) in methanol (750 ml.) was boiled and allowed to percolate rather rapidly through a resin column containing 50 g. of either "Amberlite IR 120" or "Dowex 50" in the apparatus described below in Section C. After 20 hours the colorless solution was withdrawn and the resin thoroughly washed with methanol. The solution and washings were combined, concentrated *in vacuo* and the methyl α-D-glucopyranoside isolated as above (yield 34 g. or 63%) and purified by one recrystallization (yield 25 g. or 46.5%), m.p. 166°. The reaction time of about 24 hours was adopted as a result of study in the change in concentration of free sugar, of methyl furanosides and of methyl pyranosides. After 24 hours the free sugar was at a minimum,[23] little or no furanoside could be detected by the increase in reducing power produced by heating the material (isolated by evaporating an aliquot) for 10 minutes at 100° with 0.1 *N* hydrochloric acid while pyranoside formation had reached a maximum. It was also found that the specific rotation was approaching a maximum value.

(3) A mixture of D-glucose (1.0 g.), "Amberlite IR 120" cation exchange resin (1.0 g. and methanol 15 ml.) in a sealed glass tube was heated for two hours at 110–120°. Filtration, evaporation and crystallization of the product followed by recrystallization gave methyl α-D-glucoside (yield 0.55 g. or 50%), m.p. and mixed m.p. 166°, $[\alpha]^{25}D$ +158° in water (*c* 1.2). By one retreatment of the sirupy products recovered from the mother liquors with methanol in the presence of the resin at 110–120° the yield could be increased to 70%.

(4) A mixture of D-glucose (20 g.), "Amberlite IR 120" cation exchange resin (5 g.) and methanol (300 ml.) was heated for two hours at 120° in a stainless steel autoclave. After filtering the resin, the solution was concentrated *in vacuo* and the methyl D-glucoside isolated (yield 15.0 g. or 70.5% m.p. 135–145°). Recrystallization from ethanol gave methyl α-D-glucopyranoside (10.6 g. or 49%), m.p. 165°. Retreatment of the sirupy product recovered from the mother liquor with methanol (150 ml.) and the original resin afforded more crude methyl D-glucoside (7.0 g.) from which the α-isomer (4.7 g.), m.p. 166° was obtained. Thus, the total yield of methyl α-D-glucoside obtained from 20 g. of D-glucose by a two-step process amounted to 15.3 g. or 71%.

B. Examination of Some Factors Affecting Glycoside Formation (a) Dehydrating Agents.—A series of experiments showed that the addition of "Drierite" caused no appreciable improvement in yield, no matter which of the above four methods was adopted.

(b) **Reaction Time.**—Using the procedure given either in section 3 or 4 above (temp. 110–120°) and the "Amberlite IR 120" resin as the acid catalyst, it was shown that a reaction time of two or five hours gave a 50% yield of methyl α-D-glucoside but that after 20 hours the yield fell to 30% and there was considerable decomposition of the resin resulting in a darkening of the reaction mixture.

(c) **Reaction Temperature.**—With the quantities of reactants given in section 4 above, it was shown that the optimum temperature was about 110–120°. Between 120 and 140° the yields were still of the same order (50%) but decomposition of the resin ("Amberlite IR 120") and discoloration of the methanolic reaction mixture occurred. At 160° the yield was lower and there was greater decomposition of the resin.

Temp., °C.	100	100–120	120–140	160
Yield, %	40	50	50	20

(d) **Quantity of Resin.**—A series of experiments were carried out as in section 1 above using a reaction time of 12 hours and varying amounts of resin. A ratio of one to two parts of cation exchange resin "Amberlite IR 120" per part of glucose proved to be most effective.

Ratio of resin to glucose	0.25	1.0	2.0
Yield, %	10	38.5	44.0

"Dowex 50" cation exchange resin with an equal amount of glucose furnished a yield of 43% of methyl α-D-glucoside.

At a temperature of 110–120° and using the method in section 4 above the ratio of the amount of resin to glucose could be reduced to 0.25 without affecting the yield of methyl α-D-glucoside thus:

Ratio of resin to glucose	0.05	0.25	1.0
Yield, %	7.5	47.5	47.0

(e) **Nature of the Resins.**—A series of experiments carried out with various resins using the method given in section 2 showed those resins possessing the sulfonic acid group were the most effective thus:

Resin[a]	Yield, %
Amberlite IR 120	51
Amberlite IR 100	33
Amberlite XE 69	33

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(22) G. Bodamer and R. Kunin, *Ind. Eng. Chem.*, **43**, 1082 (1951).
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Resin[a]	Yield, %
Permutit Zeo Rex	30
Permutit Zeo Karb H	25
Permutit Q	37
Dowex 50	46.5
Starch phosphate	0

[a] The "Amberlite" resins were supplied by the Rohm and Haas Company, Philadelphia, Pa., the "Dowex 50" by the Dow Chemical Company, Midland, Michigan and the "Permutit" resin by the Permutit Company, New York, N.Y. The authors thank these companies for samples of resins and Dr. G. E. Rist of the Northern Regional Research Laboratory, who kindly supplied the starch phosphate.

C. General Procedure for the Synthesis of Glycosides Using Cation Exchange Resins.—The sugar (1 part) and methanol (15 parts) were allowed to react in the presence of either "Dowex 50" or "Amberlite IR 120" (1 part) using the apparatus shown in Fig. 1 as described in section 2 above. Isolation of the glycosides was effected in the usual manner. The results of experiments with some of the more common sugars are given in Table I.

TABLE I

Sugar	Anomeric form	Methyl glycopyranoside formed M.p., °C.	$[\alpha]^{25}D$ (H_2O)	Yield, %	Ref.
D-Glucose	α	116	+135°	48	2
	β	110	− 30	..	3
D-Mannose	α	194	+ 82	69	24
D-Galactose	α	105 (hydrate)	+183	10	25
D-Arabinose	β	172	−244	30	..
L-Arabinose	β	172	+240	36.5	5
D-Xylose	β	150–157	− 54	9.0	5
L-Rhamnose	α	101	− 55.5	50	26

The above results show that this method appears to be particularly effective in the preparation of the methyl glycosides of D-glucose, D-mannose, D- and L-arabinose and L-rhamnose.

Treatment of lactose in the same manner afforded a 25% yield of methyl α-D-glucoside, m.p. and mixed m.p. 166°.

D. Resin-catalyzed Glycoside Formation Applied to Other Sugar Derivatives (a) 2,3,4,6-Tetramethyl-D-glucose.—A solution of the crystalline sugar (67 mg., m.p. 95°) in methanol (15 ml.) was boiled under reflux for 24 hours in the presence of "Dowex 50" cation exchange resin (500 mg). Filtration and removal of solvent afforded methyl 2,3,4,6-tetramethyl-D-glucoside as a colorless non-reducing mobile liquid (73 mg.), b.p. (bath temp.) 110° (0.05 mm.), $[\alpha]^{25}D$ +62° in ethanol (*c* 0.8).

(b) **D-Galacturonic Acid.**—When a solution of α-D-galacturonic acid (1.0 g.) in methanol (50 ml.) was shaken with "Dowex 50" cation exchange resin (2 g.) at 5° the concentration of acid in the solution as determined by titration changed as follows: 90% (after one hour); 82% (two hours); 69% (six hours); 65% (eight hours); 60% (10 hours); 51% (15 hours); 43% (20 hours); 30% (30 hours); 21% (40 hours); 16% (50 hours); 13% (60 hours); 10% (70 hours); 7% (100); 5% (140 hours). When the experiment was carried out at room temperature (25° approx.) esterification was complete in eight hours.[14]

When a solution of α-D-galacturonic acid (1.83 g.) in methanol (100 ml.) was boiled in the presence of "Dowex 50" cation exchange resin (2.0 g.) it showed: $[\alpha]^{25}D$ +28.5 (after one-half hour); +6.6 (4.5 hours); −12.6 (10 hours); −17.5 (13 hours); −20° (16.5 hours) constant for two more hours. Concentration and crystallization from ethanol-ether gave methyl α-D-galacturonoside methyl ester monohydrate[13] (0.26 g.), m.p. 141°, $[\alpha]^{25}D$ +128° in water (*c* 0.3). The same product was isolated in about the same yield when the reaction mixture was worked up after the specific rotation had reached a maximum positive value ($[\alpha]D$ +36°, 70 hours).

(c) **D-Glucurone.**—When a solution of D-glucurone (2.0 g.) in methanol (100 ml.) was refluxed in the presence of "Dowex 50" cation exchange resin (2.0 g.) it showed $[\alpha]^{20}D$ +28.5° (after 0.75 hour); +19.5°, 1.75 hours; +16.5°, 4 hours; −7.5°, 5 hours; −16.5°, 7 hours; −13.5°, 9 hours; −10.5°, 10 hours. Evaporation of the solution when the rotation had reached a maximum negative value afforded a crystalline product which upon recrystallization from ethanol–ether gave a mixture of two types of crystals, prisms and needles. The prisms proved to be methyl β-D-glucofururonoside 3,6-lactone,[17] m.p. 139°, $[\alpha]^{20}D$ −56.5° in water (*c* 1.4) (yield 60%). *Anal.* Calcd. for $C_7H_{10}O_6$: C, 44.3; H, 5.3; OCH_3, 16.3. Found: C, 44.8; H, 5.5; OCH_3, 17.1. The needles were shown to be methyl α-D-glucofururonoside 3,6-lactone,[18] m.p. 147.8°, $[\alpha]^{20}D$ +146.5° in water (*c* 0.5) (yield 10%). *Anal.* Calcd. for $C_7H_{10}O_6$: C, 44.3; H, 5.3; OCH_3, 16.3. Found: C, 44.4; H, 5.23; OCH_3, 16.9.

Methylation of the β-methyl-D-glucofururonoside 3,6-lactone with silver oxide and methyl iodide in the usual way yielded methyl 2,5-dimethyl β-D-glucofururonside 3,6-lactone,[15] m.p. 91°, $[\alpha]^{25}D$ +5° (*c* 3.6) in water (after recrystallization from ethanol–ether).

Similarly the methyl-α-D-glucofururonoside 3,6-lactone afforded methyl 2,5 dimethyl-α-D-glucofururonside 3,6-lactone,[15,16,17] m.p. 129°, $[\alpha]^{25}D$ +171° (*c* 0.8) in water (after recrystallization from ethanol–ether).

(d) **D-Mannurone.**—Treatment of D-mannurone[27,28] with boiling methanol in the presence of "Dowex 50" cation exchange resin gave methyl mannuronoside as a sirup, $[\alpha]^{25}D$ +85° in methanol (*c* 2.5). $[\alpha]^{25}D$ +46° in water (*c* 1.0) (found: OCH_3, 19.9). The high methoxyl value suggests that partial opening of the lactone ring takes place.

E. The Catalytic Effect of Cation Exchange Resins in Isopropylidene Formation (a) Glucose.—A mixture of D-glucose (10 g.) "Amberlite IR 120" cation exchange resin (18 g.) and Drierite (10 g.) was put into the thimble of a soxhlet (syphon type) apparatus and subjected to continuous extraction with acetone (150 ml.) for 24 hours. Filtration to remove unchanged glucose (2.0 g.) followed by concentration *in vacuo* to dryness furnished a crystalline residue. Extraction of the latter with benzene at room temperature gave 1,2-5,6-diacetone-D-glucofuranose, purified by distillation in high vacuum, b.p. (bath temp.) 156–160°, 0.05 mm.; yield 2.6 g.; m.p. and mixed m.p. 105° (from petroleum ether). The residue from which the diacetone glucose had been extracted was re-extracted with acetone to give 1,2-monoacetone-D-glucofuranose; yield 1.5 g., m.p. 150° (after crystallization from ethanol–petroleum ether) undepressed by an authentic specimen.

"Dowex 50" could replace "Amberlite IR 120" in the above reaction but "Amberlite IRC 50" proved to be a poor catalyst.

(b) **D-Fructose.**—(i) A mixture of D-fructose (5 g.) and "Dowex 50" was boiled with acetone (100 ml.) until the solution no longer reduced Fehling solution and gave no cloudiness upon cooling. The solution, which showed $[\alpha]^{25}D$ −26°, was concentrated *in vacuo* to dryness. Extraction of the residue with acetone (50 ml.) and addition of petroleum ether (b.p. 40–60°, 50 ml.) followed by removal of the solvent from the supernatant liquid afforded a pale yellow liquid consisting of a mixture of diacetone D-fructose and autocondensation products of acetone. Fractional distillation gave first the latter b.p. (bath temperature) 100° (50 mm.) and then diacetone D-fructose (mainly the α-isomer) as a pale yellow, viscous liquid (1.0 g.), b.p. 150–160° (0.05 mm.), which crystallized spontaneously, m.p. 100° (after crystallization from petroleum ether).

When the process was carried out in a Soxhlet apparatus the reaction occurred even in one hour and 1,2,-4,5-diacetone-D-fructose was isolated from the reaction mixture. There was, however, considerable production of acetone autocondensation products and consequently the method below was used.

(ii) A mixture of D-fructose (5.0 g., finely powdered), "Dowex 50" cation exchange resin (5.0 g.) and acetone (100 ml.) was shaken for 20 hours at room temperature (25°). Removal of the resin and the solvent gave crystalline 1,2-4,5-diacetone-α-fructose, m.p. 116° (without recrystalliza-

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tion). Purification by distillation *in vacuo* furnished a 60% yield of α-diacetone-D-fructose, m.p. and mixed m.p. 119° (after recrystallization from petroleum ether).

(c) Preliminary experiments indicated that "Dowex 50" cation exchange resin could be used in the condensation of acetone with methyl α-D-galactopyranoside and with methyl α-D-mannopyranoside.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DE PAUL UNIVERSITY]

Preparation of *l*-2-Aminomethyltetrahydropyran[1]

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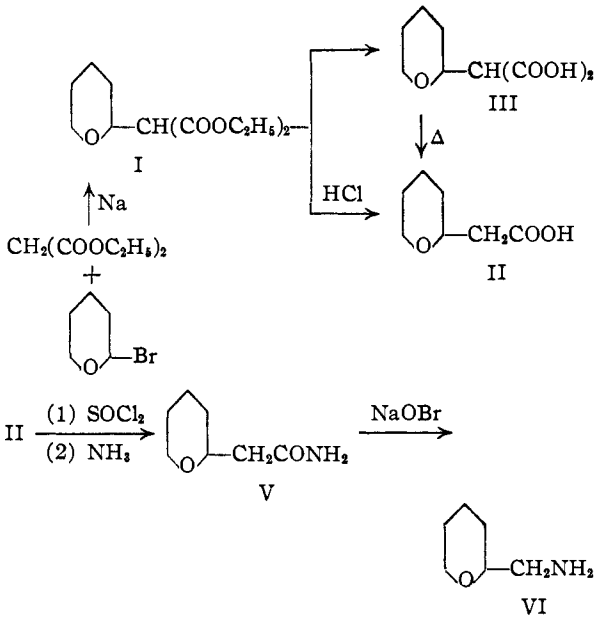
2-Aminomethyltetrahydropyran has been prepared from 2-tetrahydropyranylacetic acid. Both have been obtained in optically active form and related stereochemically.

As part of a program to relate substituted tetrahydropyrans to carbohydrates, it was of interest to prepare and resolve some 2-substituted tetrahydropyrans. A search of the literature indicates that the only other resolution of non-carbohydrate pyran compounds has been that of 2,6-dimethyl-5,6-dihydro-2H-pyran-3-carboxylic acid.[3]

When this investigation was begun a number of analogous 4-substituted tetrahydropyrans were known. Thus 4-bromotetrahydropyran, ethyl 4-tetrahydropyranylmalonate, 4-tetrahydropyranylacetic acid and 4-aminomethyltetrahydropyran had been prepared by methods simlar to ours.[4-6] The 4-aminomethyl- compound had also been obtained by reduction of 4-cyanotetrahydropyran[5,7] and by the Gabriel synthesis with 4-bromomethyltetrahydropyran.[5] Recently the preparation of ethyl 2-tetrahydropyranylmalonate (I) by a method analogous to ours has been reported.[8] *dl*-2-Aminomethyltetrahydropyran (VI) has been prepared by the reduction of 2-tetrahydropyranylcyanide,[9] and by the hydrogenation of the cyclic, trimeric aldimine formed by the action of ammonia on 3,4-dihydro-2H-pyran-2-carboxyaldehyde.[10-12]

In the syntheses reported here, ethyl malonate has been alkylated by 2-chloro- and 2-bromotetrahydropyran[13,14] to yield ethyl *dl*-2-tetrahydropyranylmalonate (I) which was in turn hydrolyzed in acid and decarboxylated to yield *dl*-2-tetrahydropyranylacetic acid (II). Alternatively, careful saponification of I yielded *dl*-2-tetrahydropyranylmalonic acid (III) which was thermally decarboxylated to II.



The tetrahydropyranylacetic acid (II) was converted to *dl*-2-tetrahydropyranylacetamide (V) through the intermediate *dl*-2-tetrahydropyranylacetyl chloride (IV). The amide, V, was in turn converted to *dl*-2-aminomethyltetrahydropyran (VI) by means of the Hofmann reaction. Efforts to apply the Schmidt reaction or the Curtius method to the preparation of VI were unsuccessful.

The partial resolution of II was effected through the quinine salt, and *l*-2-tetrahydropyranylacetic acid (IIa) $[\alpha]^{20}D$ −5.7° (95% ethanol, *c* 15) was obtained. A product of lesser purity resulted through resolution *via* D-desoxyephedrine. Compound IIa was then converted to the amide, *d*-2-tetrahydropyranylacetamide (Va), $[\alpha]^{24}D$ +12.5° (95% ethanol, *c* 1.6). Application of the Hofmann reaction to Va yielded *d*-2-aminomethyltetrahydropyran (VIa), $\alpha^{24}D$ +6.5 (homogeneous, *l* = 1 dm.). The direct resolution of *dl*-2-aminomethyltetrahydropyran *via* the tartaric acid salt gave a product having a somewhat higher rotation, $\alpha^{24}D$ +8.3 (homogeneous, *l* = 1 dm.).

The lower rotation of the pyranylamine formed *via* the Hofmann degradation from the optically active acid, IIa, is undoubtedly the result of still incomplete resolution of the *dl*-acid, II. For the stereospecificity of the Hofmann degradation has been convincingly demonstrated in instances where

(1) We gratefully acknowledge that this investigation was made possible by a grant-in-aid from the Research Corporation.

(2) Abstracted from theses, submitted in partial fulfillment of the requirements for the degree of Master of Science, by Norman G. Peterson, 1950, and Hope R. Wallner, 1951.

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