A 13.8-g. sample of this material was chromatographed on a column of alumina which was partially deactivated by slurrying with alcohol and drying at steam bath temperature. The first 2 g. of product eluted from the column by petroleum ether comprised 90–95% tri-*sec*-butyl phosphite and the balance di-*sec*-butyl phosphonate, by infrared spectral analysis. Because of the very similar boiling points and consequential difficulty in separating the diester from the triester by distillation,[12] no physical constants were obtained. Since the triester forms a solid cuprous chloride complex while the diester does not, separation and identification by this route were chosen. The crude tri-*sec*-butyl phosphite thus obtained gave a cuprous chloride complex melting 161.5–162.5°. An analogous complex prepared from the known phosphite melted at 162–163° and the mixture melting point of the two complexes was 161.5–163.0°. These complexes were somewhat sticky and oxidized readily if not kept in an inert atmosphere.

(10) The chemical shifts relative to 85% phosphoric acid for tri-*sec*-butyl phosphite, di-*sec*-butyl phosphonate, and the unknown phosphate were −139.8 p.p.m., −9.9 p.p.m., and +2.0 p.p.m., respectively. The spin-spin interaction of the P and H atoms in di-*sec*-butyl phosphonate resulted in a splitting of 660 c.p.s.

(11) The determination of tri-*sec*-butyl phosphite was based on absorption at 10.7 μ. It is not possible to draw a precise base line for this band because of other strong absorption bands in this region of the spectrum. The similarity between phosphonate and phosphate spectra in the infrared region precluded the determination of phosphate.

Acknowledgment.—The authors wish to thank Dr. T. J. Flautt for the n.m.r. spectral data.

(12) The same is true for the *n*-butyl esters. $(BuO)_2POH$, b.p. 124–5° (12 mm); $(BuO)_3P$, b.p. 122–3° (12 mm), see G. M. Kosolopoff, "Organophosphorus Compounds," Wiley, N. Y. 1950, pp. 202, 204.

The Reaction of Azulenes with Trifluoro- and Trichloroacetic Anhydride[1,2]

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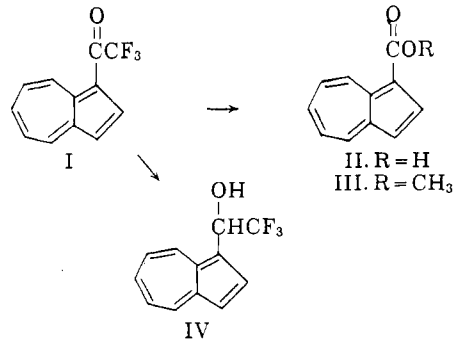
The reaction of certain azulenes with trifluoro- and trichloroacetic anhydrides gives good to high yields of the 1-trihaloacetylazulene derivatives. In these cases hydrolysis gives the corresponding carboxylic acids and the two steps provide perhaps the best route to the acids and their derivatives.

The initial efforts to prepare 1-azuloic acid by the more common methods for aromatic carboxylic acids afforded only one successful route. Reaction of 1-acetylazulene with sodium hypoiodite reagent (but not sodium hypochlorite which gave electrophilic displacement of the acetyl group) yielded the desired acid but not in pure form.[5] Subsequently it occurred to us to attempt the direct introduction of a trihaloacetyl group as a general method leading to 1-(3-)azuloic acids and derivatives.

The use of trifluoroacetic anhydride in the synthesis of ketones from aromatic compounds and carboxylic acids had been reported by Bourne and co-workers.[6] They obtained good yields of ketones from polyalkylbenzenes, phenyl ethers, furan, and thiophene under mild conditions. These reactions, which presumably proceeded through intermediate formation of the mixed anhydride, suggested that the nucleophilic 1-position of azulene might serve to displace the stable trifluoroacetate ion from trifluoroacetic anhydride and form 1-trifluoroacetylazulene (I) directly. The acylation of azulene with acetic anhydride requires a catalyst[5]; in contrast the reaction with trifluoroacetic anhydride proceeded without a catalyst and formed I in 91% yields. The identity of the product was indicated by its absorption maximum (525 mμ) in the visible region. This large hypsochromic shift is observed when a strong electron-withdrawing group occupies the 1-position.[7] The structure of I was confirmed by the formation of 1-azuloic acid (II) on treatment with aqueous sodium hydroxide and esterification with diazomethane to give the known ester (III).[8] II, obtained in 88.5% yield



(1) From the Ph.D. thesis of Robert Griffin Anderson.

(2) A preliminary communication of a portion of this work appeared in *Proc. Chem. Soc.*, 72 (1960).

(3) National Science Foundation Senior Postdoctoral Fellow, 1960–1961.

(4) National Science Foundation Predoctoral Fellow, Summer 1959; National Institutes of Health Fellow 1959–1961. Present address: California Research Corp., Richmond, California.

(5) A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

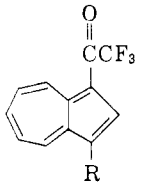
(6) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 718 (1951).

(7) A. G. Anderson and B. M. Steckler, *J. Am. Chem. Soc.*, **81**, 4941 (1959); A. G. Anderson, R. Scotoni, E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22**, 1193 (1957); E. J. Cowles, *J. Am. Chem. Soc.*, **79**, 1093 (1957); E. Heilbronner, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, ed., Interscience Publishers, Inc., New York, 1959, Chap. V.

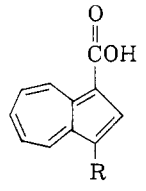
(8) A. G. Anderson and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4979 (1953).

as lavender plates, m.p. 181–182°,[9] was found to decarboxylate at temperatures above its melting point. The simplicity and high yields of the steps involved make this perhaps the best route to the acid and ester of those available.[5,9,10] Reaction of I with lithium aluminum hydride produced the corresponding alcohol (IV) in 98% yield.

The applicability of the reaction to mildly deactivated azulenes was shown by the fact that 1-trifluoroacetyl-3-chloroazulene (V) and 1-trifluoroacetyl-3-phenylazulene (VI) were obtained in 84 and 88% yields, respectively, from the corresponding halo- and phenylazulenes. The products could be hydrolyzed to the 3-substituted 1-azuloic acids (VII and VIII) in good (80–85%) yield. A much lower (24.4%; 65.8% net) yield of 1-trifluoroacetyl-3-thiocyanoazulene (IX) resulted from the substantially more deactivated 1-thiocyanoazulene.[11] With strongly deactivated compounds (1-nitroazulene and 1-trifluoroacetylazulene) no substitution product was formed, even in the presence of Lewis acid catalysts.

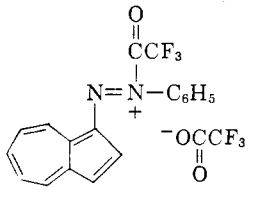


V. R = Cl
VI. R = C_6H_5
IX. R = SCN

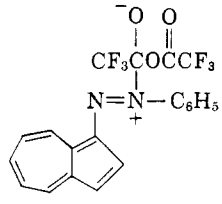


VII. R = Cl
VIII. R = C_6H_5

Upon addition of trifluoroacetic anhydride to a carbon tetrachloride solution of 1-phenylazoazulene the color of the solution changed immediately from green to red. Such a color change might have accompanied ring substitution, but the addition of 10% aqueous sodium carbonate in the work-up restored the original color and the starting material was quantitatively recovered. It is suggested that the color change indicates a reaction corresponding to the reversible protonation of 1-phenylazoazulene[5,12] and that the red species is X or XI.



X



XI

(9) W. Treibs, H. Neuport, and J. Hiebsch, *Ber.*, **92**, 1216 (1959), report m.p. 188° for this acid as obtained from the reaction of azulene with phosgene, followed by hydrolysis.

(10) W. Treibs and H. Ortmann, *Naturwissenschaften*, **45**, 85 (1958).

(11) A. G. Anderson and R. N. McDonald, *J. Am. Chem. Soc.*, **81**, 5669 (1959).

Trichloroacetic anhydride was found to react appreciably more slowly than the trifluoro anhydride but in the same manner. Thus 1-trichloroacetylazulene was obtained (48%) from azulene and basic hydrolysis afforded a nearly quantitative (99.5%) conversion to 1-azuloic acid. The rate of hydrolysis of the trichloroacetyl compound was much faster than that of the trifluoroacetyl derivative. This is in agreement with the observation of Hine and co-workers[13] that α-halogen substituents facilitate carbanion formation in the order Cl > F.

Experimental[14]

1-Trifluoroacetylazulene (I).—A solution of azulene (0.128 g., 1.0 mmole) in 10 ml. of dry carbon tetrachloride was treated with 0.5 ml. (*ca.* 3.5 mmoles) of trifluoroacetic anhydride and protected from moisture. The color of the solution immediately changed from blue to red. The mixture was swirled intermittently for 10 min. at room temperature and excess trifluoroacetic anhydride was then decomposed by the careful addition of 5 ml. of 5% sodium bicarbonate solution, followed by thorough shaking. The separated red organic phase was washed three times with 20-ml. portions of water and dried over anhydrous sodium sulfate; the solvent was removed on a steam bath. The residue was chromatographed on basic alumina. Benzene eluted an intense red band away from a small amount of dark material held tightly at the top of the column. The material from the red fraction was rechromatographed and from the final eluate was obtained 0.205 g. (91.5%) of 1-trifluoroacetylazulene as red needles, m.p. 62.5–63.5°. The ultraviolet and visible absorption spectra of an *n*-hexane solution exhibited maxima in mμ (log ϵ) at 267 (4.03), 303 (4.41), 311 (4.47), 376 (4.00), 392 (4.09), 525 (2.35), 568 (2.26), and 623 (1.81). The infrared spectrum showed absorption attributed to the carbonyl group at 6.1 μ.

Anal. Calcd. for $C_{12}H_7F_3O$: C, 64.28; H, 3.14. Found: C, 64.56; H, 3.44.

1-Trichloroacetylazulene.—To a solution of 0.256 g. (2.0 mmoles) of azulene in 10 ml. of methylene chloride protected from moisture was added 1.0 ml. (*ca.* 7 mmoles) of trichloroacetic anhydride.[15] The solution gradually became red and after 2.5 hr. it was washed four times with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed on acid-washed alumina. Pentane removed unchanged azulene (37 mg.). Then a red band was eluted with methylene chloride and the material from this was rechromatographed on neutral alumina. The red band removed by ether afforded 0.243 g. (47.6%; 52% net) of 1-trichloroacetylazulene as red needles, m.p. 94–95°, after recrystallization from cyclohexane. Absorption maxima (cyclohexane) in mμ (log ϵ) were found at 244 (4.30), 273 (4.18), 316 (4.47), 379 (4.07), 396 (4.12), 528 (2.77), 570 (2.68) and 624 (2.20). The infrared spectrum (chloroform) showed a band at 6.04 μ.

Anal. Calcd. for $C_{12}H_7Cl_3O$: C, 52.65; H, 2.56. Found: C, 52.78; H, 2.79.

1-Azuloic Acid (II). A. From 1-Trifluoroacetylazulene.—1-Trifluoroacetylazulene (0.1 g., 0.447 mmole) was dis-

(12) F. Gerson and E. Heilbronner, *Helv. Chim. Acta*, **41**, 1444 (1958); F. Gerson, J. Schulze, and E. Heilbronner, *ibid.*, **41**, 1463 (1958).

(13) J. Hine, N. Burske, M. Hine, and P. Langford, *J. Am. Chem. Soc.*, **79**, 1406 (1957).

(14) Melting points are uncorrected and were taken on a Fisher-Johns apparatus. Ultraviolet and visible spectra were taken on either a Model 11S or Model 14 Cary recording spectrophotometer. Infrared spectra were recorded with a Perkin-Elmer Model 21 recording spectrophotometer.

(15) F. Swartz, *Bull. soc. chim. France*, [3] **13**, 992 (1895).

solved in 4 ml. of a solution of 0.6 *M* sodium hydroxide in 50% aqueous ethanol and refluxed for 75 min., during which time the bright red solution became purple. The solution was flooded with water and extracted with two 20-ml. portions of ether to remove unchanged 1-trifluoroacetylazulene. The crude azuloic acid was precipitated from the separated aqueous layer by acidification with 2 *N* hydrochloric acid and extracted into ether. The ethereal solution was washed twice with water, dried over anhydrous sodium sulfate, concentrated *in vacuo*, and the residue was chromatographed over acid-washed alumina. Eluents less polar than methanol did not affect the tightly adsorbed band. Elution with methanol developed a very pale yellow band which was discarded and a dark purple fraction was then removed with glacial acetic acid. The acetic acid solution was flooded with water and extracted with ether. The organic layer was exhaustively extracted with water and dried over anhydrous sodium sulfate. Removal of the solvent gave 68 mg. (88.5%) of 1-azuloic acid as lavender plates, m.p. 181–182°. A methylene chloride solution showed λ_{max} in mμ (log ε) at 237 (4.17), 289 (4.55), 294 (4.45), 300 (4.63), 368 (3.94) and 531 (2.74). The infrared spectrum showed absorption for a carbonyl group at 6.08 μ.

Anal. Calcd. for $C_{11}H_8O$: C, 76.73; H, 4.70. Found: C, 76.53; H, 4.95.

B. From 1-Trichloroacetylazulene.—1-Trichloroacetylazulene (0.1 g., 0.366 mmole) was treated with 5 ml. of a 0.6 *M* solution of sodium hydroxide in 50% ethanol. The reaction mixture was refluxed for 30 min., then flooded with water and extracted with ether. The aqueous layer was acidified with 5% hydrochloric acid and extracted with ether. The ethereal solution was washed three times with water and the combined washings extracted once with ether. The combined ether solutions were dried over sodium sulfate and the solvent was removed. There remained 65 mg. (99.5%) of 1-azuloic acid, m.p. 181–182°, which was identical with the product obtained from method A.

Treatment of the acid with excess diazomethane (ethereal solution) afforded methyl 1-azuloate (III), m.p. 55–56°, which was identical with an authentic sample.[5]

1-(α-Hydroxy-β,β,β-trifluoroethyl)azulene (IV).—To a cold (ice bath) solution of 1-trifluoroacetylazulene (50 mg., 0.223 mmole) in 5 ml. of anhydrous ether protected from moisture was added a slight excess of lithium aluminum hydride. The color of the red solution immediately changed to blue. The reaction mixture was allowed to stand at 0° for 10 min. Excess lithium aluminum hydride was then decomposed by the dropwise addition of 5 ml. of ice water followed by 5 ml. of 5% hydrochloric acid. The organic phase which separated was washed twice with water, dried over anhydrous sodium sulfate and, after removal of the solvent, the residue was chromatographed over acid-washed alumina. The single blue band was eluted with ether and yielded 49 mg. (98%) of 1-(α-hydroxy-β,β,β-trifluoroethyl)azulene as blue needles, m.p. 61–63°. The ultraviolet absorption of a methylene chloride solution showed λ_{max} in mμ (D_{max}) at 234 (0.63), 277 (1.37), 282 (1.26), 287 (1.15), 338 (0.14) and 352 (0.06). The principal visible maximum occurred at 568 mμ.

Anal. Calcd. for $C_{12}H_9F_3O$: C, 63.72; H, 3.98. Found: C, 64.01; H, 4.12.

1-Trifluoroacetyl-3-chloroazulene (V).—1-Chloroazulene[5] (0.2 g., 1.23 mmoles) in 5 ml. of methylene chloride was treated with 0.5 ml. (*ca.* 3.5 mmoles) of trifluoroacetic anhydride, protected from moisture, and allowed to stand at room temperature for 1 hr. The solution was worked up as described for 1-trifluoroacetylazulene. The residue so obtained was crystallized from *n*-hexane and yielded 0.26 g. (84%) of 1-trifluoroacetyl-3-chloroazulene as red needles, m.p. 110–111°. Absorption of a methylene chloride solution in the ultraviolet in mμ (D_{max}) was observed at 275 (0.91), 318 (1.52), and 395 (0.52). The maximum in the visible region occurred at 536 mμ.

Anal. Calcd. for $C_{12}H_6ClF_3O$: C, 55.72; H, 2.34. Found: C, 56.14; H, 2.56.

3-Chloro-1-azuloic Acid (VII).—1-Trifluoroacetyl-3-chloroazulene (50 mg., 0.194 mmole) was treated with 4 ml. of a solution of 0.6 *M* sodium hydroxide in 50% ethanol and refluxed for 75 min. The mixture was worked up in the manner described for 1-azuloic acid (method A). The material so obtained after chromatography over silicic acid and crystallization from methylene chloride afforded 34 mg. (85%) of 3-chloro-1-azuloic acid as purple needles which did not melt but started to decompose at 230°. Ultraviolet absorption of a methylene chloride solution in mμ (D_{max}) occurred at 237 (1.20), 293 (1.61), 305 (1.98), 365 (0.31), and 380 (0.33). A maximum in the visible region was observed at 554 mμ.

Anal. Calcd. for $C_{11}H_7ClO_2$: C, 63.94; H, 3.39. Found: C, 64.17; H, 3.45.

1-Trifluoroacetyl-3-phenylazulene (VI).—To a solution of 1-phenylazulene[16] (0.101 g., 0.495 mmole) in 10 ml. of carbon tetrachloride was added under anhydrous conditions 0.5 ml. (*ca.* 3.5 mmoles) of trifluoroacetic anhydride. After standing at room temperature for 10 min., the solution was worked up as described above for 1-trifluoroacetylazulene and the material so isolated was chromatographed over acid-washed alumina. Elution with methylene chloride developed a red band from which was obtained 0.131 g. (88.2%) of product as red needles, m.p. 105–110°. Rechromatography afforded a more pure sample, m.p. 111–112°. A methylene chloride solution showed absorption in mμ (D_{max}) at 253 (0.85), 291 (1.87), 317 (1.24), and 535. The infrared spectrum of a chloroform solution had a band at 6.01 μ.

Anal. Calcd. for $C_{18}H_{11}F_3O$: C, 72.00; H, 3.67. Found: C, 72.30; H, 3.89.

3-Phenyl-1-azuloic Acid (VIII).—1-Trifluoroacetyl-3-phenylazulene (50 mg., 0.167 mmole) was boiled under reflux with 5 ml. of a 0.6 *M* solution of sodium hydroxide in 50% aqueous ethanol for 75 min. The reaction mixture was worked up in the manner described for 1-azuloic acid, and the crude product was chromatographed over silicic acid. Methylene chloride brought down a lavender fraction which was crystallized from benzene and afforded 33 mg. (79.8%) of 3-phenyl-1-azuloic acid, m.p. 206–207°. The ultraviolet absorption of a methylene chloride solution showed λ_{max} in mμ (D_{max}) at 240 (1.22), 285 (1.72), 304 (1.76), and 380 (0.39). A maximum in the visible was observed at 555 mμ.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.26; H, 4.84. Found: C, 82.49; H, 4.88.

1-Trifluoroacetyl-3-thiocyanoazulene (IX).—Trifluoroacetic anhydride (0.5 ml., *ca.* 3.5 mmoles) was added under anhydrous conditions to a solution of 1-thiocyanoazulene[11] (0.1 g., 0.54 mmole) in 10 ml. of methylene chloride. There was no immediate color change. After 30 min. (room temperature), the red solution was worked up in the manner described for 1-trifluoroacetylazulene. The residue thus obtained was chromatographed over acid-washed alumina. A 1:1 methylene chloride–hexane mixture removed 63 mg. of unchanged thiocyanoazulene. Methylene chloride then eluted a red-orange fraction which yielded 37 mg. (24.4%; 65.8% net) of 1-trifluoroacetyl-3-thiocyanoazulene as red-orange needles, m.p. 139–140°. The ultraviolet absorption of a methylene chloride solution showed λ_{max} in mμ (D_{max}) at 233 (1.47), 276 (1.38), 311 (1.37), and 384 (0.46). The absorption maximum in the visible region occurred at 492 mμ. The infrared spectrum of a chloroform solution showed a carbonyl band at 5.95 μ and a peak attributed to the thiocyano group at 4.62 μ.

Anal. Calcd. for $C_{11}H_7NS$: C, 55.52; H, 2.14; N, 4.98. Found: C, 55.69; H, 1.99; N, 4.79.

Reaction of 1-Phenylazoazulene with Trifluoroacetic Anhydride.—Redistilled trifluoroacetic anhydride (0.5 ml.,

(16) A. G. Anderson and G. M-C. Chang, *J. Org. Chem.*, **23**, 151 (1958).

ca. 3.5 mmoles) was protected from moisture and added to a green solution of 0.116 g. (0.5 mmole) of 1-phenylazoazulene[5] in 10 ml. of carbon tetrachloride; the mixture became red immediately. After standing at room temperature for 10 min., the reaction mixture was washed with 10% aqueous sodium carbonate, whereupon the original green color returned to the solution. The organic solution was then washed three times with water and dried over anhydrous sodium sulfate. The solvent was then removed and the residue was chromatographed over basic alumina. Ether eluted a green band which yielded 0.115 g. of yellow-green needles which were identified by m.p. (119–120°) and m.m.p. (no depression) as 1-phenylazoazulene.[5]

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Stereospecific Synthesis of 2-Amino-3-*O*-(D-1′-carboxyethyl)-2-deoxy-D-glucose (Muramic Acid) and Related Compounds[1,2]

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Muramic acid, 2-amino-3-*O*-(D-1′-carboxyethyl)-2-deoxy-D-glucose, an important component of the structural mucopeptide of bacterial cell walls, has been synthesized by a stereospecific method. Data are presented which indicate that the lactic acid moiety of muramic acid belongs to the D-series. The following derivatives of muramic acid and isomuramic acid have been synthesized and described: methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(D-1′-carboxyethyl)-2-deoxy-α-D-glucopyranoside, methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(D-1′-carboxyethyl)-2-deoxy-β-D-glucopyranoside, ethyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(D-1′-carboxyethyl)-2-deoxy-α-D-glucopyranoside, ethyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(methyl D-ethyl-1′-carboxylate)-2-deoxy-α-D-glucopyranoside, methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(L-1′-carboxyethyl)-2-deoxy-α-D-glucopyranoside, methyl 2-acetamido-3-*O*-(L-1′-carboxyethyl)-2-deoxy-α-D-glucopyranoside, and the potassium salt of methyl 2-acetamido-3-*O*-(D-1′-carboxyethyl)-2-deoxy-α-glucopyranoside.

A new amino sugar was discovered[5] bound to uridine pyrophosphate peptide complexes in *Staphylococcus aureus* and this amino sugar was found subsequently in bacterial spores,[6] cell walls of gram positive bacteria,[7] and cell walls of *Escherichia coli*.[8] This amino sugar, named muramic acid, has been crystallized[9] and its provisional structure[10] confirmed by Kent[11] who synthesized 2-amino-3-*O*-(1′-carboxyethyl)-2-deoxy-D-glucose. Lambert and Zilliken[12] and Gigg and Carroll[13] have also synthesized muramic acid. All of the methods employed have required the resolution of a stereoisomeric mixture to obtain the desired product.

We synthesized muramic acid following basically the method of Kent but using optically active α-chloropropionic acid as the condensing reagent. Use of the optically active compound permitted us to establish more conclusively the stereostructure of the lactic acid moiety of muramic acid and incidentally to avoid tedious chromatographic operations in the preparative work. The reaction course of our synthesis is shown in the diagram below. The preparation of optically active α-chloropropionic acid was carried out as described in the literature,[14] that is, by deamination of active alanine with a mixture of nitrous and hydrochloric acids. We obtained a yield of about 50% of the corresponding optically active α-chloropropionic acid from either L-or-D-alanine. Isolation of methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(1′-carboxyethyl)-2-deoxy-α-D-glucopyranosides proved easy since they behaved as water-insoluble, alkali-soluble organic acids. As shown in the Experimental, this initial condensation product was obtained in good yield (usually more than 70% as pure recrystallized product). After removal of the benzylidene group by heating with 66% acetic acid, methyl 2-acetamido-3-*O*-(1′-carboxyethyl)-2-deoxy-α-D-glucopyranoside was obtained. Hydrolysis with dilute hydrochloric acid gave 2-amino-3-*O*-(1′-carboxyethyl)-2-deoxy-D-glucopyranoside. It was found that L-α-chloro-

(1) This investigation was supported by a Senior Research Fellowship (SF177) and by Grant E2303 from the National Institutes of Health, U.S. Public Health Service.

(2) A preliminary report was published in *Fed. Proc.*, **20**, 782 (1961).

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