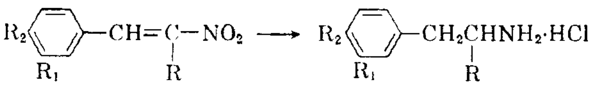
TABLE II. Reduction of Nitrosyrenes



IV V

	R	R_1	R_2	Formula	M.P.[a]	Recryst.[f] Solvent	Yield, % (G.)	Calcd., % C	Calcd., % H	Found, % C	Found, % H
IVa	H	OH	CH_3O	$C_9H_9NO_4$	162–164[b]	A	87 (17)	55.38	4.65	55.53	4.65
IVb	H	CH_3O	HO	$C_9H_9NO_4$	169[c]	A	83 (16.5)	—	—	55.43	4.20
IVc	CH_3	CH_3O	HO	$C_{10}H_{11}NO_4$	101–103	A	70 (14.5)	57.41	5.30	57.38	5.28
Va	H	HO	CH_3O	$C_9H_{13}NO_2\cdot HCl$	206–207[d]	B	80 (6.8)	53.19	6.93	52.80	6.64
Vb	H	CH_3O	HO	$C_9H_{13}NO_2\cdot HCl$	213–214[e]	B	80 (6.8)	—	—	53.08	6.93
Vc	CH_3	CH_3O	HO	$C_{10}H_{15}NO_2\cdot HCl$	262–263	B	50 (5)	55.17	7.41	55.10	7.24

[a] All melting points are uncorrected. [b] Reported[5] m.p. 161–162°. [c] 166–168°, [d] 206–207°, [e] 213–214°. [f] A = ethanol, B = methanol–ethyl acetate.

a colorless solution resulted. This solution was filtered to remove catalyst, the catalyst was washed with 100 ml. of hot water, and this added to the filtrate. To this clear solution, concentrated hydrochloric acid was added until the *p*H was 6.5; then it was heated on a water bath to 70° and more acid added to *p*H 3. The white precipitate was allowed to cool to room temperature. The white solid IIa was collected on a filter; 13 g. (80% yield), m.p. 164–166°. It was recrystallized once from dilute ethanol, m.p. 169–170°.

3-Methoxy-4-hydroxyphenylalanine hydrochloride (IIIa). To 300 ml. of dilute hydrochloric acid (1:3) was added 10 g. of IIa and this mixture was refluxed for 3 hr. (after 1 hr. solution was complete). When the mixture was cooled 3.1 g. of benzoic acid crystallized. It was removed by filtration. The clear filtrate was treated as in IIIc, yielding 8 g. (80% yield), m.p. 200° dec. The product was recrystallized once from ethanol-ether, m.p. 210° dec.

α-Methyl-3-methoxy-4-hydroxy-α-nitrostyrene (IVc). A mixture of vanillin (15.2 g., 0.1 mole), ammonium acetate (8 g.), nitroethane (25 g., 0.33 mole) and 80 ml. of glacial acetic acid was refluxed for 2 hr. The mixture was then poured into 1 l. of ice cold water. After cooling overnight gave a yellow crystalline product. It was collected on a filter and recrystallized from 50 ml. of ethanol, m.p. 101–103.° The yield was 14.5 g. (70%).

α-Methyl-β-(3-methoxy-4-hydroxyphenyl)ethylamine hydrochloride (Vc). In a Sohxlet thimble was placed 10.5 g. (0.05 mole) of IVc which was extracted into a well-stirred suspension of 5 g. of lithium aluminum hydride in 500 ml. of dry ether. When the reaction was complete (72 hr.), there was slowly added 600 ml. of ice cold 1.5*N* sulfuric acid. The aqueous layer was separated and the *p*H adjusted to 6 with solid lithium carbonate, and the mixture was then filtered. The clear filtrate was heated to 70° and a hot solution of 14 g. of picric acid in the minimum amount of ethanol was added. The mixture was cooled, whereupon the crystals which separated were collected and dissolved in 200 ml. of boiling water. To this hot solution was added 40 ml. of concd. hydrochloric acid. Cooling the solution gave picric acid which was collected. Then the filtrate was extracted three times with 100-ml. portions of nitrobenzene and twice with 100-ml. portions of ether. The aqueous portion was concentrated under vacuum until crystals formed. Recrystallization from methanol-ethyl acetate yielded 5 g. (50% yield) of white plates, m.p. 262–263°.

Acknowledgment. I am indebted to Dr. R. B. Barlow for valuable discussions and suggestions. I am also indebted to Dr. J. W. Minnis (Department of Biochemistry) for microanalyses.

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N-Acylation of D-Ribosylamine[1]

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In a previous article,[4] the *N*-acetylation of D-ribosylamine (in water) with acetic anhydride was described. Two other acylation procedures have now been studied. In the first, an aqueous solution of D-ribosylamine (RNH_2) was treated with an acyl chloride in the presence of excess magnesium oxide, according to Equation 1.

$$RNH_2 + R_1COCl + 0.5\ MgO \longrightarrow RNHCOR_1 + 0.5\ MgCl_2 + 0.5\ H_2O \quad (1)$$

$$\text{I. } R_1 = OC_2H_5$$

$$\text{II. } R_1 = CH_2Cl$$

$$\text{III. } R_1 = CHCl_2$$

In the second procedure, an *N*-substituted amino acid (prepared according to Equations 2 or Equation 3) was converted to a mixed anhydride (by Equations 4), and this anhydride was condensed with D-ribosylamine (Equation 5) in water:

$$HCO_2H + (CH_3CO)_2O \longrightarrow HCO{-}O{-}COCH_3 + CH_3CO_2H \quad (2a)$$

$$HCO{-}O{-}COCH_3 + H_2NCHR_2CO_2H \longrightarrow HCONHCHR_2CO_2H + CH_3CO_2H \quad (2b)$$

$$\text{IV. } R_2 = H$$

$$\text{V. } R_2 = CH_3\ (\text{L form})$$

$$C_6H_5CH_2OCOCl + HN(R_3)CH_2CO_2H \longrightarrow C_6H_5CH_2OCON(R_3)CH_2CO_2H + HCl \quad (3)$$

$$\text{VI. } R_3 = H$$

$$\text{VII. } R_3 = CH_3$$

$$R_4CO_2H + (C_4H_9)_3N \longrightarrow R_4COO^-(C_4H_9)_3NH^+ \quad (4a)$$

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[1] The work described herein was completed prior to June 21, 1957.

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[4] R. S. Tipson, *J. Org. Chem.*, 26, 2462 (1961).

$$R_4COO^-(C_4H_9)_3NH^+ + ClCO_2C_2H_5 \longrightarrow R_4CO{-}O{-}CO_2C_2H_5 + (C_4H_9)_3NH^+Cl^- \quad (4b)$$

$$R_4CO{-}O{-}CO_2C_2H_5 + RNH_2 \longrightarrow R_4CONHR + C_2H_5OH + CO_2 \quad (5)$$

VIII and IX. $R_4 = HCONHCHR_2$

X and XI. $R_4 = C_6H_5CH_2OCON(R_3)CH_2$

For compounds X and XI, the *N*-benzyloxycarbonyl group was then removed by catalyzed hydrogenolysis, giving XII and XIII, respectively.

$HN(R_3)CH_2CONHR$

XII. $R_3 = H$

XIII. $R_3 = CH_3$

The condensation of D-ribosylamine with *N*-formylglycine (IV) afforded a 2-formamido-*N*-D-ribosylacetamide monohydrate (VIII), the D-ribosyl residue of which was shown, by periodate oxidation, to have the pyranoid structure. Since the acetylation of D-ribosylamine has previously been shown[4] to afford pyranoid derivatives, it is probable that the D-ribosylamine used is D-ribopyranosylamine and that all the *N*-acyl derivatives thereof that are here described are D-ribopyranosyl derivatives. Furthermore, from their optical rotations, it seems likely that all of them are β-anomers.

Occasion is also taken to describe the preparation of 2-deoxy-2-(2-formamidoacetamido)-D-glucose.

EXPERIMENTAL[5]

Ethyl N-D-ribosylcarbamate [*"N-D-ribosylurethan"*] (I). In a 250-ml., three necked flask (standard-taper joints, stirrer, pentane thermometer, and pressure-equalizing dropping funnel) were placed 100 ml. of distilled water and 2.5 g. of finely powdered magnesium oxide. The mixture was cooled to 1.5°, with stirring, in an ice-salt bath. D-Ribosylamine[4] (7.5 g.) was now added, with cooling and stirring, and 3 min. thereafter, dropwise addition of ethyl chloroformate (4.8 ml.) was started from the dropping funnel; the addition was completed during 5 min., the temperature being kept at 0.5°. After the suspension had been stirred for a further 30 min. at this temperature, the cooling bath was replaced by an ice bath, and stirring was continued for 15 min. The bath was now removed and, with continued stirring, the temperature was allowed to rise to room temperature during 2 hr. The suspension was immediately filtered with suction, the excess magnesium oxide being quickly washed with aqueous washings of the flask, stirrer, and thermometer. The filtrate and washings were combined and immediately passed (fairly rapidly) through a column (200 ml.) of an anion–cation, mixed-bed resin (Amberlite MB-3), with elution with distilled water. Six 100-ml. portions of effluent were collected within 40 min. and were immediately evaporated to dryness under diminished pressure at 30°, affording colorless crystals which were dried at 0.1 mm. in the same apparatus; wt., 8.8 to 9.5 g., in four different preparations. For purification, the crystals were treated with a mixture of absolute ethanol (1 volume) and acetone (2 volumes), swirled, stoppered, refrigerated overnight, filtered with suction (rubber dam), and dried in the vacuum desiccator (Desiguard) at 0.1 mm.; yield, 5.5 g., m.p. 172–174°, $[\alpha]^{21}_{D}$ −21.9° (*c*, 1.075 in water; unchanged after 17 hr. at 21°).

Anal. Calcd. for $C_8H_{15}NO_6$: C, 43.43; H, 6.84; N, 6.33; OC_2H_5, 20.37. Found: C, 43.31; H, 6.76; N, 6.15; OC_2H_5, 19.82.

2-Chloro-N-D-ribosylacetamide (*N-chloroacetyl-D-ribosylamine*) (II). The previous experiment was repeated, except that 4 ml. of chloroacetyl chloride was the acylating agent. After removal of the excess magnesium oxide, the solution was passed through a column of 250 ml. of Amberlite MB-3 and eight 100-ml. portions of effluent were collected. These were combined, evaporated to dryness below 30°, and the resulting colorless sirup was dried at 0.1 mm.; wt., 8.3 g. Addition of absolute ethanol (1 volume) gave colorless crystals; a further 9 volumes of absolute ethanol was added, the suspension was swirled and filtered, and the colorless crystals were dried; wt., 3.6 g., m.p. 170–172°, $[\alpha]^{27}_{D}$ −15.5° (*c*, 0.997 in water).

Anal. Calcd. for $C_7H_{12}ClNO_5$: C, 37.26; H, 5.36; Cl, 15.71; N, 6.21. Found: C, 37.46; H, 5.72; Cl, 15.11; N, 6.04.

2,2-Dichloro-N-D-ribosylacetamide (III). The experiment was repeated, but with 4.9 ml. of dichloroacetyl chloride as the acylating agent. After filtration and passage through 250 ml. of Amberlite MB-3 resin,[6] eight 100-ml. portions of effluent were collected; evaporation to dryness afforded 8.4 g. of colorless gum. Treatment with absolute ethanol (42 ml.) gave 2.7 g. of colorless crystals, m.p., 160–162°. The compound readily decomposes, but cautious washing with cold methanol raised the m.p. to 177–178° (softening at 175°); $[\alpha]^{24}_{D}$ −12.5° (*c*, 1.041 in water).

Anal. Calcd. for $C_7H_{11}Cl_2NO_5$: C, 32.33; H, 4.26; Cl, 27.27; N, 5.39. Found: C, 32.39; H, 4.55; Cl, 26.06; N, 5.21.

2-Formamidoacetic acid (*N-formylglycine*) (IV). The following procedure is an improvement on that of earlier workers.[7,8] Formic acid (45.5 ml. of 98%) and 112 ml. of acetic anhydride were mixed in a wide-necked, 250-ml. Erlenmeyer flask to which was immediately attached a reflux condenser (Drierite tube); the mixture (*A*), which evolved heat, was kept for 90 min. before use. About 20 min. before the elapse of this time, glycine (37.6 g.) was placed in a 500-ml., round bottomed flask, 35 ml. of 98% formic acid was added, and the suspension was heated in a boiling-water bath, under reflux, until the glycine had dissolved (15 min.); the resulting pale yellow solution was cooled to room temperature, affording a pale yellow sirup to which was added solution *A*, and the flask was immediately placed under a reflux condenser (Drierite tube). The solution became warm and gas bubbles formed; after the solution had been kept overnight under the condenser, about half the volume consisted of colorless crystals which were filtered with suction (rubber dam), pressed dry, washed with two 25-ml. portions of acetone, and dried in the vacuum desiccator (Desiguard) at 0.1 mm.; wt., 18.1 to 21.8 g., m.p. 153–155° (softening at 144°; crystallized on cooling). The mother liquor and washings were united and cautiously evaporated to dryness under diminished pressure at 50°, giving a mass of colorless crystals which, on being stirred with 100 ml. of ethyl acetate, afforded a further 14.2 g. of colorless crystals having the same properties as the first crop. The mother liquor was evaporated to dryness and the resulting yellow gum was dissolved in 250 ml. of water; the solution was kept overnight at room temperature and then evaporated to dryness, giving a pale yellow, crystalline

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(5) Analyses by Mr. C. E. Childs, Research Division, Parke, Davis and Co., Detroit 32, Mich. The infrared absorption spectrum (2–16μ) of each of the compounds described was recorded in the Department of Chemical Physics, Mellon Institute; the spectra were particularly useful in following the progress of purification procedures.

(6) In this preparation, the mixed-bed resin was cautiously backwashed with 50% aqueous acetone (so that the two resins did not separate to give two layers) and the same solvent was used as the eluant.

(7) E. Fischer and O. Warburg, *Ber.*, **38**, 3997 (1905).

(8) E. Biilmann, K. A. Jensen, and H. B. Jensen, *Bull. soc. chim. France*, [5] **1**, 1661 (1934).

mass which, on treatment with acetone, gave 14 g. of yellow crystals, m.p. 148–150°. Crude material (18.0 g.) was recrystallized by dissolution in boiling dioxane (12.5 volumes) under reflux, filtering the hot solution, and cooling to room temperature; wt., 14.9 g., m.p. 151–153° (lit.[7,8] m.p. 151–152°).

Anal. Calcd. for $C_3H_5NO_3$: C, 34.96; H, 4.89; N, 13.59. Found: C, 34.94; H, 4.93; N, 13.52.

N-Formyl-L-alanine (V). In a manner similar to the preparation of IV, 17.8 g. (0.2 mole) of L-alanine was suspended in 20 ml. of 98% formic acid, heated under reflux in a boiling-water bath, cooled to room temperature, and treated with a previously prepared mixture of 18.5 ml. of formic acid and 48 ml. of acetic anhydride. Evaporation to dryness afforded a colorless, crystalline mass which was dried at 0.1 mm., dissolved in 26 ml. of water in a bath at 85°, cooled, nucleated, and refrigerated, giving crop 1 (11.0 g.) of colorless crystals, m.p. 128–130°; recrystallization from ethyl acetate (16 volumes) gave crop 1A (9.0 g.), m.p. 130–132°, $[\alpha]_D^{23}$ −64.8° (*c*, 1.050 in water). The mother liquor of crop 1 was evaporated to dryness, and the crystalline mass was dried at 0.1 mm., treated with 224 ml. of boiling ethyl acetate under reflux, filtered hot (thus removing 0.4 g. of pink impurity), and the filtrate combined with the mother liquor of crop 1A and evaporated to dryness; the crystals were dissolved in 205 ml. of boiling ethyl acetate, and the solution was cooled and refrigerated, giving crop 2 (8.2 g.), m.p. 130–131°, $[\alpha]_D^{23}$ −73.1° (*c*, 1.102 in water). Presumably, crop 1A contained some of the racemate, lit.[8] m.p. 147–148°.

Anal. Calcd. for $C_4H_7NO_3$: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.19; H, 6.17; N, 12.01.

N-Benzyloxycarbonylsarcosine (VII). In a 175-ml., three necked flask (equipped with an electric stirrer and two dropping funnels) was placed 50 ml. of 2*N* sodium hydroxide solution and 8.9 g. of sarcosine, and the mixture was cooled in ice. With stirring, 17.1 g. of benzyl chloroformate was slowly added dropwise from one funnel (during 27 min.) while 25 ml. of 4*N* sodium hydroxide solution was simultaneously added from the other funnel. The mixture was stirred for a further 10 min. and then extracted with two 100-ml. portions of absolute ether. The ether extracts were discarded; the aqueous layer was cooled in ice, and concentrated hydrochloric acid was cautiously added until the solution was acid to Congo red paper and an oil was precipitated After being kept for 1 hr., the mixture was extracted with three 100-ml. portions of absolute ether; the ether extracts were combined, dried with anhydrous sodium sulfate, filtered, and evaporated to dryness, giving 15.2 g. of colorless sirup. This was dissolved in dry ether (2 volumes) and 15 ml. of pentane was added dropwise to incipient opalascence. On refrigeration, a first crop of colorless crystals (3.8 g.) was obtained; by similar treatment, the mother liquor afforded a further 10.2 g. of crystalline product. It had a m.p. of 58–59° (lit.[9] m.p. 53–54°).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.52; H, 6.41; N, 6.32.

2-Formamido-N-D-ribopyranosylacetamide monohydrate (VIII). To 9.3 g. of tributylamine was added 5.2 g. of *N*-formylglycine (IV) and 37.5 ml. of acetone. The solution was cooled to −1° in ice–salt, 4.7 ml. of ethyl chloroformate was added, and the solution was kept at 0° for 10 min. This solution was added gradually (5 min.), with stirring, to a freshly prepared solution of 7.5 g. of D-ribosylamine[4] in 75 ml. of water at 0°, so that the temperature did not exceed 4°. After the solution had been stirred for a further 15 min. at 0°, gas evolution had ceased, the cooling bath was removed, and the temperature was allowed to rise to room temperature (1 hr.). The clear, pale yellow solution was diluted to 200 ml. with water, rapidly passed through a column of 300 ml. of Amberlite MB-3 resin, and eluted with water. Eight 100-ml. portions of effluent were collected; their optical rotations were determined, and then they were immediately evaporated to dryness under diminished pressure (bath temp., 35°) and dried at 0.1 mm., giving 9.6 g. of colorless, glassy product which, on treatment with absolute ethanol (5 volumes), dissolved and then deposited 7.1 g. of colorless crystals. Recrystallization from boiling absolute methanol (100 volumes) afforded colorless crystals, m.p. 156–157°, $[\alpha]_D^{26}$ −15.5° (*c*, 1.033 in water).

Anal. Calcd. for $C_8H_{14}N_2O_6 \cdot H_2O$: C, 38.10; H, 6.39; N, 11.11; H_2O, 7.14; mol. wt. (anhydrous), 234. Found: C, 38.15; H, 6.35; N, 11.04; loss on drying, 7.00; mol. wt. (anhydrous, in camphor), 228.

At *p*H 7.2 (bicarbonate buffer) at room temperature, it consumed 1.78 equivalents of periodate in 3 hr., indicating a pyranoid structure.[10] In a more detailed study, we obtained the following results (mmoles of periodate taken up, mmoles of formic acid produced per mmole, and time of reaction): 1.74, 0.844, 10 min.; 1.83, 0.93, 30 min.; 1.89, 0.977, 60 min.; constant thereafter. By paper chromatography, the compound was indistinguishable[11] from a "sample of formylglycinamide riboside which is obtainable by treating the ribotide with wheat-germ phosphatase." (The D-ribosyl residue of the natural compound has, however, the furanoid structure; its melting point and $[\alpha]_D$ were unavailable.)

2-Deoxy-2-(2-formamidoacetamido)-D-glucose. Water (75 ml.) was cooled to 0°, 10.8 g. of 2-amino-2-deoxy-D-glucose hydrochloride and 2.2 g. of powdered magnesium oxide were added, and the stirred suspension was treated at 0° with the mixed anhydride prepared (as in the synthesis of VIII) from 5.2 g. of *N*-formylglycine (IV). The reaction mixture was passed through a column of 500 ml. of Amberlite MB-3 resin,[6] and the combined effluents (9 × 100 ml.) were evaporated to dryness, affording 5.8 g. of a mixture of gum and crystals. This mixture was treated with 116 ml. of boiling absolute ethanol under reflux, cooled, and refrigerated, affording a first crop of colorless crystals (3.0 g.). On recrystallization from absolute methanol (60 volumes), it had a m.p. of 180–182°, $[\alpha]_D^{26}$ + 74.5° (*c*, 0.664 in pyridine).

Anal. Calcd. for $C_9H_{16}N_2O_7$: C, 40.93; H, 6.11; N, 10.61. Found: C, 40.70; H, 5.98; N, 10.57.

L-*(2-Formamido-N-D-ribosylpropionamide)* (IX). The preparation was conducted as for the corresponding acetamide (VIII), except that 5.9 g. of *N*-formyl-L-alanine (V) was used instead of IV. There was obtained a colorless, crystalline mass (6.8 g.) which, on treatment with absolute ethanol (2 volumes), gave 2.3 g. of colorless crystals, m.p. 194–195°, $[\alpha]_D^{22}$ −53.1° (*c*, 1.007 in water).

Anal. Calcd. for $C_9H_{16}N_2O_6$: C, 43.55; H, 6.50; N, 11.29. Found: C, 43.52; H, 6.52; N, 11.46.

Benzyl N-(D-ribosylcarbamoylmethyl)carbamate (X). This preparation was conducted as for VIII, but 10.5 g. of *N*-(benzyloxycarbonyl)glycine (VI) was used instead of IV, and the mixed-bed resin was specially treated.[6] The resulting colorless crystals (16 g.) were recrystallized from absolute methanol (3 volumes); m.p. 192–193°, $[\alpha]_D^{23}$ −2.97° (*c*, 1.009 in pyridine).

Anal. Calcd. for $C_{15}H_{20}N_2O_7$: C, 52.94; H, 5.92; N, 8 23. Found: C, 52.54; H, 6.01; N, 8.24.

Benzyl N-methyl-N-(D-ribosylcarbamoylmethyl)carbamate (XI). The preparation was conducted as for compound X, except that 11.2 g. of *N*-(benzyloxycarbonyl)sarcosine (VII) was used. The resulting colorless crystals (12.3 g.) were recrystallized from absolute methanol (10 volumes); m.p. 207° (softening at 205°), $[\alpha]_D^{23}$ −2.0° (*c*, 1.014 in pyridine).

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(9) D. Ben-Ishai and E. Katchalski, *J. Am. Chem. Soc.*, **74**, 3688 (1952).

(10) This determination was made in the laboratory of Dr. Calvin L. Stevens (December 15, 1956), to whom we are indebted.

(11) Dr. John M. Buchanan, private communication, November 24, 1956.

Anal. Calcd. for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.26; N, 7.91. Found: C, 54.57; H, 6.34; N, 7.95.

*2-Amino-N-*D*-ribosylacetamide* (XII). The benzyl ester X (1.7 g.) was dissolved in 200 ml. of boiling absolute methanol under reflux; the solution was cooled in ice, quickly added to a suspension of the catalyst (10% palladium on carbon) in 10 ml. of ice cold methanol in the bottle of a Parr hydrogenator, and hydrogenated in the customary manner. The suspension was filtered and the colorless filtrate was evaporated to dryness, giving a quantitative yield of colorless crystals which were stirred with cold methanol and filtered; m.p. 180° dec. (softens at 177°), $[\alpha]_D^{25}$ $-17.8°$ (*c*, 0.956 in water).

Anal. Calcd. for $C_7H_{14}N_2O_5$: C, 40.77; H, 6.84; N, 13.59. Found: C, 40.81; H, 6.84; N, 13.67.

*2-(Methylamino)-N-*D*-ribosylacetamide* (XIII). The benzyl ester XI (1.8 g.) was hydrogenolyzed as for the preparation of XII, giving 0.9 g. of colorless crystals, m.p. 182° dec. Recrystallized from absolute methanol (70 volumes), it had a m.p. of 192–193°, $[\alpha]_D^{26}$ $-31.9°$ (*c*, 0.094 in water).

Anal. Calcd. for $C_8H_{16}N_2O_5$: C, 43.63; H, 7.32; N, 12.72. Found: C, 43.78; H, 7.47; N, 12.88.

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(2-Carboxyethyl)succinic Anhydride[1]

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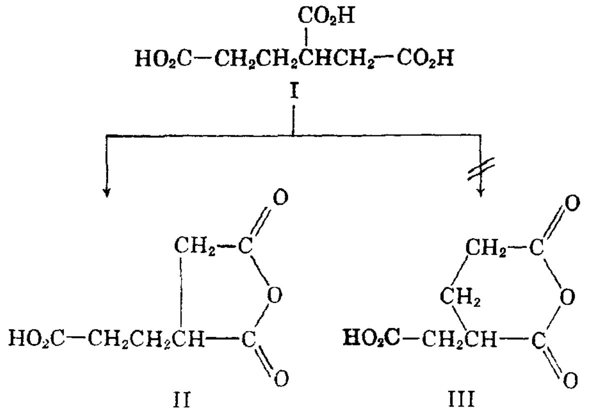
Dehydration of 1,2,4-butanetricarboxylic acid (I)[1] to (2-carboxyethyl)succinic anhydride (II) may be effected thermally or by treatment with acetic anhydride, acetyl chloride, and phosgene, respectively. The use of ethylene dichloride as a selective crystallization solvent makes possible the isolation of II in high yield and purity from hitherto intractable residues.



That the anhydro acid possesses the succinic structure, II, rather than the isomeric glutaric structure, III, is indicated by comparison of the infrared absorption maxima characteristic of the anhydride doublet as shown in the table below.

INFRARED ABSORPTION MAXIMA,[a] μ, FOR ANHYDRIDE DOUBLET

	I	Succinic Anhydride	Glutaric Anhydride
C═O	5.38	5.36	5.63
	5.60	5.60	5.70
C—O—C	8.13	8.10	8.11
	8.20	8.30	8.19

[a] Taken with a Baird Model 4–55 infrared double-beam spectrophotometer of a 1% KBr plaque, calibrated against polystyrene.

EXPERIMENTAL[2]

(2-Carboxyethyl)succinic anhydride (II). a. *By thermal dehydration of* I. A mixture of 577 g. (3 moles) of I and 1200 g. of dry nonane was heated to reflux, removing water of dehydration from the heterogeneous azeotrope over a period of 15 hr. The product mixture was cooled, nonane removed from the insoluble crude product by decantation, the anhydro acid taken up in hot ethylene dichloride, treated with decolorizing carbon, and then cooled to crystallize. Filtration gave 468 g., an 87.8% yield, of fine, white crystals (m.p. 63–64°, 96.7% purity by anhydride titration with aniline/sodium hydroxide).

Anal. Calcd. for $C_7H_8O_5$: C, 48.84; H, 4.68. Found: C, 48.83; H, 4.72.

Evaporation of the ethylene dichloride filtrates gave an additional 31 g., a 4.8% yield, of II.

b. *By dehydration with acetic anhydride.* A mixture of 380 g. (2 moles) of I, 221 g. (2.15 moles) of acetic anhydride and 700 g. of ethylbenzene was fractionally distilled at 50 ml. pressure to remove the acetic acid–ethylbenzene azeotrope (b.p. 47°/50 mm.) during 25 hr. Titration of the distillate indicated the theoretical amount of acetic acid. The reaction mixture was cooled, the supernatant ethylbenzene was decanted from the insoluble crude product, and the product was taken up in hot ethylene dichloride, treated with decolorizing carbon and cooled to crystallize. Filtration gave 313 g., a 91% yield, of fine white crystals (m.p. 62–63°, 100% purity by anhydride titration with aniline/sodium hydroxide).

Anal. Calcd. for $C_7H_8O_5$: C, 48.84; N, 4.68. Found: C, 49.14; H, 4.68.

The anilic acid prepared by reaction with aniline in chloroform melted at 144–145° (from water).

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.58; H, 5.90; N, 5.85.

c. *By dehydration with acetyl chloride.* A mixture of 190 g. (1 mole) of I, 235 g. (3 moles) of acetyl chloride, and 300 g. of 1,4-dioxane was charged to a flask and heated slowly with agitation to 60–70°. The weight of hydrogen chloride evolved was determined by bubbling the blow-off gases through a water bottle and recording the weight gain. After 7.5 hr., the evolution of hydrochloric acid had essentially ceased. The reaction mixture was cooled and stripped of excess acetyl chloride and solvent under reduced pressure at 25°. The solid residue was dissolved in hot ethylene dichloride, treated with decolorizing carbon, and filtered. Upon crystallization, there was obtained a total of 134 g., a 78% yield of II (m.p. 63–64°). Infrared maxima: 3.80, 5.38, 5.60, 8.13, 8.20, 10.85 μ.

Evaporation of the filtrate gave 30 g. of unchanged I.

d. *By dehydration with phosgene.*[3] A solution of 56 g. (0.295 mole) of I in 300 ml. of dry acetone was treated with a

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(1) For previous paper of this series, see *J. Org. Chem.*, 26, 3757 (1961).

(2) All temperatures are uncorrected.

(3) We are indebted to Dr. T. K. Brotherton for this experiment.