was extracted from the sirup and the filter cake. The combined chloroform extracts were washed with 30% potassium iodide solution and water and then dried (sodium sulfate). Evaporation under reduced pressure gave a sirup (IX) which failed to crystallize: yield 4.2 g. The sirupy product (4.0 g.) was dissolved in 60 ml. of absolute methanol containing 5 ml. of *n*-butylamine. The mixture was refluxed for 4 hr., then evaporated to an oil. The oil was distributed between chloroform and water, and the water layer was washed with chloroform. The aqueous extract was decolorized (carbon) and evaporated to a sirup: yield 3.77 g. Crystallization from methanol followed by recrystallization from aqueous methanol gave analytically pure X: m.p. 201–204°; $[\alpha]^{24}D$ +77° (*c* 0.51, water); absorption spectra data,[12] $\lambda_{max}^{H_2O}$ 269 mμ, λ_{max}^{KBr} 2.90 (OH), 5.80 (CO), 6.80 (C=N), 7.30 (methyl hydrogen), 9.15, 9.55, 9.70 (C–OH); X-ray powder diffraction data,[13] 13.10 vs (1,1,1), 9.46 w, 8.42 vs (1,1,1), 6.35 m, 5.99 m, 5.25 m, 5.00 s, 4.66 m, 4.40 s, 4.17 s, 3.68 vs (1,1,1), 3.52 w, 3.31 m, 3.21 m, 3.11 vw, 2.95 w.

Anal. Calcd. for $C_{12}H_{20}N_2O_8$: C, 45.13; H, 6.00; N, 8.78; OCH_3, 9.72. Found: C, 44.89; H, 6.73; N, 8.72; OCH_3, 9.49.

Nucleosides. XXVII. 3′-Amino-3′-deoxyhexopyranosyl Nucleosides. II. Synthesis of 1-(3′-Amino-3′-deoxy-β-D-glucopyranosyl)pyrimidines and Related Compounds[1,2]

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A simple synthesis of the 3′-nitro-3′-deoxy derivative IV of 1-β-D-glucopyranosyluracil was achieved by treatment of uridine with metaperiodate followed by condensation with nitromethane. Reduction of IV yielded the 3′-amino analog V whose structure was rigidly proved by chemical and n.m.r. studies. The 3′-aminogluco nucleoside V was converted to 1-β-D-allopyranosyluracil (XIII) and to 1-(3′-amino-3′-deoxy-β-D-glucopyranosyl)-cytosine (XVII). Degradative studies with V, proceeding *via* a 5,6-dihydro nucleoside VII, yielded anomers of the known methyl-3-acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-D-glucosides.

The past decade has witnessed the discovery of several 3-amino-3-deoxy sugars as antibiotics.[3] Nucleosides containing 3-amino-3-deoxy-D-ribose have also been found in nature,[4–6] some of which have since been synthesized chemically,[7] and have exhibited interesting biological properties.[8]

Nucleosides containing the 3-amino-3-deoxy*hexose* moiety have not as yet been isolated from natural sources.[9–11] The only recorded chemical synthesis of nucleosides containing a 3-aminohexosyl moiety is that reported by Baker, *et al.*,[12] who condensed suitably protected 3-aminohexoses (of the allosyl and altrosyl configuration) with the mercuri salts of certain purine derivatives.

This paper deals with a facile synthesis and a study of the chemical properties of 3′-amino-3′-deoxyhexosylpyrimidines which should have wide application in the nucleoside area. Preliminary communications on this subject have appeared.[2,13]

Baer and Fischer[14] showed that dialdehydes derived from aldopento- and aldohexopyranosides could be condensed with nitromethane to yield 3-nitro-3-deoxypyranosides, which, upon reduction, yielded glycosides of 3-amino sugars. Their procedure was adapted to 1-β-D-ribofuranosyluracil (uridine)[15] (see Scheme I).

Uridine (I) was oxidized with sodium metaperiodate to the dialdehyde II which was condensed with nitromethane in ethanol in the presence of sodium methoxide to yield the insoluble sodium salt of the *aci*-nitro nucleoside III. Neutralization of III was achieved under anhydrous conditions (to prevent the Nef reaction)[16,17] and gave a mixture of several isomers.[18] Neutralization under aqueous conditions, however, proceeded smoothly and a crystalline product (IV) was easily obtained in *ca.* 60% over-all yield from I. Hydrogenation of IV with Raney nickel under pressure[19] yielded the nucleoside V. The ultraviolet absorption spectrum of V resembled that of a 1-glycopyranosyluracil.[20] Compound V consumed 2 moles of periodate per mole, consistent with a hexopyranosyl structure and gave a positive ninhydrin test. The strong infrared absorption at ~6.4 μ[21] found in IV (due to the nitro group) was totally absent in V. The elemental

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Grant No. CA 03190-09.

(2) Paper I: K. A. Watanabe and Jack J. Fox, *Chem. Pharm. Bull.* (Tokyo), **12**, 975 (1964); Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 5D.

(3) For review articles, see A. B. Foster and D. Horton, *Adv. Carbohydrate Chem.*, **14**, 432 (1959); J. D. Dutcher, *ibid.*, **18**, 259 (1963).

(4) C. W. Waller, P. W. Fryth, B. L. Hutchings, and J. H. Williams, *J. Am. Chem. Soc.*, **75**, 2025 (1953).

(5) N. N. Gerber and H. A. Lechevalier, *J. Org. Chem.*, **27**, 1731 (1962).

(6) N. M. Kredich and A. J. Guarino, *J. Biol. Chem.*, **236**, 3300 (1961).

(7) See (a) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955), for the synthesis of puromycin; (b) B. R. Baker, R. E. Schaub, and H. M. Kissman, *ibid.*, **77**, 5911 (1955), for the synthesis of 3′-amino-3′-deoxyadenosine.

(8) See (a) M. A. Darken, *Pharmacol. Rev.*, **16**, 223 (1964), for puromycin; (b) ref. 5, for 3′-amino-3′-deoxyadenosine; (c) A. J. Guarino, M. L. Ibershof, and R. Swain, *Biochim. Biophys. Acta*, **72**, 62 (1963), for homocitrullylaminoadenosine.

(9) Gougerotin, an antibiotic from *Streptomyces gougerottii*, was originally reported to have a 3-amino-3-deoxyallose structure in the molecule.[10] This was corrected to the 4-amino-4-deoxygalactose structure.[11]

(10) H. Iwasaki, *Yakugaku Zasshi*, **82**, 1387, 1393 (1962).

(11) J. J. Fox, Y. Kuwada, K. A. Watanabe, T. Ueda, and E. B. Whipple, *Antimicrobial Agents Chemotherapy*, in press.

(12) B. R. Baker, J. P. Joseph, and R. E. Schaub, U. S. Patent 2,852,505 (Sept. 16, 1958); *Chem. Abstr.*, **53**, 8175*d* (1959).

(13) A brief communication by F. W. Lichtenthaler, H. P. Albrecht, and G. Olfermann [*Angew. Chem.*, **77**, 131 (1965)] has very recently appeared which also deals with the application of the nitromethane procedure to nucleosides. These authors were regretfully unaware of our previous paper[2] in this series (personal communication from Dr. F. W. Lichtenthaler).

(14) H. H. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **81**, 5184 (1959).

(15) Adaptation of this procedure to purine nucleosides will be reported in another paper in this series: *J. Heterocylic Chem.*, in press

(16) N. Kornblum and G. E. Graham, *J. Am. Chem. Soc.*, **73**, 4041 (1953).

(17) H. H. Baer and H. O. L. Fischer, *ibid.*, **81**, 5184 (1959).

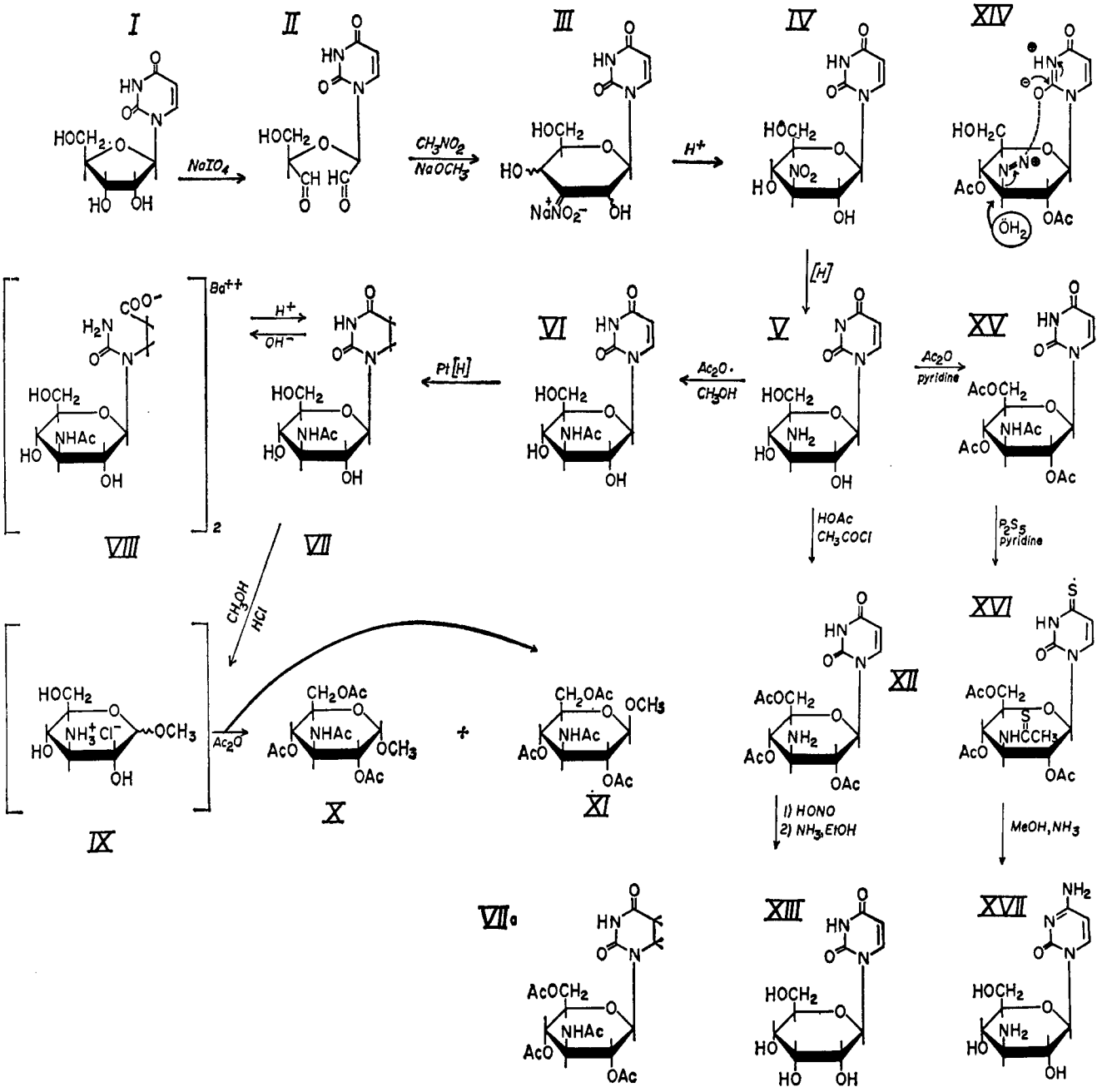
(18) K. A. Watanabe, H. A. Friedman, J. Beránek, and J. J. Fox, unpublished experiments.

(19) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).

(20) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

(21) T. Urbanski, *Bull. soc. chim. France*, 1475 (1961).

SCHEME I



analyses of V was consistent with that for an amino-hexosyluracil. N acetylation of V with acetic anhydride in methanol yielded the N-acetate VI, which was resistant to oxidation with metaperiodate, thus establishing the 3′-amino-3′-deoxyhexosyl structure in V. Proof of the 1-β-D-gluco configuration of V was obtained by a combination of chemical and n.m.r. studies.

Reduction of VI with Adams catalyst afforded the 5,6-dihydro nucleoside VII in 90% yield. Treatment of VII with alkali gave the barium salt of the ureido-propionic acid derivative VIII. Attempts to cleave the sugar moiety from this derivative by acid only regenerated VII. The reversion of certain ureido acids to a 5,6-dihydrouracil has been observed previously.[22] Cleavage of the sugar–base linkage in VII was efficiently achieved by refluxing VII for 8 hr. in methanolic hydrogen chloride. A sirup (IX) was obtained which, without isolation, was acetylated with acetic anhydride in pyridine. Two crystalline anomers of the known methyl glycoside tetraacetates of 3-amino-3-deoxy-D-glucose, X[23–25] and XI,[26,27] were obtained. These data establish the gluco configuration in IV and V.

When the treatment of VII with methanolic hydrogen chloride was carried out for only 3 hr., cleavage of the glycosyl linkage was incomplete. Acetylation of the reaction products gave a high yield of the crystalline tetraacetyl derivative of 3′-aminoglucosyl-5,6-dihydrouracil (VIIa).

(22) (a) R. D. Batt, J. K. Martin, J. M. Ploeser, and J. Murray, *J. Am. Chem. Soc.*, **76**, 3663 (1954); (b) W. E. Cohen and D. G. Doherty, *ibid.*, **78**, 2863 (1962); (c) M. Green and S. S. Cohen, *J. Biol. Chem.*, **225**, 397 (1957).

(23) H. H. Baer, *J. Am. Chem. Soc.*, **83**, 1882 (1961).

(24) M. J. Cron, D. L. Evans, F. M. Palermiti, D. F. Whitehead, I. R. Hooper, P. Chu, and R. U. Lemieux, *ibid.*, **80**, 4741 (1958).

(25) S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1810 (1938).

(26) H. H. Baer, *Chem. Ber.*, **93**, 2865 (1960).

(27) B. Lindberg and O. Theander, *Acta Chem. Scand.*, **13**, 1226 (1959).

The n.m.r. spectrum[28] of VI in D_2O showed the easily identifiable anomeric proton doublet at δ 5.9. The width of this doublet ($J_{H_1',H_2'}$ = 9 c.p.s.) is diagnostic[29] of an axial–axial configuration of 1′- and 2′-protons. Since the C1 conformation for VI should be the most stable, the n.m.r. data for the anomeric proton establishes the β configuration. It is therefore concluded that VI, and thereby V and IV, are of the 1-β-D-glucopyranosyl configuration, and V is 1-(3′-amino-3′-deoxy-β-D-glucopyranosyl)uracil.

It was reported that the nitrous acid deamination of *O*-acetylated kanosamine (3-amino-3-deoxy-D-glucose) followed by reacetylation afforded α-D-glucopyranose pentaacetate[30] (no net inversion). In order to examine this reaction in the nucleoside area, V was *O*-acetylated to XII and treated with ethyl nitrite in acetic acid. A glass was obtained which was not purified but treated directly with ethanolic ammonia at room temperature. A crystalline product (XIII) was obtained (32% yield) which gave an ultraviolet absorption spectrum and elemental analyses consistent with a 1-hexosyluracil structure. This product differed from 1-β-D-gluco- and -galactopyranosyluracils[31] with respect to its paper chromatographic and electrophoretic behavior, melting point, optical rotation, and infrared spectrum. Since XII is of the gluco configuration, it is almost certain that XIII is 1-β-D-allopyranosyluracil and the reaction, XII → XIII, proceeds (at least in part) with inversion. A plausible mechanism for this inversion might be the influence of the 2-carbonyl group of the pyrimidine which might stabilize the intermediate diazonium derivative as shown in structure XIV. An examination of molecular models shows the possibility of such a structure with the conformation in the 1C or boat conformations. The net effect of such a transition would be to favor rearward attack on C-3′ by solvent to give the allo configuration.

Conversion of the uracil nucleoside V to its cytosine counterpart XVII was achieved by the general procedure described by Fox, *et al.*[32] Compound V was acetylated to XV and then treated with phosphorus pentasulfide in pyridine to yield XVI in which *both* the 4-position of the pyrimidine and the acetamido group in the sugar were thiated. The absorption spectrum of XVI gave a maximum at 325 mμ as expected for the 4-thiouracils and a maximum at 265 mμ for the thioacetamido[33] function. Ammonolysis of XVI with methanolic ammonia at 95° for 18 hr. removed *all* the protecting groups and afforded 1-(3′-amino-3′-deoxy-β-D-glucopyranosyl)cytosine (XVII). It is noteworthy that the N-thioacetyl group, unlike N-acetyl groups, was easily removed under these ammonolysis conditions. This fact may find application in the chemistry of amino sugars where N-acyl blocking groups are used.

(28) The authors are indebted to Dr. Earl B. Whipple of the Union Carbide Research Institute, Eastview, N. Y., for the n.m.r. data reported herein.

(29) R. U. Lemieux, R. K. Kulling, H. J. Bernstein, and W. G. Schneider *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(30) M. J. Cron, O. B. Fardig, D. L. Johnson, D. F. Whitehead, I. R. Hooper, and R. U. Lemieux, *ibid.*, **80**, 4115 (1958).

(31) (a) J. J. Fox, N. C. Yung, I. Wempen, and I. L. Doerr, *ibid.*, **79**, 5060 (1957); (b) G. E. Hilbert, *ibid.*, **59**, 330 (1937).

(32) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *ibid.*, **81**, 178 (1959).

(33) D. Rosenthal and T. I. Taylor, *ibid.*, **79**, 2684 (1957).

Experimental[34]

1-(3′-Nitro-3′-deoxy-β-D-glucopyranosyl)uracil (IV).—To an ice-cooled solution of 58.5 g. of uridine (0.24 mole) in 240 ml. of water was added 57.4 g. of sodium metaperiodate (0.27 mole) in 240 ml. of water and the reaction mixture was stored in a refrigerator overnight. The inorganic material was filtered and the filtrate was poured into 1500 ml. of ethanol and stirred. The white precipitate of inorganic material was filtered and washed with 500 ml. of ethanol. The combined filtrate and washings were evaporated to *ca.* 300 ml. under reduced pressure at 35–40°. Then 100 ml. of benzene was added and the mixture was concentrated to *ca.* 150 ml. Finally, the solution was evaporated to dryness with 200 ml. of a 1:1 mixture of ethanol and benzene.

The residue was dissolved in 300 ml. of absolute ethanol. A small amount of inorganic impurities was removed by filtration. Nitromethane (13.2 ml., 0.24 mole) was added to the filtrate followed by dropwise addition with vigorous stirring of a solution of sodium methylate [5.25 g. (0.23 g.-atom) of sodium in 175 ml. of methanol]. The sodium salt of the *aci*-nitro compound III precipitated during the addition of the sodium methoxide solution. Stirring was continued for an additional 2 hr.

The alkaline reaction mixture was neutralized with a 200-ml. slurry of Dowex 50 (H^+) in water. The milky supernatant became clear. After filtration, the resin was washed well with 200 ml. of ethanol, 200 ml. of methanol, and finally with 500 ml. of water. The filtrate and washings were combined and, after concentration to *ca.* 500 ml., kept overnight in a refrigerator. The white crystalline nitro compound IV, m.p. 175–176° (36.7 g., 51%), which precipitated was collected by filtration. An additional 7 g. (9%) was obtained from the mother liquor. After one recrystallization from water the melting point was unchanged, $[\alpha]^{25}D$ +33° (*c* 0.75, methanol), $\lambda_{max}^{H_2O}$ 256.5 mμ (ϵ_{max} 9200). The elemental analyses were consistent for IV.[2]

1-(3′-Amino-3′-deoxy-β-D-glucopyranosyl)uracil (V).—Fifteen grams (0.05 mole) of crystalline IV was hydrogenated in a 1:1 mixture of methanol and water (100 ml.) with *ca.* 50 g. of Raney nickel (wet weight) at an initial pressure of 3 atm. After 1 hr. the reaction was complete. The catalyst was removed and washed with 700 ml. of 50% aqueous methanol. The filtrate and washings were combined and evaporated to dryness under reduced pressure below 40°. The residual sirup was dissolved in 30 ml. of hot water and decolorized with charcoal. From the pale yellow solution, white fine needles precipitated (80% yield): m.p. 166–167° (sintered), 179–182° eff.; $[\alpha]^{25}D$ +33° (*c* 0.88, water); $\lambda_{max}^{pH\ 7}$ 257 mμ, $\lambda_{max}^{pH\ 1}$ 258 mμ, $\lambda_{max}^{pH\ 13}$ 259 mμ. Elemental analyses were consistent with V.[2]

1-(3′-Acetamido-3′-deoxy-β-D-glucopyranosyl)uracil (VI).—A mixture of 3.16 g. of V (0.012 mole) in 500 ml. of methanol was refluxed for 1.5 hr. to obtain an homogeneous solution. After cooling to room temperature, the solution was treated with 1.62 ml. of acetic anhydride. The solution was stirred at room temperature for 5 hr. and then concentrated to dryness under reduced pressure at 40°. The residue was crystallized from methanol. The yield of colorless prisms, m.p. 170–172° eff., $[\alpha]^{23}D$ −14° (*c* 0.75, water), was 3.30 g. (90%).

Anal. Calcd. for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.40; N, 13.33. Found: C, 45.59; H, 5.60; N, 13.14.

1-(3′-Acetamido-3′-deoxy-β-D-glucopyranosyl)-5,6-dihydrouracil (VII).—A mixture of 1.10 g. of platinum dioxide and 4.22 g. (0.013 mole) of VI in 42.3 ml. of water was shaken for 96 hr. in a hydrogen atmosphere at room temperature. The catalyst was filtered through a column of Celite and the column was washed with 100 ml. of water. The combined filtrate and washings were evaporated to a sirup under reduced pressure at ~40°. The residual sirup was crystallized from methanol. The yield of colorless prisms of VII, m.p. 152° eff., $[\alpha]^{23}D$ −11° (*c* 1.47, water), was 3.95 g. (93%). The elemental analysis was consistent with VII.

Methyl 3-Acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-α- and -β-D-glucoside (X and XI).—Methanol (80 ml.) containing 2.8 g. (0.009 mole) of VII was saturated with dry hydrogen chloride at ~0° and gently refluxed for 8 hr. The slightly reddish yellow solution was evaporated to dryness at *ca.* 40°. The residue (IX, ninhydrin positive), after evaporating three times with 100-ml. portions of benzene, was dissolved in 50 ml. of pyridine and

(34) All analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Some of the analyses were reported in the previous communication.[2]

treated with 25 ml. of acetic anhydride. After standing overnight at room temperature, the solution was evaporated to a sirup under reduced pressure at ~40°, after which 100 ml. of benzene was added and also removed by evaporation. The benzene treatment was repeated twice, after which the residue was dissolved in 100 ml. of benzene and chromatographed over an acid-washed alumina column (18 × 2.1 cm.). The column was washed with the following solvents: 500 ml. of benzene, which eluted 1.77 g. of a mixture of the anomers (54%), $[\alpha]^{23}D$ +11° (*c* 1.47, chloroform); 20% ethyl acetate in benzene (500 ml.), which eluted 0.87 g. of sirup (27%), $[\alpha]^{23}D$ +88° (*c* 0.74, chloroform), which was crystallized from ethanol to afford 235 mg. of cubes, m.p. 175–176°, $[\alpha]^{22}D$ + 101° (*c* 0.92, chloroform) [lit. (for pure α-anomer X) m.p. 179–180°,[23] 172.5–173°,[24] 178°,[25] $[\alpha]^{23}D$ +110°[23], 105°,[24] 101.8°[25]]. Additional α-anomer was obtained by eluting the column with 50% ethyl acetate in benzene. A sirupy substance (14%) was obtained which, after crystallization from ethanol–ether, gave white cubes, m.p. 175–176° (alone or in an admixture with α-anomer obtained above).

The $[\alpha]^{23}D$ +11° fraction obtained above by elution of the column with benzene was a mixture of anomers. Crystallization of this material from ethanol–petroleum ether (b.p. 30–60°) gave pure β-anomer XI, m.p. 155–156°, $[\alpha]^{23}D$ −20° (*c* 0.79, $CHCl_3$). These data are sufficiently close to reported values[26,27] of methyl-3-acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-β-D-glucoside.

Attempted Cleavage of Nucleoside Linkage. A. Preparation of 5,6-Dihydro-1-(3′-acetamido-3′-deoxy-2′,4′,6′-tri-*O*-acetyl-β-D-glucosyl)uracil (VIIa).—Compound VII (2.61 g., 0.008 mole) was treated with 130 ml. of methanolic hydrogen chloride under conditions similar to those described above and the solution was refluxed for only 3 hr. The solvent was removed under reduced pressure, bath temperature *ca.* 40°. The residue was dried by three additions of 100-ml. portions of a 1:1 mixture of ethanol–benzene followed by removal of the solvent *in vacuo* and then dissolved in 50 ml. of pyridine and treated with 10 ml. of acetic anhydride at room temperature overnight. The solvent was removed under reduced pressure. The residue was treated three times with 100-ml. portions of an ethanol–benzene mixture (1:1) and dried to remove traces of acetic acid. Benzene (50 ml.) was added to the resultant semicrystalline material. The insoluble crystalline portion (2.72 g., 75%) was filtered and washed with additional benzene. Recrystallization from ethanol gave an analytical sample, m.p. 283–284°. The infrared spectrum showed strong absorption bands at 5.7 (O-acetyl), 6.0 (acetamide), and 9.6 μ (sugar lactol ring). Analytical data were consistent with the structure of 5,6-dihydro-1-(3′-acetamido-3′-deoxy-2′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)uracil (VIIa).

Anal. Calcd. for $C_{18}H_{25}N_3O_8$: C, 48.76; H, 5.64; N, 9.48. Found: C, 48.67; H, 5.80; N, 9.22.

Only a small amount (38 mg.) of crystalline X could be isolated from the benzene extract.

B. Ring Opening and Closure of 5,6-Dihydrouracil Nucleoside VII.—The dihydro nucleoside VII (1.27 g., 0.004 mole) was dissolved in 160 ml. of 0.2 *N* barium hydroxide and the solution was stirred for 1 hr. at room temperature. Solid carbon dioxide was added and the mixture was stirred for an additional 30 min. The precipitated barium carbonate was filtered and washed with a small amount of water. The filtrate and washings were combined and evaporated to dryness under reduced pressure. The residue was added to 10 ml. of water and the insoluble inorganic material was filtered. The filtrate was once again evaporated to dryness under reduced pressure. A white powder (VIII) was obtained by further drying of the resultant sirup by azeotropic distillation with absolute ethanol. The yield of VIII was 1.57 g. (83%). The infrared spectrum of this compound exhibited maxima at 6.4 and 7.1 μ (carboxylate ion) and showed no absorption at *ca.* 5.8 μ (expected for the dihydrouracil structure). This salt was not purified further.

Compound VIII (207 mg.) was dissolved in 24 ml. of 0.2 *N* sulfuric acid and kept in a refrigerator overnight. The precipitated barium sulfate was removed and the filtrate was neutralized with 1 g. of a 1:1 mixture of crystalline barium hydroxide [$Ba(OH)_2 \cdot 8H_2O$] and barium carbonate. The mixture was stirred overnight at room temperature and filtered. The filtrate was evaporated to dryness under reduced pressure. The infrared spectrum of the residue was similar to that of VIII. The residue was added to 20 ml. of 0.2 *N* sulfuric acid and was refluxed for 1.5 hr. After filtration of the precipitate, 1 g. of barium carbonate was added to the filtrate and the slurry was stirred vigorously for 10 min. The filtrate, after removal of the precipitate, gave a positive Fehling's test and was evaporated to dryness under reduced pressure. The residue (152 mg.) was dissolved in *ca.* 5 ml. of water. A small amount of insoluble material formed which was filtered and washed with three 1-ml. portions of water. The combined filtrates and washings were evaporated under reduced pressure. The glassy residue thus obtained was dried azeotropically with 1 ml. of a 1:1 ethanol–benzene mixture. The residue was dissolved in 3 ml. of methanol, and, upon standing, crystalline material (75 mg.) separated, m.p. 157–158° eff. A mixture melting point with VII was 152–155°. The infrared spectrum of this product was identical with that of VII. The compound gave negative tests with both Fehling's solution and ninhydrin. However, both tests were positive on the filtrate, indicating that some cleavage of the glycosyl bond and the N-acyl group had occurred.

1-(3′-Acetamido-3′-deoxy-2′,4′,6′-tri-*O*-acetyl-β-D-glucosyl)-uracil (XV).—A stirred suspension of 2.72 g. (0.01 mole) of V in acetic anhydride (20 ml.) was treated with 5 ml. of pyridine. After 15 min. of reflux, the clear solution was cooled to room temperature. Methanol was added to destroy the excess acetic anhydride and the solvent was evaporated under reduced pressure to *ca.* 25 ml. Ice–water (50 ml.) was added and the mixture was extracted twice with 50-ml. portions of chloroform. The combined extracts were dried over calcium chloride, filtered, and evaporated to dryness. The crystalline residue was recrystallized from methanol. The yield of white needles was 2.40 g. (54%), m.p. 253–254°, $[\alpha]^{23}D$ 0° (*c* 0.75, in chloroform).

Anal. Calcd. for $C_{18}H_{23}N_3O_{10}$: C, 48.98; H, 5.22; N, 9.52. Found: C, 48.88; H, 5.29; N, 9.54.

1-(3′-Thioacetamido-3′-deoxy-2′,4′,6′-tri-*O*-acetyl-β-D-glucosyl)-4-thiouracil (XVI).—A well-stirred suspension of XV (2.08 g., 0.0047 mole) and 2.11 g. (0.0095 mole) of phosphorus pentasulfide in 80 ml. of reagent grade pyridine was heated at reflux temperature for 2.5 hr. The reddish reaction mixture was chilled and the liquid portion was decanted. The decantate was evaporated to dryness under reduced pressure and the sirupy residue was dissolved in 50 ml. of chloroform. Small amounts of insoluble impurities were removed by filtration and the filtrate was extracted with an equal volume of water, then with 0.2 *N* sulfuric acid, and finally with water. After drying over anhydrous magnesium sulfate, the chloroform layer was evaporated to dryness under reduced pressure. The residue was crystallized from ethanol. The yield of dried VII was 2.02 g. (90%), m.p. 234–235°, $[\alpha]^{23}D$ −111° (*c* 0.70, chloroform).

Anal. Calcd. for $C_{18}H_{23}N_3O_8S_2$: C, 45.67; H, 4.86; N, 8.88; S, 13.53. Found: C, 45.39; H, 4.92; N, 8.96; S, 13.82.

1-(3′-Amino-3′-deoxy-β-D-glucopyranosyl)cytosine (XVII).—A mixture of 0.815 g. (0.0017 mole) of XVI in 50 ml. of absolute methanol was saturated with anhydrous ammonia below 0° and heated for 18 hr. at 95° in a steel container. The solvent was evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml. of water and was treated with 15 ml. of Dowex AG-1 (OH^- form). A precipitation of sulfur occurred. The resin and precipitate were filtered and washed with a small volume of water. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue, after two recrystallizations from methanol, gave m.p. 248–250° (with browning), 260.5–261° eff., $[\alpha]^{23}D$ +36° (*c* 0.94, water). The yield was 0.25 g. (54%). Analytical data have been reported.[2]

1-(3′-Amino-3′-deoxy-2′,4′,6′-tri-*O*-acetyl-β-D-glucosyl)uracil Hydrochloride (XII).—A mixture of 3.012 g. (0.011 mole) of V and 30 ml. of glacial acetic acid was warmed until solution was complete. After cooling to room temperature, 10 ml. of acetyl chloride was added. A white precipitate which formed immediately dissolved upon standing at 45° for 30 min. After standing overnight at 40°, the solvent was removed by evaporation under reduced pressure. The residual glassy brownish material was evaporated twice with toluene (50-ml. portions) and then crystallized from ethanol to afford colorless needles, m.p. 200–205°. Upon recrystallization from *n*-propyl alcohol, the material gave 3.42 g. (71%) of colorless needles, m.p. 238° (with browning), 241–241.5° eff., $[\alpha]^{23}D$ +27° (*c* 1.44, water). Analytical data have been reported.[2]

1-β-D-Allopyranosyluracil (XIII).—An ice-cooled mixture of 1.14 g. (0.0029 mole) of XII in 10 ml. of 50% aqueous acetic acid was treated with 4 ml. of a mixture of ethyl nitrite in ethanol (1:21) with stirring. The mixture was gradually warmed to room temperature and allowed to stand overnight. The solvent was evaporated and the residue was dried azeotropically with 20 ml. of toluene. The process was repeated twice. A brownish glass

which was obtained was treated with 15 ml. of ethanolic ammonia (previously saturated at 0°) at room temperature for 2 days. After evaporation of the solvent and washing of the residue with chloroform to remove acetamide, the sirupy residue was dissolved in 10 ml. of methanol. A small amount of chloroform was added to the methanol solution to incipient cloudiness and kept overnight in a refrigerator. A brownish sirup that formed was separated by decantation of the solvent and crystallized from 10 ml. of a 1:1 mixture of methanol and ethanol. The compound, 250 mg. (32%), m.p. 231° (sintered), 241–242° dec., crystallized as white stars, $[\alpha]^{23}D$ +2.0 (*c* 0.37, water). For analytical data see ref. 2.

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Homogeneous Hydrogenation of Methyl Linolenate Catalyzed by Iron Pentacarbonyl. Formation of Methyl Octadecatrienoate–Iron Tricarbonyl Complexes[1]

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Studies with $Fe(CO)_5$ as a soluble catalyst for the hydrogenation of unsaturated fatty esters have been extended to methyl linolenate. The products were separated into monoenes, dienes, trienes, and iron carbonyl complexes of dienes and trienes by countercurrent distribution. Further separation of isomers was carried out by argentation (countercurrent distribution and chromatography). Trienes included isomers in which two and three double bonds are conjugated. Dienes were 50% conjugated with double bonds distributed between the 5- and 16-positions. Nonconjugated dienes had double bonds separated by several methylene groups. Monoenes had a distribution of double bonds consistent with a reduction of the complexed conjugated dienes by 1,2-addition. The diene–$Fe(CO)_3$ complexes have the same structure as the corresponding complexes of linoleate but have a wider distribution of positional isomers. The triene complexes were characterized as a mixture of isomers containing a stable conjugated diene–$Fe(CO)_3$ unit and a noncomplexed olefinic bond either α,β to the π-complexed system (I) or separated by several methylene groups (II). These triene complexes are postulated as intermediates in the homogeneous hydrogenation.

The homogeneous hydrogenation of olefins catalyzed by complexes of transition metals constitutes an important development in coordinated ligand reactions.[3] Metal complexes used as homogeneous hydrogenation catalysts include those of ruthenium(II),[4] pentacyanocobaltate(II),[5–7] metal carbonyls,[8–10] Ziegler-type catalysts,[11] and platinum(II)–tin(II).[12,13] Metal carbonyl complexes of unsaturated compounds have been studied extensively[14] and their role in catalyzing hydrogen transfer reactions has been well documented.[8,9]

We have previously reported the homogeneous hydrogenation of methyl linoleate catalyzed by $Fe(CO)_5$.[15] This reaction yielded isomeric conjugated methyl octadecadienoate–iron tricarbonyl complexes which were shown to be efficient homogeneous hydrogenation catalysts. This paper reports an extension of these studies to the hydrogenation of methyl linolenate.

Results

Hydrogenation.—Reduction with $Fe(CO)_5$ was achieved under the same conditions as linoleate.[15] Rates were more difficult to follow analytically because of the greater complexity of the reaction products. Composition data in Table I show that monoenoic fatty esters are the main hydrogenation products. Other products determined by gas–liquid chromatography (g.l.c.) include dienes, conjugated diene–trienes (trienes with two double bonds conjugated and one isolated), and small amounts of stearate. Conjugated trienes were also determined in minor amounts by ultraviolet spectrophotometry. The level of conjugated products increased with catalyst concentration. Infrared analyses showed isolated *trans* unsaturation in large proportions and iron tricarbonyl complex. The concentration of this complex was directly related to the initial concentration of $Fe(CO)_5$.

Typical rate curves are shown in Figure 1. A 50% reduction of trienes occurred after 3 hr. with 0.1 *M* $Fe(CO)_5$ and after approximately 1 hr. with 0.5 *M* $Fe(CO)_5$. Diene is formed in lower concentration than is monoene, but a large proportion of the diene is conjugated and complexed with iron carbonyl. Methyl

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(3) For a review, see J. Halpern, Proceeding of the 3rd International Congress on Catalysis, Amsterdam, 1964; North-Holland Publishing Co., in press.

(4) J. Halpern, J. F. Harrod, and B. R. James, *J. Am. Chem. Soc.*, **83**, 753 (1961).

(5) B. DeVries, *Koninkl. Ned. Akad. Wetenschap. Proc., Ser. B.*, **63**, 443 (1960); B. DeVries, *J. Catalysis*, **1**, 489 (1962).

(6) J. Kwiatek, I. L. Mador, and J. K. Seyler, *J. Am. Chem. Soc.*, **89**, 304 (1962); Advances in Chemistry Series, Vol. 37, American Chemical Society, Washington, D. C., 1962, p. 201.

(7) A. F. Mabrouk, H. J. Dutton, and J. C. Cowan, *J. Am. Oil Chemists Soc.*, **41**, 153 (1964).

(8) H. W. Sternberg and I. Wender, International Conference of Coordination Chemistry, London, April 6–11, 1959; Special Publication No. 13, The Chemical Society, London, 1959, p. 35.

(9) D. A. Brown, J. P. Hargaden, C. M. McMullin, N. Gogan, and M. Sloan, *J. Chem. Soc.*, 4914 (1963).

(10) E. N. Frankel, H. M. Peters, E. P. Jones, and H. J. Dutton, *J. Am. Oil Chemists' Soc.*, **41**, 186 (1964); E. N. Frankel, E. P. Jones, V. L. Davison, E. Emken, and H. J. Dutton, *ibid.*, **42**, 130 (1965).

(11) M. F. Sloan, A. S. Matlack, and D. S. Breslow, *J. Am. Chem. Soc.*, **85**, 4014 (1963).

(12) R. D. Cramer, E. L. Jenner, R. V. Lindsey, Jr., and V. G. Stolberg, *ibid.*, **85**, 1691 (1963).

(13) J. C. Bailar, Jr., and H. Itatani, Proceedings of the Symposium on Coordination Chemistry, Tihany, 1964; Publishing House of the Hungarian Academy of Science, in press.

(14) For a review, see M. A. Bennett, *Chem. Rev.*, **62**, 611 (1962).

(15) E. N. Frankel, E. A. Emken, H. M. Peters, V. L. Davison, and R. O. Butterfield, *J. Org. Chem.*, **29**, 3292 (1964).