The Synthesis and Hydrolysis of 2′,3′-Dideoxyuridine

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Contribution No. 8 from the Syntex Institute for Molecular Biology, Palo Alto, California

Received December 26, 1963

Treatment of 2′-deoxy-3′-O-methanesulfonyl-5′-O-trityluridine with sodium iodide in 1,2-dimethoxyethane gave 2′,3′-dideoxy-3′-iodo-5′-O-trityluridine. After acid detritylation, the resulting 2′,3′-dideoxy-3′-iodouridine was hydrogenated in the presence of a palladium catalyst and triethylamine to give crystalline 2′,3′-dideoxyuridine in good yield. The relative rates of acidic hydrolysis of uridine, 2′-deoxyuridine, 2′,3′-dideoxyuridine, and of the corresponding thymidine derivatives have been determined and related to current views on the mechanism of hydrolysis of nucleosides.

In recent years a number of analogs of deoxynucleosides have been prepared in which the normal 2-deoxyribofuranosyl moiety is replaced by other deoxy and polydeoxypentoses. These compounds, which have been prepared both as exercises in organic synthesis and in order to provide possible antimetabolites for biological screening, have been obtained by several routes. In one approach, a deoxy sugar is condensed, by conventional routes, with a heterocyclic base as in the synthesis of 5′-deoxyadenosine.[1] More frequently, a sugar hydroxyl group in a pre-existing ribo- or deoxyribonucleoside is converted into a halogen- or sulfur-containing derivative and subsequently removed by metal-catalyzed hydrogenolysis. Thus, 3′-deoxyadenosine,[2] 3′-deoxyuridine,[3] 5′-deoxyuridine,[4] 3′-deoxythymidine,[5] 5′-deoxythymidine,[5] and 3′,5′-dideoxythymidine[5] have been prepared with varying success.

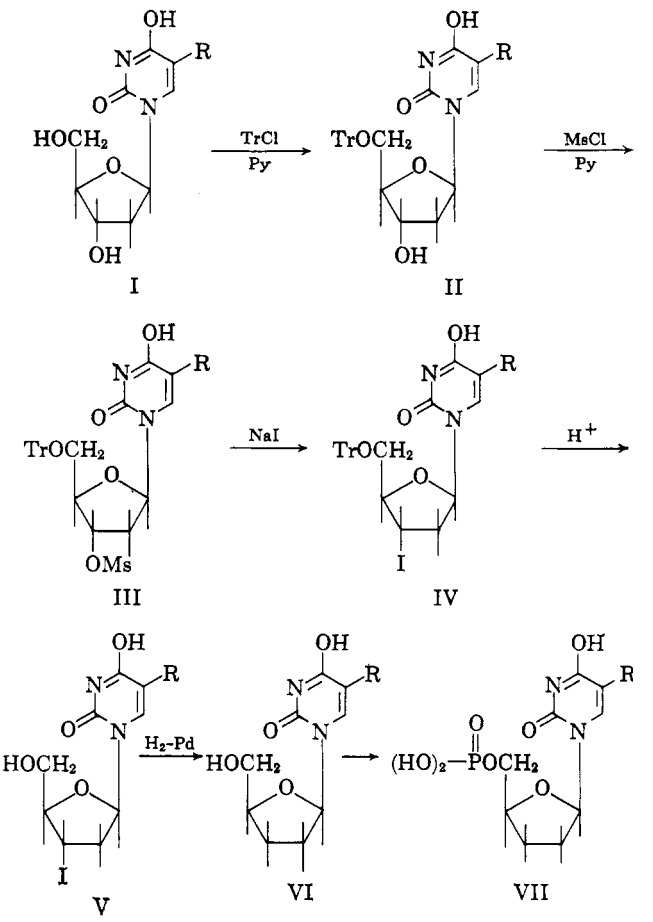
As part of another project in this laboratory,[6] we have recently had need to obtain samples of 3′-deoxythymidine 5′-phosphate (VII, R = CH_3) and 2′,3′-dideoxyuridine 5′-phosphate (VII, R = H). A synthesis of VII (R = CH_3) has recently been briefly mentioned by Ikehara and Ohtsuka[7] through phosphorylation of 3′-deoxythymidine[5] (VI, R = CH_3) with P^1-diphenyl P^2-morpholinophosphorochloridate. Neither 2′,3′-dideoxyuridine (VI, R = H) nor its 5′-phosphate has, however, been previously described and in this paper we provide details of their synthesis. A study of the relative rates of acidic hydrolysis of the ribo-, 2′-deoxy-, and 2′,3′-dideoxynucleosides derived from uracil and thymine is also included.

The route to 3′-deoxythymidine (VI, R = CH_3) previously described by Michelson and Todd[5] and outlined in Chart I has been repeated with minor variations and the over-all results are quite comparable. The yields obtained in the various steps are summarized in the Experimental section and the changes made have been incorporated into the presently described synthesis of 2′,3′-dideoxyuridine (VI, R = H).

Throughout these and other reactions dealing with substituted nucleosides, the utility of thin layer chromatography on Silica G or Alumina G as a qualitative or quantitative diagnostic tool cannot be over emphasized. This is particularly so when a phosphor (see Experimental section for details) is added to the adsorbant before application to the glass plates. The addition of a phosphor such as Radelin GS-115 (Type P-1) permits the detection of extremely small quantities of nucleosides by ultraviolet examination. Since in the 200–400-mμ region the pre-extracted phosphor itself has only a very weak end adsorption at 200 mμ, it is possible to obtain quantitative and undistorted ultraviolet spectra from single spots on the plate by scraping off the silica layer and extracting the product with methanol. This technique has found wide applicability in this laboratory and it has been possible to demonstrate excellent accuracy and reproducibility.

The reaction of 2′-deoxyuridine (I, R = H) with a slight excess of trityl chloride (TrCl) in pyridine (py)

CHART I



(1) H. M. K. Kissman and B. R. Baker, *J. Am. Chem. Soc.*, **79**, 5534 (1957).

(2) (a) A. Todd and T. L. V. Ulbricht, *J. Chem. Soc.*, 3275 (1960); (b) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961).

(3) D. M. Brown, D. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

(4) (a) I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 1624 (1960); (b) J. Smrt, *Collection Czech. Chem. Commun.*, **27**, 1056 (1962).

(5) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(6) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963), and unpublished results.

(7) M. Ikehara and E. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **10**, 997 (1962).

at 100° for 45 min.[8] gave crystalline 2′-deoxy-5′-O-trityluridine (II, R = H) in 75% yield.

Mesylation of II (R = H) with an excess of methanesulfonyl chloride in pyridine resulted in the quantitative formation of 2′-deoxy-3′-O-methanesulfonyl-5′-O-trityluridine as judged by thin layer chromatography. In spite of repeated attempts, however, it was not possible to obtain this product in crystalline form even after chromatography on a column of silicic acid. A similar lack of crystallinity has been observed previously by others (and in this laboratory) for the thymidine analog of this compound (III, R = CH_3). A totally acceptable analysis was not obtained; but, in view of the thin layer chromatographic homogeneity of this compound, it was used directly in the next step. Thus III (R = H) was treated with an excess of sodium iodide in refluxing 1,2-dimethoxyethane for several hours giving 2′,3′-dideoxy-3′-iodo-5′-O-trityluridine (IV, R = H) in 64% yield (including retreatment of some unchanged starting material). The use of dimethoxyethane as the solvent for this reaction proved to be convenient rather than using acetone in a sealed tube at 100° as described by Michelson and Todd.[5] It was, however, necessary first to reflux the dimethoxyethane over lithium aluminum hydride to avoid serious coloration of the reaction, presumably due to the liberation of iodine in the presence of peroxides. By analogy with the established over-all retention of configuration during conversion of 5′-O-acetyl-2′-O-tosyluridine to 5′-O-acetyl-2′-deoxy-2′-iodouridine,[9] it is likely that IV (R = H) also has the structure indicated with the iodine atom in the *ribo* configuration.

Removal of the trityl group from IV (R = H) was readily accomplished by treatment with 80% acetic acid at 100° for 45 min. This is a somewhat longer time than is usually necessary for the removal of 5′-trityl groups under these conditions, but examination of the mixture by thin layer chromatography indicated that a little starting material was still present after 30 min. The resulting crystalline 2′,3′-dideoxy-3′-iodouridine (V, R = H) was hydrogenated at room temperature in the presence of a commercial 10% palladium-on-carbon catalyst[10] and 2 equiv. of triethylamine. Hydrogen uptake was very rapid and, after removal of the catalyst, the free iodide ion was removed by passing the reaction mixture through a small column of Dowex 2 (HCO_3^-) resin and evaporation of the resulting triethylammonium bicarbonate. This procedure was found to be very much more convenient and efficient than hydrogenation in the presence of ammonium hydroxide,[5] in which case complete removal of ammonium iodide was difficult. It is also worth noting that, in the absence of a base, almost complete reduction of the 5,6-double bond in the uracil ring occurred with the catalyst used. The resulting 2′,3′-dideoxyuridine was obtained in crystalline form in 83% yield but even under these mild conditions was contaminated by 4% uracil which was not readily removed by recrystallization. A completely pure sample was obtained by preparative paper chromatography followed by crystallization.

(8) Essentially the method used by J. P. Horwitz, J. A. Urbanski, and J. Chua [*J. Org. Chem.*, **27**, 3300 (1962)] for the tritylation of thymidine.

(9) D. M. Brown, D. B. Parihas, and A. R. Todd, *J. Chem. Soc.*, 4242 (1958).

(10) Obtained from Matheson Coleman and Bell.

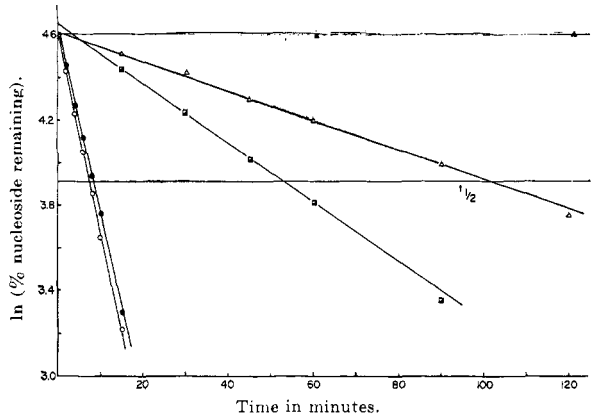


Fig. 1.—Kinetics of the hydrolysis of ribo-, 2-deoxyribo-, and 2′,3′-dideoxyribonucleosides in 1 *N* HCl at 100°: ▲, uridine; △, 2-deoxyuridine; ◪, thymidine; ●, 2′,3′-dideoxyuridine; ○, 3′-deoxythymidine.

Phosphorylation of 2′,3′-dideoxyuridine and of 3′-deoxythymidine by the method of Tener[11] resulted in the ready isolation of the respective 5′-phosphates (VII) in good yield. Some further reactions of these compounds will be described in a future paper.

While it is well recognized that the N-glycosidic bond in a 2′-deoxynucleoside is very much more susceptible to acid hydrolysis than is that in the corresponding ribonucleoside, few quantititave comparative studies have been described.[12] With the availability of 2′,3′-dideoxyuridine and 3′-deoxythymidine, it was of interest to determine whether the removal of yet another hydroxyl group from the 3′-carbon would lead to a further labilization. Accordingly, samples of uridine, 2′-deoxyuridine, 2′,3′-dideoxyuridine, thymidine, and 3′-deoxythymidine were treated under identical conditions with 1 *N* hydrochloric acid in sealed capillaries at 100°. The rates of hydrolysis were determined by spectral examination of the individual aliquots in 1 *N* alkali. The ratio of the optical densities at the absorption maxima of the pyrimidine base and of the nucleoside (276 mμ/263 mμ for the uracil nucleosides and 281 mμ/267 mμ for the thymine nucleosides) was found to provide a sensitive measure of the degree of hydrolysis, and good first-order kinetics were obtained for all the deoxynucleosides up to 65–75% hydrolysis. Under these conditions, uridine was virtually unaffected, only 2% hydrolysis being detected in 5 hr. The kinetic results are shown in Fig. 1 from which it can be seen that thymidine is hydrolyzed roughly twice as fast ($k_1 = 2.33 \times 10^{-4}$ sec.$^{-1}$; $t_{1/2}$ = 56 min.) as 2′-deoxyuridine ($k_1 = 1.14 \times 10^{-4}$ sec.$^{-1}$; $t_{1/2}$ = 104 min.). 3′-Deoxythymidine and 2′,3′-dideoxyuridine were, however, much more labile, the rates being 1.55×10^{-3} sec.$^{-1}$ ($t_{1/2}$ = 7.5 min.) and 1.45×10^{-3} sec.$^{-1}$ ($t_{1/2}$ = 8.2 min.), respectively. Thus the removal of the hydroxyl group from C-3′ does indeed result in a considerably increased rate of hydrolysis. This observation is quite consistant with those made earlier on the relative rates of hydrolysis of ethyl glucopyranoside, ethyl 2-deoxyglucopyranoside, and ethyl 2,3-dideoxyglucopyranoside by Butler,

(11) G. M. Tener, *J. Am. Chem. Soc.*, **83**, 159 (1961).

(12) See *e.g.* (a) A. Wacker and L. Trager, *Z. Naturforsch.*, **18b**, 13 (1963); (b) W. Pollman and G. Schramm, *ibid.*, **16b**, 673 (1961); (c) F. Micheel and A. Heesing, *Chem. Ber.*, **94**, 1814 (1961).

et al.,[13] and of the anilides of glucose and 2-deoxyglucose by Richards.[14]

The mechanism of hydrolysis of nucleosides is not altogether clear, but the suggestion has been made by Kenner [15] and amplified by Dekker[16] that the site of effective protonation is the ring oxygen of the sugar rather than the glycosidically bound nitrogen. Further, it has been suggested by Richards[14] that the relative stability of normal glycosides as compared with the 2-deoxyglycosides is due to the competitive protonation of the relatively acidic hydroxyl group at C-2 which then electrostatically opposes further protonation at either of the acetal oxygens.[17] The pronounced increase in lability on further removal of the hydroxyl groups at C-3′ of 2-deoxyuridine and thymidine lends some support to Kenner's suggestion[15] of protonation on oxygen rather than nitrogen. Thus, it is somewhat difficult to explain the increased lability by a decrease in electrostatic shielding of the rather remote N-1 of the uracil ring, but it is quite compatible with decreased shielding of the sugar ring oxygen which is roughly equidistant from the hydroxyl groups on both C-2′ and C-3′.

It is intended to make a more comprehensive study of the rates of hydrolysis of other deoxy- and polydeoxynucleosides now being prepared in this laboratory in order to gain clear knowledge of the mechanism of these reactions.

Experimental[18]

General Techniques.—Thin layer chromatography was performed on 0.25-mm. layers of Merck Silica G evenly spread on glass plates with a Desaga applicator. In order to detect ultraviolet absorbing products with a high degree of sensitivity, Radelin GS-115 (Type P-1) phosphor[19] (25 mg.) was mixed for 30–45 sec. with the Silica G (50 g.) and water (100 ml.) in a Waring Blendor prior to application to the glass plates.[20] The phosphor was first continually extracted for 12 hr. with boiling methanol in a Soxhlet extractor in order to remove a small amount of ultraviolet absorbing impurity. Compounds detected on such plates under an ultraviolet lamp may be quantitatively eluted with methanol and spectrally examined. Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer, and infrared spectra were obtained from potassium bromide pellets on a Perkin-Elmer Model 237 spectrophotometer. Paper chromatography was performed by the descending technique on Schleicher and Schuell No. 589 orange ribbon paper using solvent I, 2-propanol–concentrated ammonium hydroxide–water (7:1:2).

2′-Deoxy-5′-O-trityluridine (II, R = H).—2′-Deoxyuridine (4.56 g., 20 mmoles) was dissolved in anhydrous pyridine (50 ml.) containing triphenylchloromethane (6.67 g., 24 mmoles) and heated at 100° for 45 min. with exclusion of moisture. After cooling, the solution was poured slowly into 1 l. of vigorously stirred ice–water, and after 30 min. the precipitated solid was removed and washed with water. The crude product was dried *in vacuo* and crystallized from acetone–benzene giving a product of m.p. 192–196° which still contained a little triphenylcarbinol. One further crystallization from acetone–benzene gave 5.40 g. of pure 2′-deoxy-5′-O-trityluridine of m.p. 204–205°. A further 1.64 g. of pure product (total yield 75%) was recovered from the mother liquors by chromatography on a column of silicic acid.[21] The trityl ether was eluted with chloroform–acetone (19:1).

Anal. Calcd. for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95. Found: C, 71.60; H, 5.61; N, 5.98.

2′-Deoxy-3′-O-methanesulfonyl-5′-O-trityluridine (III, R = H).—Methanesulfonyl chloride (5 ml.) was added slowly to an ice-cooled solution of 2′-deoxy-5′-O-trityluridine (5.47 g., 11.6 mmoles) in anhydrous pyridine (25 ml.). After storage overnight at 0°, water (2 ml.) was added and the solution was slowly poured into 2 l. of well-stirred ice–water. The precipitate was filtered, washed well with water, and dried *in vacuo*. It was then dissolved in hot ethanol (100 ml.), treated with carbon (1 g. of Darco G-60), and poured into a large excess of ice–water. The amorphous precipitate was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide giving a quantitative yield of 2′-deoxy-3′-O-methanesulfonyl-5′-O-trityluridine which was homogeneous by thin layer chromatography (chloroform–ethyl acetate, 1:1) but could not be obtained in crystalline form and did not give acceptable analyses.

2′,3′-Dideoxy-3′-iodo-5′-O-trityluridine (IV, R = H).—2′-Deoxy-3′-O-methanesulfonyl-5′-O-trityluridine (5.48 g., 10 mmoles) and sodium iodide (15 g., 0.1 mole) were dissolved in 1,2-dimethoxyethane[22] (100 ml.) and refluxed for 5 hr. The solvent then was evaporated, and the residue was partitioned between methylene chloride and water. The organic layer then was extracted twice with 5% sodium thiosulfate, once with water, and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was dissolved in benzene–methylene chloride (1:1) and applied to a column containing 300 g. of silicic acid.[21] After removal of 0.4 g. of unidentified material with methylene chloride–ether (9:1), 2′,3′-dideoxy-3′-iodo-5′-O-trityluridine was eluted with methylene chloride–ether (3:1) and crystallized from hot methanol (2.65 g., 46%, m.p. 138–140°). Continued elution with the same solvent gave a further 2.26 g. of unchanged mesylate (III, R = H) which was retreated as above with sodium iodide in 1,2-dimethoxyethane. The total yield was 3.65 g. (64%) and after one further recrystallization from acetone–methanol, the melting point was raised to 142–143° with excellent recovery.

Anal. Calcd. for $C_{28}H_{25}IN_2O_4$: C, 57.94; H, 4.34; I, 21.87; N, 4.83. Found: C, 57.36; H, 4.42; I, 21.40; N, 4.65.

2′,3′-Dideoxy-3′-iodouridine (V, R = H).—2′,3′-Dideoxy-3′-iodo-5′-O-trityluridine (2.08 g., 3.58 mmoles) was dissolved in 80% acetic acid (100 ml.) and heated at 100° for 45 min. After cooling to room temperature, the solvent was evaporated *in vacuo* and last traces of acetic acid were removed by coevaporation with methanol several times. The residue was dissolved in methylene chloride–ethyl acetate (1:1) from which pure, crystalline 2′,3′-dideoxy-3′-iodouridine (0.58 g., 45%, m.p. 161° dec.) quickly separated. The mother liquors were directly applied to a column containing 200 g. of silicic acid.[21] Triphenylcarbinol and a small amount of an unidentified impurity were removed with methylene chloride–ethyl acetate (1:1) and subsequent elution with ethyl acetate gave a further 0.3 g. of the desired product. The combined products were recrystallized from acetone giving 0.79 g. (62%) of chromatographically pure (ethyl acetate) 2′,3′-dideoxy-3′-iodouridine of m.p. 162° dec., $\lambda_{max}^{0.1\ N\ HCl}$ 263 mμ (ϵ_{max} 11,300), $\lambda_{max}^{0.1\ N\ NaOH}$ 263 mμ (ϵ_{max} 8720).

Anal. Calcd. for $C_9H_{11}IN_2O_4$: C, 31.95; H, 3.29; N, 8.28. Found: C, 32.15; H, 3.47; N, 8.11.

2′,3′-Dideoxyuridine (VI, R = H).—2′,3′-Dideoxy-3′-iodouridine (730 mg., 2.15 mmoles) was dissolved in 50% aqueous methanol (100 ml.) containing triethylamine (0.7 ml., 5 mmoles) and vigorously stirred in an atmosphere of hydrogen in the presence of 10% palladium on carbon (200 mg.)[10] Hydrogen uptake was complete within 15 min. at room temperature. After removal of the catalyst by filtration, the filtrate and washings were evaporated to dryness *in vacuo*. The residue was then dissolved in aqueous methanol and passed through a small column containing 10 ml. of Dowex-2 (HCO_3^-) resin. The resin was washed with water until it was free of ultraviolet absorbing material, and the combined eluates were evaporated to dryness

(13) K. Butler, S. Laland, G. W. Overend, and M. Stacey, *J. Chem. Soc.*, 1433 (1950).

(14) G. N. Richards, *Chem. Ind.* (London), 228 (1955).

(15) G. W. Kenner in Ciba Foundation Symposium, Chemistry and Biology of Purines, Little, Brown and Co., Boston, Mass., 1957, p. 312.

(16) C. A. Dekker, *Ann. Rev. Biochem.*, **29**, 463 (1960).

(17) As applied to pyranosides, this has been explained as a conformational phenomena by J. T. Edward [*Chem. Ind.* (London), 1102 (1955)]. Such an explanation seems to be less satisfactory when applied to the relatively planar furanose system in nucleosides.

(18) Melting points are uncorrected and elemental analyses were obtained by Midwest Microlabs, Inc., Indianapolis, Ind.

(19) U. S. Radium Corp., Morristown, N. J.

(20) J. S. Matthews, A. L. Pereda, and A. Aguilera, *J. Chromatog.*, **9**, 331 (1962).

(21) Davidson Chemical Co., Baltimore, Md., grade 923, 100–200 mesh.

(22) 1,2-Dimethoxyethane was purified by distillation from lithium aluminum hydride.

in vacuo. The residue was crystallized from acetone–petroleum ether (b.p. 30–60°) giving 2′,3′-dideoxyuridine (375 mg., 83%) of m.p. 115°. This product contained 4% uracil which was difficult to remove by crystallization. A completely pure product was, however, readily obtained by preparative paper chromatography in solvent I which gave material of m.p. 116–117° after crystallization from acetone–ether, $\lambda_{max}^{0.01\ N\ HCl}$ 263 mμ (ϵ_{max} 10,050), $\lambda_{max}^{0.01\ N\ NaOH}$ 263 mμ (ϵ_{max} 7220).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.90; H, 5.70; N, 13.20. Found: C, 50.81; H, 5.75; N, 13.22.

3′-Deoxythymidine.—This compound was prepared *via* the same sequence of steps as described above for 2′,3′-dideoxyuridine, except that the starting material was 5′-O-tritylthymidine.[8] The procedure is a direct adaptation of that described by Michelson and Todd[5] and the intermediates prepared were as follows: 3′-O-methanesulfonyl-5′-O-tritylthymidine (100%, amorphous), 3′-deoxy-3′-iodo-5′-O-tritylthymidine (70%, m.p. 147–148°), 3′-deoxy-3′-iodothymidine (79%, m.p. 166° dec., 3′-deoxythymidine (61%, m.p. 147–149°).

2′3′-Dideoxyuridine 5′-Phosphate (VII, R = H).—A mixture of pyridinium cyanoethyl phosphate[11] (0.2 mmole) and 2′,3′-dideoxyuridine (0.1 mmole) was rendered anhydrous by three evaporations with 2-ml. portions of dry pyridine. The final residue was dissolved in anhydrous pyridine (1 ml.) and dicyclohexylcarbodiimide (124 mg., 0.6 mmole) was added. After 24 hr. at room temperature, a small amount of water (0.5 ml.) was added and, after a further 30 min., the solvent was evaporated *in vacuo*. The residue was well stirred with water (5 ml.) and ether (5 ml.) and filtered to remove crystalline dicyclohexylurea. The water layer was extracted once more with ether, made 0.5 *M* with lithium hydroxide, and heated at 100° for 1 hr. After cooling in ice, the precipitated lithium phosphate was removed and the filtrate and washings (with 0.01 *M* LiOH) were passed through a column containing 3 ml. of Dowex-50 (H^+) resin. The eluates gave a single spot on paper with solvent I (R_f 0.11, while dideoxyuridine itself had R_f 0.63) and, based upon the ultraviolet spectrum, the yield was 80%. The pH of the solution was brought to 8.0 with barium hydroxide and after removal of a trace of barium phosphate the volume was reduced to 3–4 ml. The addition of three volumes of ethanol gave a white precipitate which was washed with ethanol and dried *in vacuo*. The barium salt of 2′,3′-dideoxyuridine 5′-phosphate thus obtained was spectrally shown to be a tetrahydrate and was poorly soluble in water, λ_{max} 263 (pH 2) and 263 mμ (1 *N* lithium hydroxide).

Anal. Calcd. for $C_9H_{11}BaN_2O_7P\cdot 4H_2O$: P, 6.20, P/dideoxyuridine, 1.0. Found: P, 6.51; P/dideoxyuridine, 1.05.

3′-Deoxythymidine 5′-Phosphate (VII, R = Me).—Phosphorylation of 3′-deoxythymidine (0.1 mmole) was carried out in identical manner to that of 2′,3′-dideoxyuridine above. The yield of chromatographically pure product (R_f 0.14; *cf.* 3′-deoxythymidine, R_f 0.72 in solvent I) was 85% and the barium salt was an octahydrate.

Anal. Calcd. for $C_{10}H_{13}BaN_2O_7\cdot 8H_2O$: P, 5.30; P/deoxythymidine, 1.0. Found: P, 5.70; P/deoxythymidine, 1.08.

Kinetics of Acid Hydrolyses. A. Uracil Nucleosides.—Samples of uridine, 2′-deoxyuridine, and 2′,3′-dideoxyuridine (2.0 mg.) were separately dissolved in 0.5-ml. portions of cold, 1.0 *N* hydrochloric acid. Approximately 20-μl. aliquots of these solutions were sealed in capillary tubes and placed in a boiling water bath. At intervals the tubes were removed and, if necessary, stored in Dry Ice. The tubes were then broken and the contents were mixed directly with approximately 1.5 ml. of 1 *N* lithium hydroxide in a quartz spectrophotometer cell. The extent of the hydrolysis was followed by the ratio of the optical densities at 276 and 263 mμ: O.D. 276/263 = 0.556 for uracil nucleosides, 276/263 = 1.29 for uracil in 1 *N* lithium hydroxide.

B. Thymine Nucleosides.—The procedure in A was repeated exactly, except that thymidine and 3′-deoxythymidine were used in place of the uracil nucleosides. The extent of hydrolysis was determined from the optical density ratios at 281 and 267 mμ: 281/267 = 0.596 for thymidine and 3′-deoxythymidine, and 1.184 for thymine in 1 *N* lithium hydroxide. The results are shown in Fig. 1, the various deoxynucleosides all obeying first-order kinetics until 60–75% hydrolysis had occurred.

Alkylbenzenes. XIII. Rearrangements and Reorientations of C14-Labeled *n*-Propyltoluenes and *n*-Propylxylenes

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Received August 27, 1963

The reactions of *p*-*n*-propyl-α-C14-toluene and 1,3-dimethyl-4-*n*-propyl-β-C14-benzene with aluminum chloride at temperatures from 23 to 98° were studied. At lower temperatures the main reactions were reorientation to *m*-*n*-propyltoluene and 1,3-dimethyl-5-*n*-propylbenzene, respectively; at higher temperatures a complex mixture of products was formed by competing reactions which included reorientation of methyl as well as propyl groups, and rearrangements of *n*-propyl groups to isopropyl groups and to *n*-propyl groups in which C14 was interchanged between α- and β-positions of the side chains. The results of the present work and previous work lead to the conclusion that the susceptibility toward aluminum chloride-induced rearrangement of *n*-propyl side chains decreases in the series *n*-propylbenzene, *n*-propyltoluene, and *n*-propylxylene. An explanation for this order is suggested.

Reorientation reactions of the type *p*-xylene → *m*-xylene[1,2] and *p*-ethyltoluene → *m*-ethyltoluene[3] take place under milder conditions than those which produce rearrangements of side chains in propyl-[4] and butylbenzenes.[5] However, in some studies of reorientation reactions,[6,7] conditions were similar to those which produce rearrangement; it thus seemed worthwhile to determine the extent to which rearrangements may occur in these systems.

Nightingale and Shackelford[7] reported that the major products of reaction of 1,3-dimethyl-4-*n*-propylbenzene and 1,3-dimethyl-4-*n*-butylbenzene were 1,3-dimethyl-5-*n*-propylbenzene and 1,3-dimethyl-5-*n*-butylbenzene, respectively, but they stated that it was quite possible that their products contained minor amounts of side chain-rearranged isomers. We particularly were interested in investigating the C14-labeled *n*-propyl case, since rearrangements could be detected with more precision in this system than the butyl. This paper reports the results of investigation of the reaction of 1,3-dimethyl-4-*n*-propyl-β-C14-benzene and of the structurally related *p*-*n*-propyl-α-C14-toluene with aluminum chloride.

(1) G. Baddeley, G. Holt, and D. Voss, *J. Chem. Soc.*, 100 (1952).

(2) (a) D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1952); (b) H. C. Brown and H. Jungk, *ibid.*, **77**, 5579 (1955).

(3) R. H. Allen, *ibid.*, **82**, 4856 (1960).

(4) R. M. Roberts and J. E. Douglass, *J. Org. Chem.*, **28**, 1225 (1963); *cf.* references to previous papers.

(5) R. M. Roberts, Y. W. Han, C. H. Schmid, and D. A. Davis, *J. Am. Chem. Soc.*, **81**, 640 (1959).

(6) G. Baddeley and J. Kenner, *J. Chem. Soc.*, 303 (1935).

(7) (a) D. V. Nightingale and J. M. Shackelford, *J. Am. Chem. Soc.*, **76**, 5767 (1954); (b) **78**, 1225 (1956).