Nucleosides. XXIV. 1-(2′,5′- and 3′,5′-Epoxy-β-D-lyxofuranosyl)uracils[1]

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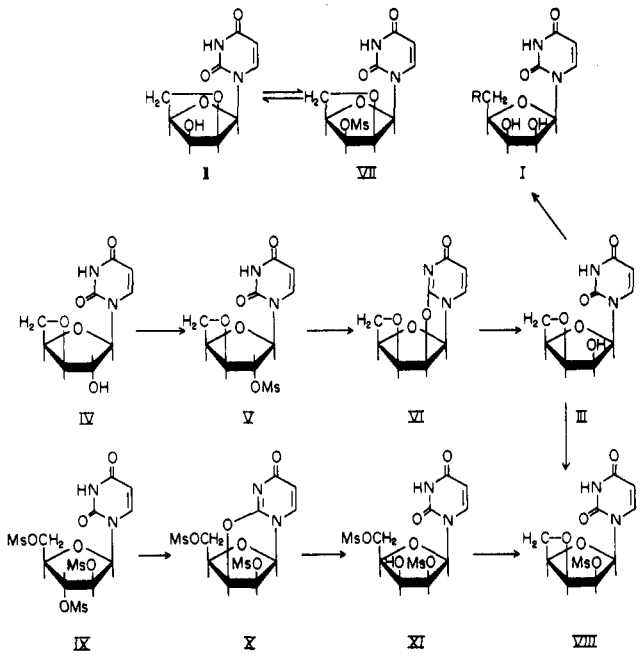
The structure of the crystalline epoxy nucleoside formed upon base treatment of 1-(5′-*O*-mesyl-β-D-lyxofuranosyl)uracil (I, R = OMs) was unequivocally proven to be 1-(2′,5′-epoxy-β-D-lyxofuranosyl)uracil (II) by synthesis of the only other possible product, 1-(3′,5′-epoxy-β-D-lyxofuranosyl)uracil (III). Mesylation of 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (IV) gave a crystalline mesyloxy derivative V. Heating V with sodium *t*-butoxide led to a crystalline "tetracyclic" nucleoside, 2,2′-anhydro-1-(3′,5′-epoxy-β-D-lyxosyl)uracil (VI). Alkaline cleavage of the 2,2′-anhydro linkage of VI gave the desired III in crystalline form. Mesylation of III gave a crystalline mesyloxy derivative VIII, 1-(3′,5′-epoxy-2′-*O*-mesyl-β-D-lyxosyl)uracil. VIII was synthesized by an independent route by the conversion of the known 2′,3′,5′-tri-*O*-mesyl-β-D-arabinosyluracil (IX) to the 2,3′-anhydro derivative X. Cleavage of the anhydro bond of X with aqueous acid yielded XI. Treatment of XI with base gave the epoxide VIII. Mesylation of II in pyridine gave a monomesyloxy derivative VII. Reaction of the crystalline VII with sodium benzylate in benzyl alcohol produced II in high yield by a transmesylation reaction. Re-examination of the preparation of 1-(5′-*O*-mesyl-β-D-lyxofuranosyl)uracil (I, R = OMs) from 2,2′-anhydro-1-(3′,5′-di-*O*-mesyl-β-D-arabinosyl)uracil (XIV, R = OMs) in refluxing water suggested the probable structure of a crystalline intermediate, isolated previously from the reaction mixture, as a 2,2′-anhydro nucleoside (XVIII, R = OMs) formed from the 2,3′-anhydro nucleoside (XVI, R = OMs) by an internal rearrangement. Reaction of XVIII (R = OMs) with sodium methylate in methanol gave VI.

The possible application of nucleoside epoxides as useful intermediates in the synthesis of biologically active analogs of nucleic acid components led to the synthesis of epoxides of the *lyxo* configuration. The foregoing paper in this series[2] described the first synthesis of a 2′,5′-epoxy nucleoside, as well as the first 3′,5′-epoxyaldopentofuranosyluracil.[3,4] These epoxides are of the *arabino* and *xylo* configurations, respectively. The syntheses of 1-(2′,3′-epoxy-β-D-lyxofuranosyl)-uracil and several 5′-substituted derivatives were described earlier.[5] The present paper presents the preparation of 2′,5′- and 3′,5′-epoxides of 1-β-D-lyxofuranosyluracil, thus completing the synthesis of all possible epoxide types in the 1-β-D-lyxofuranosyluracil series.

Treatment of 1-(5′-*O*-mesyl-β-D-lyxofuranosyl)uracil[6] (compound I, R = OMs, Figure 1) with base gave a crystalline product characterized by a high melting point and a large positive rotation.[7] Elemental analysis and ultraviolet absorption characteristics were in agreement with an epoxy nucleoside structure. Two possible compounds, II and III, were indicated. Attack upon C-5′ to displace the mesyloxy group could conceivably have been effected by an anionoid hydroxyl either at C-2′[2] or C-3′.[2,4] In order to establish the structure of the product an unequivocal synthesis of one of the two possible structures, namely, 1-(3′,5′-epoxy-β-D-lyxofuranosyl)uracil (III), was undertaken.

Mesylation of 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil[2] (IV, Scheme I) gave a crystalline monomesyloxy derivative V. Heating V with sodium *t*-butoxide in dimethylformamide[8] gave a "tetracyclic" nucleoside, 2,2′-anhydro-1-(3′,5′-epoxy-β-D-lyxosyl)uracil (VI), as colorless prisms. The ultraviolet absorption spectrum of VI was characteristic of previously described 2,2′-anhydropentofuranosyluracils[9–11] with maxima at 250 and 223 mμ, and its infrared spectrum showed an absorption at 6.05 μ, characteristic of anhydro nucleosides of this type but different from the singlet or doublet found for the 1-β-D-aldopentofuranosyluracils centered at about 5.85 μ.

SCHEME I



In order to avoid cleavage of the acid-labile 3′,5′-epoxy linkage of VI the 2,2′-anhydro bond was broken in aqueous base to give the desired 1-(3′,5′-epoxy-β-D-lyxofuranosyl)uracil (III) in crystalline form. As shown in Table I, compound III differed markedly

(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 03190-08).

(2) I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Org. Chem.*, **30**, 467 (1965).

(3) The synthesis of 1-(3′,5′-epoxy-2′-deoxy-β-D-xylosyl)thymine was reported recently.[4]

(4) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, **28**, 942 (1963).

(5) J. F. Codington, R. Fecher, and J. J. Fox, *ibid.*, **27**, 163 (1962).

(6) R. Fecher, J. F. Codington, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 1889 (1961).

(7) The original synthesis of this material was made by Ronald Fecher, who was associated with this laboratory during the years 1957–1961.

(8) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961).

(9) D. M. Brown, A. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).

(10) J. F. Codington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960).

(11) N. C. Yung and J. J. Fox, *ibid.*, **83**, 3060 (1961).

TABLE I

POLARIMETRIC AND SPECTROPHOTOMETRIC DATA

	Polarimetric data				Ultraviolet absorption data				
Compd.	$[\alpha]_D$, deg.	Temp., °C.	Solvent	Concn.	λ_{max}, mμ	ϵ_{max}	λ_{min}, mμ	ϵ_{min}	Solvent
II	+234	20	Water	0.6	263	10,950	230	2110	Water
III	+102	25	Water	0.1	260	9,420	230	2020	Water
					205	8,430			
V	~+12	25	Acetone	0.1	259	8,540	228.5	1940	Water
					204	7,480			
VI	−103	23	Water	0.1	250	7,590	235	6000	Water
					223	7,880			
					250	7,290	238	6680	Ethanol
					224	9,820			
VII	+163	25	Dioxane	0.4	262	9,600	230	1720	Water
					205	7,480			
VIII	+165	23	Water	0.1	257.5	9,020	228	2050	Water
					204	8,090			
X	~+8	24	Water–ethanol (1:1)	0.1	230	9,280	214	5690	Water
					245 sh	8,620			
1-(2′,3′-Epoxy-β-D-lyxofuranosyl)uracil[a]					259	10,230	228	2250	Water
					204	9,600			
1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil[a]					258.5	10,120	228	2310	Water
					204	9,560			

[a] See ref. 5.

in physical properties from the unknown epoxide II. Since only two possible structures, II or III, for the latter were envisioned, the epoxide obtained from I (R = OMs) was tentatively assigned the 2′,5′-epoxide structure II, 1-(2′,5′-epoxy-β-D-lyxofuranosyl)uracil. Mesylation of the epoxides II and III in pyridine gave crystalline mesyloxy derivatives VII and VIII (Scheme I), respectively, in good yields. As expected, VII differed markedly from VIII with respect to melting point and ultraviolet and infrared spectra, although optical rotations of the two compounds were almost identical. These values are given in Table I. Confirmation of the structures of both II and III (and VII and VIII) is based upon the studies presented below.

Consistent with epoxide structures, neither II nor III consumed metaperiodate at 20–25°. When refluxed with aqueous sulfuric acid, however, the two compounds reacted very differently. After 3-hr. reflux with 0.25 *N* sulfuric acid, III had undergone a quantitative conversion to 1-β-D-lyxofuranosyluracil (I, R = OH). Cleavage of the epoxy linkage by attack at C-5′ without glycosylic cleavage is consistent with a 3′,5′-epoxy structure.[2,4] The fact that I (R = OH) was obtained under acid hydrolysis is confirmation of the *lyxo* configuration of III. On the other hand, reflux of II with aqueous acid (0.2 *N* sulfuric acid for 2.5 hr.) resulted in a complete cleavage of the glycosylic bond to give uracil and as yet unidentified sugar fragments. A similar result had likewise been obtained with the known 1-(2′,5′-epoxy-β-D-arabinofuranosyl)uracil in refluxing aqueous sulfuric acid.[2]

In order to further substantiate the structure of III, and thus of II, the 2′-mesyloxy derivative of III, namely VIII, was synthesized by a second and potentially more advantageous route, using as starting material the known 1-(2′,3′,5′-tri-*O*-mesyl-β-D-arabinosyl)-uracil (IX).[6] Upon heating with sodium acetate in DMF or by the addition of 1 equiv. of sodium hydroxide in ethanol–water, IX gave a crystalline 2,3′-anhydro derivative X. The ultraviolet absorption spectrum showed marked similarity to that of a 2,3′-anhydro nucleoside previously reported[11] but was considerably different from that of the 2,2′-anhydro nucleosides[9–11] and 2,5′-anhydro nucleosides.[12] Acid cleavage of the 2,3′-anhydro bond proved extremely difficult and was not completed even after more than 23 hr. of reflux with dilute sulfuric acid in ethanol–water. Compound XI, 1-(2′,5′-di-*O*-mesyl-β-D-lyxofuranosyl)uracil, crystallized readily, as contrasted to its previously reported isomer, 1-(3′,5′-di-*O*-mesyl-β-D-arabinofuranosyl)uracil,[6] which has resisted all attempts at crystallization. Treatment of XI with aqueous sodium hydroxide yielded VIII, as colorless needles. This sample of VIII proved to be identical with that obtained by the route described above, IV → V → VI → III → VIII.

These data firmly establish III as the 3′,5′-epoxide of 1-β-D-lyxofuranosyluracil. Therefore, the epoxide obtained by base treatment of I must be 1-(2′,5′-epoxy-β-D-lyxofuranosyl)uracil (II).

In the reaction I (R = OMs) to II no evidence was obtained for the presence of the 3′,5′-epoxide III in the reaction mixture. The greater reactivity of the 2′-hydroxyl group than the 3′-hydroxyl group under alkaline conditions may be due to several factors. Among these may be the greater acidity of the 2′-hydroxyl group than the 3′-hydroxy group.[13–15] Another factor that may obtain here is related to steric considerations. Although from molecular models it would appear that the 3′-hydroxyl is in at least as close proximity to C-5′ as the 2′-hydroxyl for attack at C-5′ to form an epoxide linkage, it is probable that greater strain exists in the C-3′-O···C-5′···OMs

(12) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).

(13) Although no direct evidence is available regarding the relative acidities of the 2′- *vs.* the 3′-hydroxyl in 1-β-D-aldopentofuranosyluracils, Fox and co-workers[14] have presented spectral evidence consistent with the conclusion that the 2′-hydroxyl in such compounds is more acidic than the 3′-hydroxyl. The work of Kuhn and Sobotka[15] gives clear indication that in the case of several *O*-glucosides the 2′-hydroxyl is indeed more acidic than the 3′-hydroxyl.

(14) J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Am. Chem. Soc.*, **75**, 4315 (1953).

(15) R. Kuhn and H. Sobotka, *Z. Physik. Chem.* (Leipzig), **109**, 65 (1924).

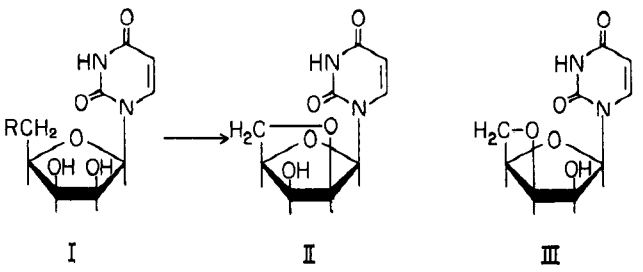


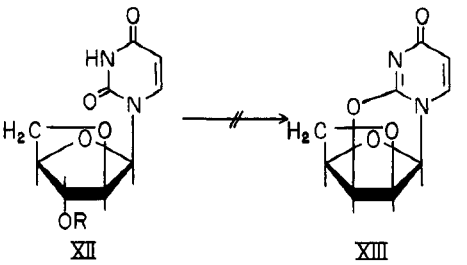
Figure 1.

transition state, which involves the formation of a four-membered ring, than in the C-2′-O···C-5′···OMs transition state, in which a less-strained five-membered ring is formed. Thus, there would be greater probability for the formation of the five-membered butylene oxide ring, as in II, than for the four-membered propylene oxide type ring found in III.

An interesting difference is observed in the ultraviolet absorption spectra of II and III. The 2′,5′-epoxide II shows a bathochromic shift of 3 mμ compared with the 3′,5′-epoxy isomer, and has an ϵ_{max} (263 mμ) of 10,950, 14% higher than that of III (ϵ_{max} at 260 mμ, 9420). Such a relationship was also observed[2] with 1-(2′,5′-epoxy-β-D-arabinofuranosyl)-uracil (ϵ_{max} at 264 mμ, 10,700) and 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil, (ϵ_{max} at 260 mμ, 9700), an extinction coefficient difference of 9.3%. The corresponding mesyloxy compounds of II and III, namely VII and VIII, respectively, and the mesyloxy derivatives of 1-(2′,5′-epoxy-β-D-arabinofuranosyl)uracil[2] and 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil, namely V, show similar differences, the monomesyloxy-2′,5′-epoxides having far greater ϵ_{max}-values than the corresponding 3′,5′-epoxy isomers. It is interesting to note that the ϵ_{max}-values for the 2′,3′-epoxides in the *lyxo* series, also presented in Table I, show intermediate values between the 2′,5′- and 3′,5′-epoxy nucleosides.[16,17] No simple explanation for these differences in forthcoming. Both hypsochromic and ϵ_{max}-augmenting influences were observed for the 2′-chloro and 2′-bromo substituents in the 2′-halogeno-2′-deoxyuridines,[18] although mesyloxy groups substituted at the 2′- or 3′-positions in the sugar moiety of aldopentofuranosyluracils generally have a hypsochromic effect and an ϵ_{max}-reducing effect.[6] It appears probable that these phenomena find their explanation in terms of (1) polar interaction between the pyrimidine (probably through the 2-carbonyl group) and the sugar moiety (anhydro oxygen in the epoxides) and (2) electron-attracting or electron-repulsing properties of substituents in the sugar (mainly exerted by C-2′-substituted groups).

Reactions of the 3′-Mesyloxy Group of 2′,5′-Epoxy Nucleosides.—In view of the successful synthesis of the "tetracyclic" nucleoside VI containing 3′,5′-epoxy and 2,2′-anhydro structures an effort was made to prepare the isomeric 2,3′-anhydro-1-(2′,5′-epoxy-β-D-lyxosyl)uracil (XIII, Scheme II) from 1-(2′,5′-epoxy-3′-*O*-mesyl-β-D-arabinosyl)uracil (XII, R = OMs).[2] An examination of molecular models led to the conclusion, however, that it was highly improbable that such a structure as XIII could, in fact, exist, owing to steric interference between the two ring (anhydro- and epoxy-) oxygen atoms. Such a conclusion was borne out by the reaction results. The method of Letters and Michelson,[8] heating with sodium *t*-butoxide in DMF, resulted in a nearly quantitative recovery of starting material XII. An attempt to convert 1-(2′,5′-epoxy-3′-*O*-mesyl-β-D-lyxosyl)uracil (VII) to the *arabino* configuration, compound XII (R = OBz), by reflux with sodium benzoate in DMF,[19] led only to the recovery of starting material. The difficulty of SN2-type displacements of the mesyloxy group on the 3′-bridge carbon of XII (R = OMs) may be related to the marked unreactivity of the tosyloxy group under solvolytic conditions reported in the 7-norborneol system of Winstein and co-workers.[20] From a stereochemical point of view the sulfonyloxy group on C-7 in 7-norborneol is essentially equivalent to that on C-3′ in compounds VII and XII.[2]

SCHEME II



The mesyloxy group of VII was removed with retention of the 2′,5′-epoxy linkage and of the configuration at C-3′ under different conditions and by a different mechanism. Heating VII with sodium benzylate in benzyl alcohol led to a nearly quantitative yield of the 3′-hydroxy derivative II (Scheme I). This type of reaction, involving displacement of an isolated sulfonyloxy group without inversion, was described as trans-sulfonylation by Cope and Shen[21] and designated an SN2S-type reaction.

As was expected, compound VII showed marked stability when boiled in water at neutral pH. Reflux of VII in water for 9 hr. resulted in the liberation of absolutely no methanesulfonic acid. These results conform to the expected lack of reactivity of the 3′-mesyloxy group of VII (and of XII, R = OMs)[2] when compared with the 3′-mesyloxy group of 3′-mesyloxyuridine,[11] which when subjected to similar hydrolytic conditions for 10 hr. released 0.5 equiv. of methanesulfonic acid.

Mechanism for the Formation of 1-β-D-Lyxofuranosyluracils.—It was reported from this laboratory a few years ago[6] that the reaction of 2,2′-anhydro-1-(3′-*O*-mesyl-β-D-arabinosyl)uracils (XIV) in boiling water gave in high yield 1-β-D-lyxofuranosyluracils (I, R = H, OBz, OMs), as shown in Scheme III. The mechanism proposed at that time for the reaction (illustrated by broken-line arrows) involved two intermediates, XV and XVI. An initial cleavage of the 2,2′-anhydro

(16) Comparable ϵ_{max}-values are reported for uridine, 10,100 (261 mμ), and deoxyuridine, 10,200 (262 mμ).[17]

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

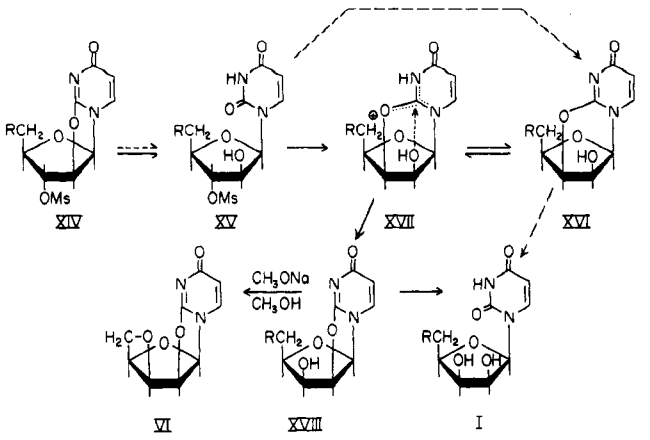
(18) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964).

(19) E. G. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5775 (1958).

(20) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4184 (1955); S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

(21) See A. C. Cope and T. Y. Shen, *ibid.*, **78**, 5912 (1956), and leading references.

SCHEME III



bond of XIV gave XV, a 2′-hydroxy derivative of the *arabino* configuration. When the starting material was XIV (R = OMs), such a compound (XV, R = OMs) was, in fact, isolated from the reaction mixture and its structure established. A second step involved attack by the 2-carbonyl of XV upon C-3′ to give the 2,3′-anhydro derivative XVI. A crystalline compound corresponding in elemental analysis to XVI and possessing an anhydro linkage was isolated from the reaction mixture when XV was refluxed in water. This material was assigned the logical 2,3′-anhydro structure XVI. The final step in the reaction involved cleavage of the anhydro bond to yield the product I.

The mechanism presented earlier was consistent with the available data and there appeared at that time to be no reason to question the 2,3′-anhydro structure XVI for the second intermediate. Recent studies,[2] however, which have demonstrated that a 2,5′-anhydro nucleoside can rearrange to a 2,2′-anhydro nucleoside under neutral aqueous conditions, have made a re-examination of the assigned structure XVI necessary. If a similar transformation took place in this reaction, with the 2,3′-anhydro nucleoside XVI rearranging to a 2,2′-anhydro nucleoside through a resonant cation, such as illustrated by the structure XVII, the crystalline intermediate might indeed be 2,2′-anhydro-1-(5′-*O*-mesyl-β-D-lyxofuranosyl)uracil (XVIII), rather than XVI.

With the synthesis of certain compounds illustrated in Scheme I, chemical methods appeared to be available for the determination of the structure of the intermediate XVI or XVIII. If it were indeed the 2,3′-anhydro nucleoside XVI, as postulated, mesylation should yield the known 2,3′-anhydro-1-(2′,5′-di-*O*-mesyl-β-D-lyxosyl)uracil (X). Treatment of the unknown anhydro derivative with excess methanesulfonyl chloride in pyridine for 18 hr. at 4° resulted in the formation of considerable color and in a 30% recovery of starting material. Paper chromatography (acetone–chloroform–water, 5:1:1) of the mother liquor indicated the presence of at least two products in addition to starting material. One of these migrated with the desired product X (R_f 0.81), but was present only in small amount and could not be isolated or characterized further.

As the above approach did not appear promising, a second approach was attempted. If the unknown intermediate were the 2,2′-anhydro nucleoside XVIII

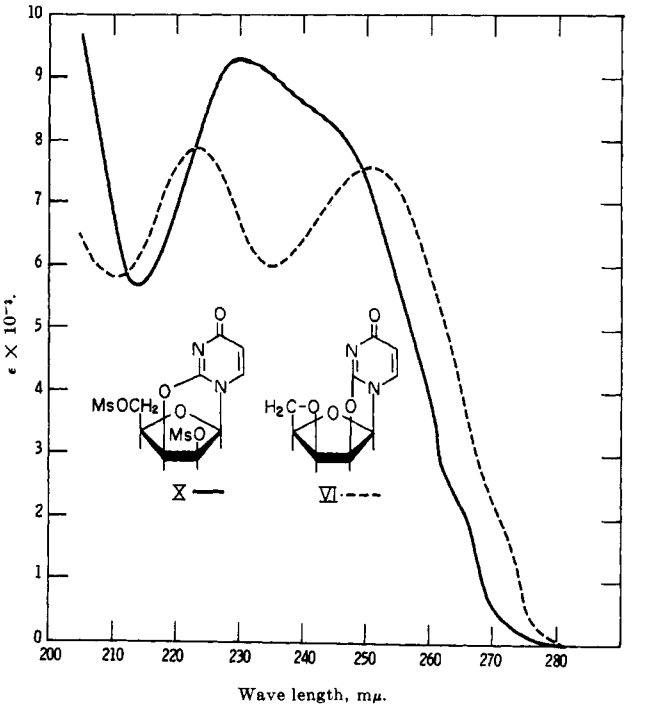


Figure 2.—Ultraviolet spectra in water.

(R = OMs), it would be expected to yield on base treatment the known "tetranucleoside," 2,2′-anhydro-1-(3′,5′-epoxy-β-D-lyxosyl)uracil (VI), resulting from attack by the anionic 3′-hydroxyl on C-5′. In order to minimize cleavage of the anhydro bond during the reaction, the exclusion of all moisture was mandatory. Such a reaction was carried out using excess sodium methylate in methanol. After 19 hr. at 24–26°, only starting material was detected, suggesting either a 2,3′-anhydro structure XVI or an exceedingly unreactive 3′-hydroxyl of the 2,2′-anhydro nucleoside XVIII. After refluxing with sodium methylate in methanol, however, colorless prisms were isolated. These proved to be identical with compound VI, 2,2′-anhydro-1-(3′,5′-epoxy-β-D-lyxosyl)uracil.

This synthesis of VI supports the 2,2′-anhydro structure XVIII (R = OMs) for the intermediate, but unfortunately cannot be considered proof of this structure. Under the strenuous conditions required for the reaction, it is conceivable that compound XVI could have undergone a rearrangement to XVIII, but by a mechanism different from that shown in Scheme III. Attack by the 2′-anionic hydroxyl upon C-2 of XVI could possibly have led to XVIII.

The most conclusive evidence for the 2,2′-anhydro structure is found in the ultraviolet absorption data. A comparison of the ultraviolet absorption spectra of known 2,2′- and 2,3′-anhydro nucleosides reveals a characteristic spectrum for each structure.[22] This is illustrated in Figure 2 by curves for compounds VI and X. The spectrum of 2,2′-anhydro-1-(3′,5′-epoxy-β-D-lyxosyl)uracil (VI) is almost identical with that for the unknown intermediate (XVI or XVIII) with maxima at 250 and 224 mμ. This spectrum corresponds also to the spectra of the unsubstituted 2,2′-anhydro-1-β-D-arabinofuranosyluracil reported by Brown and co-workers,[9] with maxima at 249.5–251

(22) No distinguishing feature between 2,2′- and 2,3′-anhydro nucleosides has been found in their infrared spectra.

and 223–223.5 mμ, and of 2,2′-anhydro-1-β-D-lyxofuranosyluracil reported by Yung and Fox,[11] with maxima at 249.5 and 222 mμ.

On the other hand, compound X, 2,3′-anhydro-1-(2′,5′-di-*O*-mesyl-β-D-lyxosyl)uracil, has a single maximum at 230 mμ and a shoulder at 245 mμ. The unsubstituted 2,3′-anhydro-1-β-D-xylofuranosyl)uracil[11] was found to have a similarly shaped spectral curve, although the maximum is hypsochromically shifted slightly to 229 mμ, and the shoulder at 245 mμ in X has become a weak maximum at 245 mμ.

On the basis of both chemical and spectral evidence, it seems probable, although it is not conclusively established, that the crystalline intermediate isolated from the reaction of XV (R = OMs) in water is the 2,2′-anhydro derivative XVIII (R = OMs), rather than the previously reported 2,3′-anhydro nucleoside XVI (R = OMs).

If indeed the structure were that of XVIII (R = OMs), the mechanism for the reaction proposed in an earlier publication[6] would still be essentially correct but would require some modification.[23] A proposed mechanism is illustrated by solid arrows in Scheme III. It is suggested, as postulated earlier,[6] that the first step in the reaction is a cleavage of the 2,2′-anhydro bond of XIV to give XV. The second step would involve attack of the 2-carbonyl on C-3′ to eliminate the 3′-mesyloxy group with the formation of a resonant cation XVII, of the type described in the previous paper in this series.[2] XVII could conceivably yield a 2,3′-anhydro nucleoside XVI, the formation of which was postulated earlier,[6] or the more probable 2,2′-anhydro derivative XVIII. It appears likely that, if the 2,3′-anhydro compound XVI were, in fact, formed, it would rearrange to the 2,2′-anhydro lyxosyl nucleoside XVIII through the intermediate XVII, rather than undergo cleavage of the 2,3′-anhydro bond, as previously suggested. If so, the final product, a 1-β-D-lyxofuranosyluracil (I), is probably formed as a result of cleavage of the 2,2′-anhydro bond of XVIII.

Experimental[24]

1-(2′,5′-Epoxy-β-D-lyxofuranosyl)uracil (II). Method A.—To 80-ml. of a solution of sodium methylate (13 mmoles) in methanol was added 0.80 g. (2.6 mmoles) of 1-(5′-*O*-mesyl-β-D-lyxofuranosyl)uracil (I).[6] The solution was stirred at 20–25° for 2.3 hr. Solvent was removed *in vacuo*, and 20 ml. of water was added to the residue. After treatment with Dowex 50 (H^+), the acidic solution was diluted with ethanol and reduced in volume. After repeated additions of ethanol, followed by distillation *in vacuo*, an ethanolic solution (10 ml.) was cooled. Colorless needles, 0.41 g. (73%),[2] m.p. 199–201°, were collected. Crystallization from methanol gave colorless needles melting at 220–223°. Ultraviolet absorption and polarimetric properties are reported in Table I.

Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.78; H, 4.42; N, 12.39. Found: C, 47.43; H, 4.20; N, 12.39.

Method B.—A solution of 0.15 g. (0.49 mmole) of 1-(2′,5′-epoxy-3′-O-mesyl-β-D-lyxosyl)uracil (VII) in 5 ml. of benzyl alcohol containing 2.7 mmoles of sodium benzylate was heated at 90–95° for 2 hr. The mixture was taken to dryness *in vacuo* and triturated with hot ethanol. After filtration of the hot solution, the ethanol was removed by distillation. The residue was triturated with ether and filtered. Colorless crystals, 0.10 g. (90%), m.p. 204–210°, were collected. Crystallization from methanol yielded colorless needles, m.p. 220–223°. This sample was identical with a sample prepared by method A with regard to melting point, ultraviolet absorption spectrum, and optical rotation. A mixture of samples prepared by the two methods showed no depression of melting point.

1-(2′,5′-Epoxy-3′-*O*-mesyl-β-D-lyxosyl)uracil (VII).—The dropwise addition of 0.28 g. (2.4 mmoles) of methanesulfonyl chloride to 0.29 g. (1.3 mmoles) of II was carried out in 20 ml of pyridine at 0° with stirring. After an additional 17 hr. at 5° the colorless mixture was treated with 5 drops of ethanol. After removal of solvent *in vacuo*, the residue was triturated well with ether, and the ether was decanted. The addition of 20 ml. of ice–water gave colorless platelets. These were collected, 0.38 g. (97%), m.p. 207–208° eff. dec. Crystallization from 80% ethanol gave colorless needles melting at 190–191° eff. dec.

Anal. Calcd. for $C_{10}H_{12}N_2O_7S$: C, 39.47; H, 3.98; N, 9.21; S, 10.54. Found: C, 39.24; H, 4.16; N, 9.00; S, 10.47.

1-(3′,5′-Epoxy-2′-*O*-mesyl-β-D-lyxosyl)uracil (V).—To a solution of 0.10 g. (0.44 mmole) of 1-(3′,5′-epoxy-β-D-xylofuranosyl)-uracil (IV)[2] in 8 ml. pyridine at 0° was added with stirring 0.11 g. (0.98 mmole) of methanesulfonyl chloride. After 40 hr. at 0–5° 3 drops of ethanol were added. The mixture was taken to dryness *in vacuo* and the residue was triturated in ether. After decanting, the material was crystallized from ethanol giving colorless needles, 0.08 g., m.p. 173–174.5° (color at 185°, 197° eff.). An additional 0.04 g., m.p. 172–175° (yield 89%), was crystallized from the mother liquor. Recrystallization from 80% ethanol gave colorless needles melting at 172–174°.

Anal. Calcd. for $C_{10}H_{12}N_2O_7S$: C, 39.47; H, 3.98; N, 9.21; S, 10.54. Found: C, 39.52; H, 4.02; N, 9.19; S, 10.47.

2,2′-Anhydro-1-(3′,5′-epoxy-β-D-lyxosyl)uracil (VI). Method A.—A solution of 0.05 g. (0.16 mmole) of compound V and 2.0 ml. of sodium *t*-butoxide (0.10 *M*) in 10 ml. of DMF was heated at 90–95° for 1 hr. The pale yellow solution was taken to dryness *in vacuo*, the residue was triturated with ether, and the ether was decanted. The residue was heated in 25 ml. of acetone, and inorganic solids were removed from the hot solution by filtration. Acetone was evaporated from the filtrate, and the residue was crystallized from a small amount of ethanol giving colorless prisms, 0.015 g. (44%), m.p. 225–228° dec.

Anal. Calcd. for $C_9H_8N_2O_4$: N, 13.46. Found: N, 13.21.

Method B.—A mixture of 7 mg. (0.023 mmole) of 2,2′-anhydro-1-(5′-*O*-mesyl-β-D-lyxofuranosyl)uracil (XVIII, probable structure, see discussion) and 0.10 ml. (1.3 mmoles) of sodium methylate in 3 ml. of methanol was refluxed under anhydrous conditions for 30 min. The clear colorless solution produced no crystalline starting material upon cooling. It was therefore treated with freshly prepared Dowex 50 (H^+) and filtered. The ultraviolet absorption spectrum of the filtrate showed the presence of nucleoside material in which the anhydro bond had been cleaved (λ_{max} 256 mμ) in the reaction. After washing the resin with a small amount of water, it was washed with 0.2 *N* ammonium hydroxide. The filtrate gave a characteristic 2,2′-anhydro nucleoside spectrum. Solvent and ammonia were removed *in vacuo*. The residue was dried by the repeated addition and evaporation of ethanol *in vacuo*. To the dry residue was added 2 drops of ethanol. Upon cooling, material crystallized as colorless prisms. The ethanol was withdrawn through a capillary, and the prisms were dried. These melted at 225–227°. The ultraviolet absorption spectrum was identical with that of material obtained by method A (λ_{max} 250 and 233 mμ). The infrared spectrum was identical in every detail with that obtained from material synthesized by method A.

1-(3′,5′-Epoxy-D-β-lyxofuranosyl)uracil (III).—The reaction was carried out in a polarimeter cell. A solution containing 0.0131 g. (0.063 mmole) of VI in 3.0 ml. of water had an optical rotation, $[\alpha]^{25}D$ −98°. The addition of 1 drop of sodium hydroxide (10 *N*) resulted in a rapid change in optical rotation. This reached a constant value within 75 min. of −4°. The addition of 1 drop of hydrochloric acid (12 *N*) gave a value, $[\alpha]^{25}D$ +23°. The ultraviolet absorption spectrum confirmed the complete cleavage of the anhydro bond: in water, λ_{max} 260 mμ and λ_{min} 230 mμ. The excess acid was neutralized with 1 drop of triethylamine, and the solution was taken to dryness *in vacuo*. The residue was heated with ethanol to which a little ether had been added, and inorganic salts were removed by fil-

(23) It appears reasonable to assume, as was done earlier,[6] that the reaction to yield 1-β-D-lyxofuranosyluracils (I) occurs independently of the 5′-substituent (R = H, OMs, OBz), and that a mechanism which applies to the reaction of XIV (R = OMs) has general applicability.

(24) Melting points are corrected. Elemental analyses were made by Spang Microanalytical Laboratory, Ann Arbor, Mich. Ultraviolet absorption data were obtained using the Cary recording spectrophotometer, Model 15. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer.

tration. The filtrate was reduced to about 2 ml. and cooled. A yield of 0.008 g. (57%) of colorless prisms melting at 220–223° was obtained.

Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.78; H, 4.42; N, 12.39. Found: C, 47.70; H, 4.41; N, 11.89.

Acidic Hydrolysis of III.—A solution of 1 mg. of III in 3 ml. of 0.25 *N* sulfuric acid was refluxed for 3 hr. Water (2 ml.) was added, and the solution was treated with excess barium carbonate. After filtration the filtrate was taken to dryness *in vacuo*, and the residue was triturated with 8 ml. of hot ethanol. After removal of additional inorganic material, the solution was evaporated to dryness *in vacuo*, and the residue was dissolved in 3 drops of water. Ultraviolet absorption data were as follows: in water, λ_{max} 262 and 205 mμ, λ_{min} 230 mμ, ratio 260/230 mμ 4.8; in sodium hydroxide (0.1 *N*), λ_{max} 262 mμ, λ_{min} 241 mμ, ratio 260/280 mμ 2.9. Paper electrophoresis in borate buffer, pH 6.03, using Whatman 3MM paper for 2.3 hr. at 800 v. and 12–18 ma. gave only one spot (intense) of anodic migration 8.0 cm., which corresponded to 1-β-D-lyxofuranosyluracil, anodic migration 8.0 cm. Paper chromatography in a system of acetone–chloroform–water (5:1:1) showed only one spot corresponding to that of 1-β-D-lyxofuranosyluracil, R_f 0.43.

2,3′-Anhydro-1-(2′,5′-di-*O*-mesyl-β-D-lyxosyl)uracil (X).—A solution of 0.22 g. (0.46 mmole) of 1-(2′,3′,5′-tri-*O*-mesyl-β-D-arabinosyl)uracil (IX) and 0.25 g. (3.0 mmoles) of anhydrous sodium acetate in 25 ml. of dimethylformamide was heated at 100–104° for 30 min. Solvent was removed *in vacuo*, the residue was triturated with ether, the ether was decanted, and the residue was dried. Crystals, 0.12 g. (68%), were filtered after trituration with 2 ml. of cold water. In the ultraviolet region these possessed a maximum at 230 mμ and a shoulder at 245 mμ. Crystallization from 90% ethanol gave colorless needles melting at 219–221°, 225° eff.

Anal. Calcd. for $C_{11}H_{14}N_2O_9S_2$: C, 34.55; H, 3.69; N, 7.33; S, 16.75. Found: C, 35.00; H, 3.86; N, 7.35; S, 16.94.

1-(2′,5′-Di-*O*-mesyl-β-D-lyxofuranosyl)uracil (XI).—A solution containing 0.07 g. (0.18 mmole) of X, 5 ml. of 1 *N* sulfuric acid, and 20 ml. of ethanol–water (1:1) was refluxed for 23 hr. Ultraviolet spectra indicated incomplete cleavage of the anhydro bond. After treatment with excess barium carbonate and filtering, the solution was taken to dryness *in vacuo*. Pale yellow crystals separated from a small amount of cold water. These melted at 219–221° with decomposition, and had an optical rotation, $[\alpha]^{25}D$ (acetone), of +57°. Ultraviolet absorption properties in water were λ_{max} 259 mμ, λ_{min} 228 mμ, ratio 260/230 mμ 4.11. The infrared spectrum was consistent with the expected product. The mother liquor showed (paper chromatography with acetone–chloroform–water, 5:1:1) the presence not only of the desired product, but of starting material and a small amount of uracil. Due to the difficulty encountered in obtaining a sufficient amount of pure product, an elemental analysis was not obtained. The crude material was used in the synthesis of 1-(3′,5′-epoxy-2′-*O*-mesyl-β-D-lyxosyl)uracil (VIII).

1-(3′,5′-Epoxy-2′-*O*-mesyl-β-D-lyxosyl)uracil (VIII). Method A.—A solution of 47 mg. (0.12 mmole) of XI, containing 33% X (determined by paper chromatographic separation, elution, and ultraviolet absorption at 260 and 230 mμ) in 4 ml. of 0.1 *N* sodium hydroxide was stirred at 20–25° for 18 hr. After treatment with Dowex 50 (H^+) and neutralization of the solution with 1 drop of triethylamine, solvent was removed *in vacuo*. Crystallization occurred upon cooling a 90% ethanolic solution. Colorless needles, 14.5 mg. (41%), m.p. 177–178°, were collected. Crystallization from 60% ethanol gave colorless needles, 11.6 mg., m.p. 177–178°.

Anal. Calcd. for $C_{10}H_{12}N_2O_7S$: C, 39.47; H, 3.98; N, 9.21. Found: C, 39.07; H, 4.16; N, 9.31.

Method B.—A solution of 11.1 mg. (0.049 mmole) of V in 3 ml. of 0.2 *N* sodium hydroxide was allowed to stand at 23–25° for 17 hr. After removal of sodium ions with Dowex 50 (H^+) the acidic solution was neutralized with 1 drop of triethylamine. The mixture was evaporated to dryness *in vacuo* with added ethanol. Paper chromatography in a system of acetone–chloroform–water (5:1:1) gave only one spot migrating with a sample of 1-(3′,5′-epoxy-β-D-lyxofuranosyl)uracil (III), R_f 0.71. The residue was dried well *in vacuo*, dissolved in 2 ml. of pyridine, and treated with 0.035 g. (0.30 mmole) of methanesulfonyl chloride in the cold. After standing at 4° overnight 1 drop of ethanol was added. After 30 min. the mixture was evaporated to dryness several times with ethanol, then dried. To the residue was added 3 drops of water. The mixture was allowed to stand 2 days at 23–25°. Needles, 3.5 mg. (32%), m.p. 165–175°, were collected. Crystallization from water gave colorless needles, m.p. 175–179°. A mixture of this sample and a sample prepared by method A, m.p. 176–179°, melted at 176.5–179°. Infrared and ultraviolet absorption spectra of samples prepared by the two methods were identical.

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Ozonation of 2,5-Diphenylfuran[1]

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Ozonations of 2,5-diphenylfuran (Ib) in both participating and nonparticipating solvents are described. The percentages of 1,2-bond-cleavage products [1,2-dibenzoylethylene (VIIb) or ozonolysis products thereof] and of 2,3-bond-cleavage products [β-benzoyloxycinnamaldehyde (IXb) or peroxidic precursors or decomposition and ozonolysis products thereof] have been accurately determined. Both the type of solvent and the reaction temperature affect the competition between the two types of reactions involved. General mechanisms are proposed to account for the competitive reactions which occur during ozonation of furans.

Wibaut and co-workers[3–5] were the first[3] to report the ozonation of furans and pyrroles to give not only the expected ozonolysis products, but also products resulting from cleavage of bonds other than the double bonds of the classical valence structures (*e.g.*, methylglyoxal, Xa, from 2,5-dimethylfuran, Ia).

In 1957 we published a preliminary report on the ozonation of 2,5-diphenylfuran (Ib, in methanol–acetone solvent) to give a 12% yield of *cis*-1,2-dibenzoylethylene (VIIb), with 1 mole equiv. of ozone, or a 14% yield of phenylglyoxal (Xb) with 2 mole equiv. of ozone.[1] We suggested that (1) VIIb was produced *via* a 1,4-

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