Experimental Section[9]

3,3′-Thiobis(methyl 3-deoxy-β-D-gulopyranoside) (II).—The method was based on that used for the preparation of 1,2-*O*-isopropylidene-6-thio-α-D-glucofuranose.[6] A suspension of barium hydroxide hydrate (31.2 g., 0.10 mole) in 120 ml. of water at 0° was saturated with hydrogen sulfide. Methyl 3,4-anhydro-β-D-galactopyranoside[4] (I) (17.6 g., 0.10 mole) was added, and hydrogen sulfide was passed into the solution for 140 min. at 0°. After standing 30 min. gaseous carbon dioxide was passed into the mixture until it was no longer basic to precipitate the barium ions as insoluble barium carbonate. The solution was filtered, and the filtrate was evaporated to dryness at 45° on the evaporator. The crude yield was 19 g. Unreacted oxide was removed by extraction with hot ethyl acetate, leaving 14 g. of crude II, m.p. 215–217°, 94% yield based on the oxide consumed. Recrystallization from dioxane gave a constant melting point of 219–220°. Ethanol can also be used as a recrystallization solvent: $[\alpha]^{25}\mathrm{D}$ −76.0° (*c* 2.1, water).

Anal. Calcd. for $C_{14}H_{26}O_{10}S$: C, 43.52; H, 6.74; S, 8.29. Found: C, 43.54; H, 6.55; S, 8.37.

Methyl 3-Deoxy-β-D-*xylo*-hexopyranoside (III) from II by Reductive Desulfuration.—Raney nickel catalyst was prepared from 15.0 g. of nickel–aluminum alloy by the method of Mozingo, *et al.*,[10] final heating being carried out at 50° for 1 hr. To the catalyst, freed from excess alcohol by decantation, was added a solution of 0.45 g. of II in 20 ml. of ethanol, followed by 7 ml. of water. After refluxing on a steam bath for 2 hr., the mixture was cooled and filtered free of catalyst, the catalyst was washed well with ethanol and water, and the combined filtrates were evaporated to dryness. The residue was recrystallized from isopropyl alcohol to give 0.31 g. (73%) of III, m.p. 175–176°, showing no depression in melting point when mixed with an authentic sample of methyl 3-deoxy-β-D-*xylo*-hexopyranoside, m.p. 174–175°.[4]

The above reductive desulfuration was repeated and the crude reduction product was hydrolyzed by heating in 0.2 *N* sulfuric acid for 5 hr., followed by treatment with Duolite A4 anion-exchange resin (amine form) to remove the acid and evaporation to a small volume. A chromatogram of this material using Whatman 1MM paper (*n*-butyl alcohol–acetic acid–water, 4:1:1; 16 hr.) when sprayed with aniline hydrogen phthalate in *n*-butyl alcohol and heated at 125° for 5 min. showed only one spot with R_{xylose} 1.30, very close to the value of R_{xylose} 1.33 reported[4] for 3-deoxy-D-*xylo*-hexose.

Reaction of 3,3′-Thiobis(methyl 3-deoxy-β-D-gulopyranoside) (II) with Benzaldehyde.—A mixture of 5.0 g. of II, 20 ml. of benzaldehyde, and 5.0 g. of fused anhydrous zinc chloride was shaken for 1 hr., then left to stand overnight at room temperature. When the reaction mixture was poured into ice–water a gummy layer separated from the water solution. The water was decanted and the organic layer was washed several times with small portions of pentane to remove benzaldehyde. The residue was treated with hot benzene and upon cooling there was obtained 4.0 g. of crude product. Several recrystallizations from benzene resulted in a white waxy solid with a double melting point: shrank and became wet at 119–120°, melted completely at 139–140°. The infrared spectrum showed some absorption still present at 2.82 μ, indicating the presence of free hydroxyl groups. A molecular weight determination (Rast) gave a value of 598, which is close to the value of 601 calculated for the dibenzylidene derivative containing 0.5 mole of benzene of recrystallization. Attempts were made to purify the benzylidene derivative on an aluminum oxide column. Only one substance was eluted (with chloroform as solvent) and this seemed to be identical with the original product when recrystallized from benzene. The most likely structure for this derivative would appear to be 3,3′-thiobis(methyl 4,6-*O*-benzylidene-3-deoxy-β-D-gulopyranoside) (IV), containing 0.5 mole of benzene of recrystallization: $[\alpha]^{28}\mathrm{D}$ −29.1° (*c* 1.052, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{34}O_{10}S \cdot 0.5C_6H_6$: C, 61.90; H, 6.16; S, 5.32. Found: C, 62.84; H, 6.21; S, 5.32.

3,3′-Thiobis(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-β-D-gulopyranoside) from IV.—Acetic anhydride (1.0 ml.) was added to 0.3 g. of IV in 3 ml. of pyridine in the cold; after standing overnight the mixture was poured into ice–water, yielding 0.3 g. of a white solid, m.p. 253–256°. Recrystallization to constant melting point (95% ethanol) gave 0.24 g., m.p. 259–260°, $[\alpha]^{28}\mathrm{D}$ −24.9° (*c* 2.084, $CHCl_3$). The infrared spectrum showed no absorption band at 2.82 μ.

Anal. Calcd. for $C_{32}H_{38}O_{12}S$: C, 59.44; H, 5.88; S, 4.95. Found: C, 59.33; H, 6.02; S, 5.26.

3,3′-Thiobis(3-deoxy-D-gulopyranose) (V).—A solution of II (2.5 g.) in 250 ml. of water was refluxed with 25 ml. of Amberlite IR-120 (H^+) ion-exchange resin until constant rotation was obtained (6 hr.). The resin was removed by filtration and washed well with water. The filtrate was evaporated to a small volume and filtered through a thin mat of Norit and Celite No. 535, then taken to dryness (<55°) on the flash evaporator, final removal of water being accomplished by several evaporations with small portions of ethanol and benzene. The residue was repeatedly extracted with acetone, and the combined acetone extracts were evaporated to dryness, leaving a fluffy white waxy solid with a rather sweet odor, m.p. 92°, $[\alpha]^{25}\mathrm{D}$ −27.6° (*c* 1.068, absolute ethanol). Upon standing the free sugar appeared to undergo decomposition.

3,3′-Thiobis(3-deoxy-D-gulopyranose) Octaacetate (VI).—The acid hydrolysis of 4.2 g. of II with 0.2 *N* sulfuric acid for 5 hr. at 95° gave 3.4 g. of crude V which was acetylated immediately by addition of 25 ml. of pyridine and 15 ml. of acetic anhydride in the cold. After standing overnight, the mixture was poured over ice, and the solid which formed was removed by filtration. It amounted to 4.3 g., m.p. 170–173°. It was recrystallized to a constant melting point of 202–203° (95% ethanol), $[\alpha]^{28}\mathrm{D}$ +1.0° (*c* 2.0, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.48; S, 4.61. Found: C, 48.85; H, 5.35; S, 4.63.

Acknowledgments.—Gratitude is expressed to Miss Barbara H. Chastain and Mrs. Ru-Jen Lee Han for the preparation of methyl 3,4-anhydro-β-D-galactopyranoside and to Miss Rosalie Kelsey for technical assistance.

Nucleosides. II. Reactions of 5′-Trityluridine 2′,3′-*O*-Thionocarbonate

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A recent communication by Fox and Wempen[1] described an attempt to prepare a 2′,3′-unsaturated nucleoside by an application of the olefin synthesis of Corey and Winter.[2] When 5′-*O*-trityluridine (I) was heated with bis(imidazol-1-yl)thione[3] in refluxing toluene,[2] 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)-uracil (III) was obtained in good yield instead of the expected 5′-*O*-trityluridine 2′,3′-thionocarbonate (II). Our results from the use of these experimental conditions are in precise agreement with those of Fox and Wempen.[1] In addition, we have found that II can be obtained by conducting the reaction of I with bis-(imidazol-1-yl)thione in tetrahydrofuran at room temperature. As expected,[1] II is easily converted to III by treatment with base, *e.g.*, imidazole in refluxing toluene or potassium *t*-butoxide in ethanol. The conversion of II to 2′,3′-didehydro-2′,3′-dideoxy-5′-*O*-trityluridine (IVa)[4] was accomplished in low yield by

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[9] Microanalyses were performed by Schwarzkopf Microanalytical Laboratory. The descending technique was used in paper chromatography.

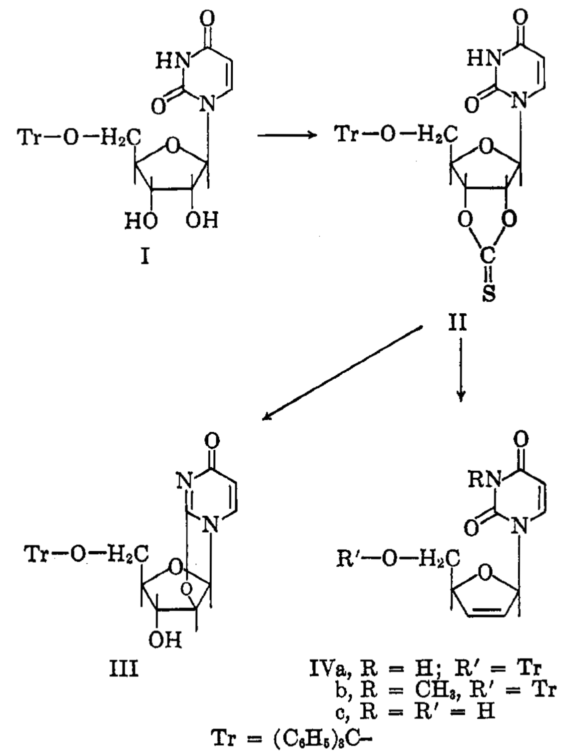
[10] R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

[1] J. J. Fox and I. Wempen, *Tetrahedron Letters*, **No. 11**, 643 (1965).

[2] E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

[3] H. A. Staab and G. Walther, *Ann.*, **657**, 98 (1962).

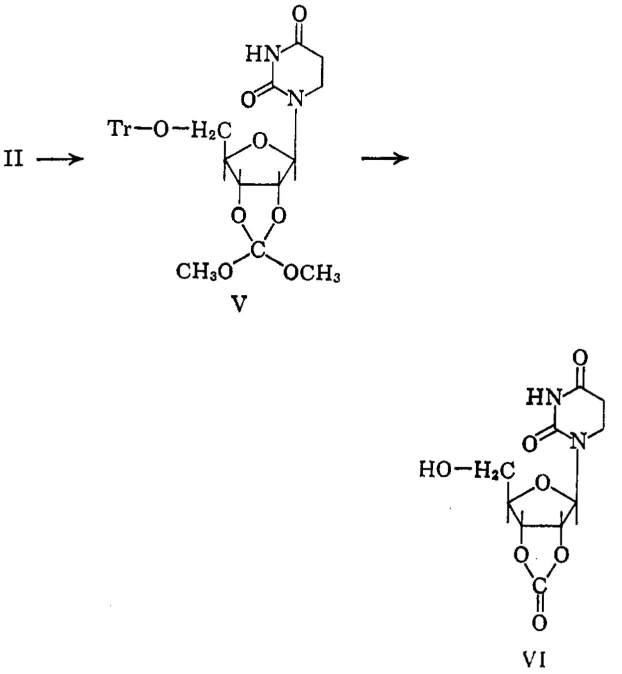
[4] J. P. Horwitz, *et al.*, *J. Am. Chem. Soc.*, **86**, 1896 (1964).



heating II with inactivated Raney nickel. A considerable amount of the cyclonucleoside III was also produced in the reaction.

The preparation of IVa by the reaction of II with trimethyl phosphite[2] was not feasible because of concomitant methylation at N^3 by this reagent. When II was boiled with trimethyl phosphite for 65 hr., a product was obtained which had an analysis and n.m.r. spectrum consistent with 3-*N*-methyl-5′-*O*-trityl-2′,3′-didehydro-2′,3′-dideoxyuridine (IVb). Conclusive proof that methylation had occurred at N^3 was obtained by acid hydrolysis of IVb, which yielded trityl alcohol and 3-methyluracil.

When II was stirred with silver carbonate in methanol, a crystalline compound was obtained for which the orthocarbonate structure V is proposed on the basis of the integrated n.m.r. spectrum and methoxyl determination.



Under conditions for detritylation (80% acetic acid), V was converted to uridine 2′,3′-carbonate (VI). A strong peak at 5.55 μ in the infrared spectrum was indicative of the cyclic carbonate structure.

In the course of an investigation of the optical rotatory dispersion curves of various pyridimine nucleosides it was found that compounds II and IV were exceptional in that they showed *negative* Cotton effects (Table I).

TABLE I

Compd.	Solvent	Molecular rotation[a] λ, mμ	[φ]	Amplitude[b] a
II	MeOH	300 (infl.)	−3,930	
		265	−14,700	−566
		254	0	
		242	+41,900	
III	MeOH	261	+6,900	+235
		250	0	
		232	−16,600	
IVa	MeOH	273	−7,210	−176
		258	0	
		239 (infl.)	+10,400	
		226	+19,400	
		220	0	
IVb	MeOH-1 *N* NaOH, 1:1	276	−8,790	. . .[c]
		261	0	
IVc[d]	Water	276	−9,900	−277
		261	0	
		245	+12,800	

[a] O.R.D. measurements were made with a Cary Model 60 spectropolarimeter. [b] Amplitude, $a = ([\phi]_1 - [\phi]_2)/100$. [c] The second extremum could not be measured. [d] For method of preparation, see ref. 4.

The factors responsible for the "reversal" of the Cotton effect in these compounds are not known definitely, but it appears that the sign of the Cotton effect is indeed influenced by certain changes involving the sugar portion of the nucleoside. Such factors would constitute an addition to the list of factors reported recently by Ulbricht.[5]

Experimental Section[6]

5-*O*-Trityluridine 2′,3′-Thionocarbonate (II).—A solution of 4.5 g. (9.3 mmoles) of 5′-*O*-trityluridine[7] and 1.85 g. (12 mmoles) of bis(imidazol-1-yl)thione[3] in 45 ml. of tetrahydrofuran was kept at room temperature for 5 days. The reaction mixture was concentrated *in vacuo* at 25° to a small volume and was partitioned between 150 ml. of methylene chloride and 30 ml. of water. The organic layer was washed three times with 30-ml. portions of water, dried over magnesium sulfate, and concentrated to a syrup. The crude product was chromatographed on a column of 150 g. of silica gel. The thionocarbonate II was eluted with 40:1 methylene chloride–methanol, yield 90%. The compound dissolves readily in warm ethanol and, on cooling, precipitates as an amorphous powder: λ_{max}^{EtOH} 234 mμ (ε 24,400); λ_{max}^{Nujol} 5.9 μ (pyrimidinone), 7.4, 7.6 μ (thionocarbonate)[2]; t.l.c. R_f 0.45.

Anal. Calcd. for $C_{29}H_{24}N_2O_6S$: C, 65.90; H, 4.58; N, 5.30; S, 6.06. Found: C, 65.71; H, 4.31; N, 5.09; S, 5.82.

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(5) T. L. V. Ulbricht, T. R. Emerson, and R. J. Swan, *Biochem. Biophys. Res. Commun.*, **19**, 643 (1965); T. L. V. Ulbricht, J. P. Jennings, P. M. Scopes, and W. Klyne, *Tetrahedron Letters*, **No. 13**, 695 (1964).

(6) Melting points were determined on a calibrated Kofler hot stage. Thin layer chromatography (t.l.c.) was performed with silica gel plates using methylene chloride–methanol, 19:1, as the solvent unless otherwise noted.

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

2,2′-Anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (III). A.[1]—A solution of 3.25 g. (6.7 mmoles) of 5′-*O*-trityluridine and 1.34 g. (7.4 mmoles) of bis(imidazol-1-yl)thione in 30 ml. of toluene was heated at reflux for 0.5 hr. After cooling, the solid product was collected and recrystallized from ethanol. The yield of III, was 2.7 g. (86%), m.p. 217–219°, $[\alpha]^{24}\text{D}$ −20.5° (*c* 1, CH_3OH).

B.—A solution of 100 mg. of 5′-*O*-trityluridine 2′,3′-thionocarbonate (II) and 25 mg. of imidazole in 4 ml. of toluene was heated at reflux for 0.5 hr. After a work-up as in part A, a nearly quantitative yield of III was obtained. Similar results were obtained when 200 mg. of II was heated at reflux with 30 mg. of potassium *t*-butoxide in 4 ml. of ethanol for 5 min.

2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-trityluridine (IVa).—Raney nickel (1.5 g.) was boiled with a mixture of 75 ml. of acetone, 15 ml. of ethanol, and 1 ml. of ethyl acetate for 2 hr. After the addition of 1.6 g. of the thionocarbonate II, refluxing was continued for 6 hr. After removal of the catalyst and solvent, the residual syrup was triturated with ether to obtain 400 mg. of the crystalline cyclonucleoside III. The ethereal filtrate was chromatographed on silica gel (40 g.). Elution with methanol–methylene chloride, 1.5:98.5, furnished 250 mg. of the unsaturated nucleoside IVa, m.p. 193°, t.l.c. R_f 0.62. The melting point, mixture melting point, t.l.c. running rate, and infrared spectrum were identical with those of a sample of IVa prepared by the method of Horwitz.[4]

3-*N*-Methyl-5′-*O*-trityl-2′,3′-didehydro-2′,3′-dideoxyuridine (IVb).—A mixture of 3.4 g. of the thionocarbonate II and 15 ml. of trimethyl phosphite was heated at reflux under a nitrogen atmosphere for 65 hr. Most of the trimethyl phosphite was removed *in vacuo*, and the residue was stirred with 300 ml. of 0.5 *N* sodium hydroxide for 0.5 hr. The product was extracted into ether and dried over magnesium sulfate, and the solvent was pumped off. The crude product was obtained as a glass, 2.76 g. (89%). Thin layer chromatography showed a large spot with R_f 0.92 and a much smaller spot with R_f 0.60. A sample of the crude product was extracted repeatedly with hot petroleum ether (b.p. 30–60°). Upon cooling the extracts, an amorphous solid separated, m.p. 60–80°, which now showed one spot, R_f 0.92. The n.m.r. spectrum in deuteriochloroform showed a signal at τ 6.68 for 3-NCH_3, and no signal corresponding to 3-NH: $\lambda_{\max}^{\text{EtOH}}$ 260 mμ (ϵ 7370), $\lambda_{\max}^{\text{EtOH}}$ 244 mμ (ϵ 5120). The spectrum was essentially unchanged in alkaline solutions.

Anal. Calcd. for $C_{29}H_{26}N_2O_4$: C, 74.66; H, 5.62; N, 6.01. Found: C, 74.03; H, 5.80; N, 6.16.

Acid Hydrolysis of IVb.—A solution of 1.7 g. of IVb in 80% acetic acid was heated on the steam bath for 10 min. After dilution with water, trityl alcohol was separated by extraction with ether. Evaporation of the aqueous layer yielded 0.95 g. of oil, which was chromatographed on silica gel. Elution with methanol–methylene chloride, 1:24, yielded crystals of 3-methyluracil: m.p. 179–181°[8]; $\lambda_{\max}^{\text{pH 7}}$ 259 mμ; $\lambda_{\min}^{\text{pH 7}}$ 230 mμ; $\lambda_{\max}^{\text{pH 12}}$ 283, 223 mμ; $\lambda_{\min}^{\text{pH 12}}$ 243 mμ.[9]

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.69; H, 4.87; N, 22.15.

5′-*O*-Trityluridine 2′,3′-dimethylorthocarbonate (V).—A solution of 528 mg. of the thionocarbonate II in 20 ml. of dry methanol was stirred overnight with 2.5 g. of silver carbonate at room temperature. After filtration, the solvent was removed *in vacuo*. The crude product was taken up in ether and filtered, and the solution was evaporated. Recrystallization from ethanol yielded 320 mg. of V: m.p. 198–200°, t.l.c. R_f 0.60, $\lambda_{\max}^{\text{EtOH}}$ 258 mμ (ϵ 9730), $\lambda_{\min}$ 242 mμ. The n.m.r. spectrum in deuteriochloroform showed signals at τ 6.55 (doublet, H-5′), 6.52, and 6.60 (–OCH_3). The integrated curve indicated eight protons for this group of signals. In pyridine solution the signals occurred at τ 6.30 (multiplet, H-5′), 6.44, and 6.54 (–OCH_3). The remainder of the spectrum is consistent with the nucleoside structure.

Anal. Calcd. for $C_{31}H_{30}N_2O_8$: C, 66.90; H, 5.07; N, 5.03, methoxyl, 11.4. Found: C, 66.70; H, 5.52; N, 5.26; methoxyl, 10.3.

Uridine 2′,3′-Carbonate (VI).—A solution of 100 mg. of V in 2 ml. of 80% glacial acetic acid was heated on the steam bath for 15 min. After removal of trityl alcohol, the nucleoside was recrystallized from ethanol. The substance forms a viscous melt at 95° and liquifies at 140°: $\lambda_{\max}^{\text{Nujol}}$ 5.55 (cyclic carbonate), 2.9 (OH), 5.9–6.0 (pyrimidinone) μ; t.l.c. R_f 0.16.

Anal. Calcd. for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.37. Found: C, 44.38; H, 4.00; N, 10.24.

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[9] D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

The Reaction of β-Chloro-α,β-alkenoic Esters with Nucleophiles

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It has been reported[2] that displacement of the halogen atom of ethyl β-chloro-*cis*- and -*trans*-crotonates by sodium benzenethiolate gave products with partial inversion of configuration. Jones, *et al.*,[2] state that the *cis*-chloro isomer gave 12% of the *trans* product and the *trans* isomer gave 36% of the *cis* product. We found that the reaction of the sodium benzene- and mesitylenethiolates with the isomeric chlorocrotonates gave products of essentially retained configuration (<5% inversion), Table I. In addition, the reaction of ethyl 3-chloro-4-methyl-2-pentenoate with sodium benzenethiolate gave only one replacement product, ethyl 3-phenylthio-4-methyl-2-pentenoate. From infrared and n.m.r. spectra and stability considerations we believe that both reactant and product have the *cis* configuration.[3] We found no evidence for the existence of the *trans* isomer.

TABLE I

THE REACTION OF ETHYL β-CHLORO-*cis*- AND -*trans*-CROTONATES WITH CERTAIN NUCLEOPHILES

Chlorocrotonate	Nucleophile	Product, % *cis*	Product, % *trans*	Product yield, %
cis	PhS^-	97	3	80
trans	PhS^-	5	95	95
cis	$MesS^{-}$[a]	100	0	95
trans	$MesS^{-}$[a]	5	95	55

[a] $MesS^-$ refers to the mesitylthio anion.

The discrepancy between our work and that reported earlier[2] appears to be owing to the method of estimation of the *cis–trans* isomer ratio. It is known[2] that the *trans* isomer undergoes thermal isomerization, and thus any method depending upon distillation or gas chromatographic techniques is questionable. We determined the isomer ratio by using the areas of the vinylic proton peaks in the n.m.r. spectra of the crude esters as a quantitative measure of the amount of each isomer present. The reaction mixture was kept at 3° and the crude esters were isolated at room temperature, thus keeping thermal isomerization to a

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