Preparation of the Sulfates of 5-Fluorodeoxyuridine with Pyridine–Sulfur Trioxide[1,2]

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The synthesis of the sulfate esters of 5-fluorodeoxyuridine with pyridine–sulfur trioxide has been investigated as a preparative method for potential inhibitors of the enzymes of nucleic acid metabolism. The direct esterification of the nucleoside in dry pyridine with different reagent concentrations showed that esterification of the primary hydroxyl group is 2.4 times more frequent than reaction of the secondary group. The two monosulfate isomers were identified by chromatographic migration and comparison with sulfate esters prepared from specifically blocked derivatives of 5-fluorodeoxyuridine. The starting material for the synthesis of 5-fluorodeoxyuridine 3′-sulfate was 5′-O-trityl-5-fluorodeoxyuridine, and 5-fluorodeoxyuridine 5′-sulfate was prepared from 3′-O-acetyl-5-fluorodeoxyuridine. Steady-state initial velocity measurements with bovine pancreatic ribonuclease A revealed that 5-fluorodeoxyuridine and 5-fluorodeoxyuridine 3′-sulfate are competitive inhibitors of this enzyme.

Introduction

Current evidence suggests that in the biosynthesis of deoxyribonucleic acid an essential intermediate, thymidine 5′-phosphate, is produced by the methylation of deoxyuridine 5′-phosphate with thymidylate synthetase.[3,4] The compound, 5-fluorodeoxyuridine 5′-phosphate, is a potent antimetabolite for the uridine deoxynucleotide due to the competitive inhibition of the synthetase enzyme.[5,6] The chemical synthesis of 5-fluorodeoxyuridine 5′-sulfate (FUDR 5′-sulfate) has been attempted in order to compare the inhibition potency of this compound with the 5′-phosphate.

The synthesis of ribonucleoside sulfates with chlorosulfonic acid has been reported.[7,8] Of particular interest is the observation that, in contrast with the nucleotides, the cell membrane is permeable to the ribonucleoside 5′-sulfate.[9] In the experiments reported here, the mild reagent, pyridine–sulfur trioxide[10] (PST), has been used to esterify the primary and secondary hydroxyl groups of 5-fluorodeoxyuridine (FUDR). The deoxyribonucleoside 3′-sulfate may be of some interest as a potential inhibitor of certain enzymes which degrade nucleic acids to produce the nucleoside 3′-phosphates.[11]

Discussion

The work of Peat, et al., shows that the treatment of monosaccharides with PST at temperatures between 18 and 70° produces esterification of both primary and secondary alcohol groups.[12] On the basis of these findings, the incomplete reaction of PST with FUDR should lead to the nucleoside disulfate ester, the two

monosulfate isomers, and unreacted FUDR in the reaction mixture.

To provide a comparison of the reactivity of the primary and secondary hydroxyl groups it is necessary to utilize a method for separation and quantitative determination of each of the two monosulfate isomers. A good separation of 5-fluorodeoxyuridine 3′-sulfate (FUDR 3′-sulfate) and FUDR 5′-sulfate has been accomplished by a partition chromatographic method which is based on structural considerations. The molecular models of the monosulfates in the acid form suggest that an intramolecular hydrogen bond could form between the strong sulfuric acid group and the fluorine atom on the pyrimidine ring. In the case of FUDR 3′-sulfate, the 5′-hydroxyl group would be located in close proximity to the 2-carbonyl group of the pyrimidine portion of the molecule. Thus, a second hydrogen bond could form which would decrease the interaction of the hydroxyl group with the solvent. The formation of a sulfuric acid to fluorine hydrogen bond for the FUDR 5′-sulfate, on the other hand, does not tend to shield the 3′-hydroxyl group from the solvent. The 3′-monosulfate isomer should be less polar, therefore, than the 5′-monosulfate isomer. This hypothesis is substantiated by the observation that FUDR 3′-sulfate in the acid form migrates more rapidly than FUDR 5′-sulfate on paper or cellulose thin layer chromatography.
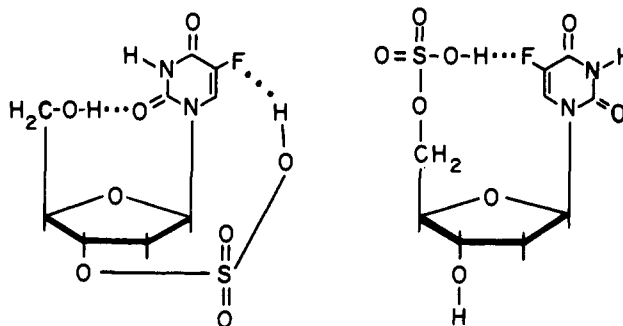
The results of four different direct sulfate esterification experiments may be found in Table I. In these experiments, the FUDR in dry pyridine was treated with an excess of PST in a mole ratio from 1.6 to 5.0, and inorganic sulfate was removed. The mixture of FUDR and sulfate esters was treated with an excess of Rexyn AG-50 (H⁺ form), and fractionation was performed by paper chromatography with aqueous 2-propanol.

(1) This research was supported by Grant No. T-222 from the American Cancer Society and by Grant No. CA-06696 from the National Cancer Institute of the Public Health Service.

(2) Presented in part before the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(3) M. Friedkin and A. Kornberg, "The Chemical Basis of Heredity," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1957, p. 609.

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(11) R. J. Hilmoe, J. Biol. Chem., 235, 2117 (1960).

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Table I

The Yield and Chromatographic Migration of the Products of the Reaction between Pyridine–Sulfur Trioxide and 5-Fluorodeoxyuridine at 28°

				Yield, mole %			
			A	B	C	D	
	Time,	PST	FUDR	FUDR	FUDR	FUDR	
Expt.	hr.	FUDR		3'-sulfate	5'-sulfate	disulfate	
I	24	1.6	66	9	23	2	
II	45	1.6	71	8	20	1	
III	48	2.5	33	11	45	11	
IV	48	5.0				97	
			0.70	0.47	0.39	0.23	$R_f{}^a$

^{a} The acid form on Whatman 3MM with 2-propanol–water (80:20).

The paper chromatographic method was quite successful in the separation of the two monosulfate isomers (see Table I for the R_f values). Similar results were obtained when 0.05 mg. of the reaction mixture was applied to a cellulose thin layer plate and developed with aqueous 2-propanol for 5 hr. Attempts to apply the same approach to a large scale fractionation were unsuccessful because the sulfate esters gradually decompose in acidic solvent.

From the data of Table I it is possible to calculate the relative reactivity of the primary and secondary hydroxyl groups of FUDR with respect to sulfate esterification. Reaction at the primary group produces FUDR 5'-sulfate (fraction C) and the disulfate (fraction D); reaction at the secondary group produces FUDR 3'-sulfate (fraction B) and the disulfate. A value of 2.4 for expt. I–III may be calculated from the sum of the yields in fractions C and D divided by the sum of the yields in fractions B and D. Thus, the esterification of a primary hydroxyl is 2.4 times more frequent than the reaction of the secondary hydroxyl. This finding suggests that the reaction at each position is an independent event; conversion from monosulfate to disulfate probably occurs with the same frequency as the conversion from nucleoside to monosulfate.

The identification of the two monosulfate fractions was confirmed by synthesis from nucleoside derivatives where the hydroxyl groups were specifically blocked. The compound, 5'-O-trityl-5-fluorodeoxyuridine, was prepared in excellent yield from FUDR and triphenylmethyl chloride.[13] This substance then
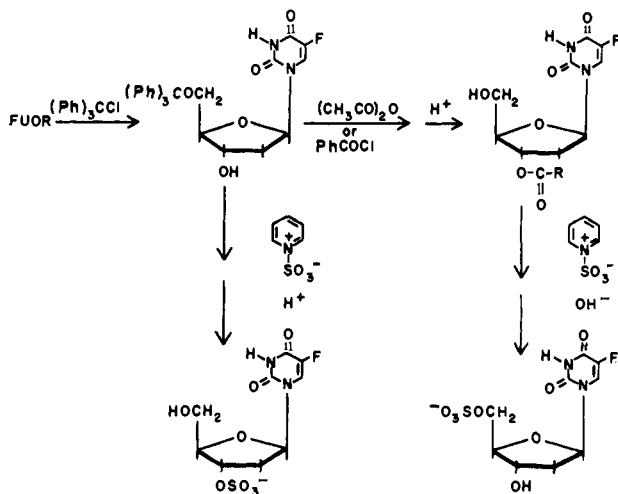
(13) H. Brederick, *Ber.*, **66**, 198 (1933); J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).
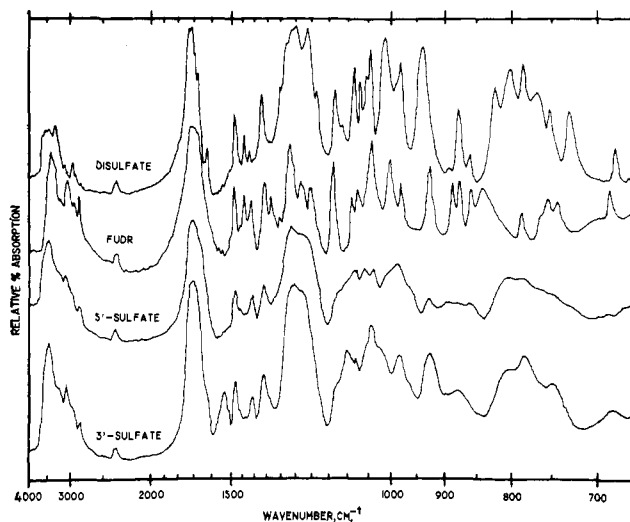
Fig. 1.—Infrared spectra of 5-fluorodeoxyuridine and the sulfate esters of this nucleoside (in 500 mg. of KBr): top curve, 1.5 mg. of 5-fluorodeoxyuridine 3',5'-disulfate; second curve, 1.2 mg. of 5-fluorodeoxyuridine; third curve, 1.6 mg. of 5-fluorodeoxyuridine 5'-sulfate; bottom curve, 0.7 mg. of 5-fluorodeoxyuridine 3'-sulfate.

was treated with PST and hydrolyzed with acid to yield the FUDR 3'-sulfate, which migrates as a single zone on paper with an R_f identical with fraction B.

Two different methods were used for the synthesis of FUDR 5'-sulfate. In the first approach, the trityl derivative was treated with benzoyl chloride and subjected to relatively vigorous acid hydrolysis to produce 3'-O-benzoyl-5-fluorodeoxyuridine. The benzoyl ester then was exposed to PST and a sample of 3'-O-benzoyl-5-fluorodeoxyuridine 5'-sulfate was isolated and found to produce a single zone on paper chromatography. The benzoyl ester linkage in this compound proved to be relatively stable in alkali. Upon partial alkaline hydrolysis and chromatography, a new zone was found with a migration which was identical with that observed for fraction C.

In spite of the fact that 3'-O-acetyl-5-fluorodeoxyuridine is more difficult to crystallize than the benzoyl derivative, the acetyl derivative was tested as a synthetic intermediate. Acid hydrolysis to remove the trityl group from the acetyl derivative may be accomplished by a more mild procedure than in the case of the benzoyl ester. Furthermore, the quantitative removal of the acetyl group from 3'-O-acetyl-5-fluorodeoxyuridine 5'-sulfate was accomplished under conditions of mild alkaline hydrolysis. A pure sample of the 5'-sulfate, which has a migration on paper chromatograms identical with fraction C, was isolated in good yield.

The infrared spectra of FUDR and the three sulfate esters are given in Fig. 1. An intense band at 1250 and a broad band at 800 cm.$^{-1}$ are due to the absorption of the sulfate ester group.

The effect of FUDR 3'-sulfate on the steady-state initial velocity of ribonuclease A (RNase) at pH 7.0 was tested with cytidine 2',3'-cyclic phosphate as substrate. The results of a plot of $(S)/v$ vs. (I) according to the method of Wigler and Alberty[14] are given in Fig. 2. It is possible to calculate from this figure a Michaelis constant of 560 μM, a maximal velocity of 2.0 sec.$^{-1}$, and an inhibition constant

(14) P. W. Wigler and R. A. Alberty, *J. Am. Chem. Soc.*, **82**, 5482 (1960).
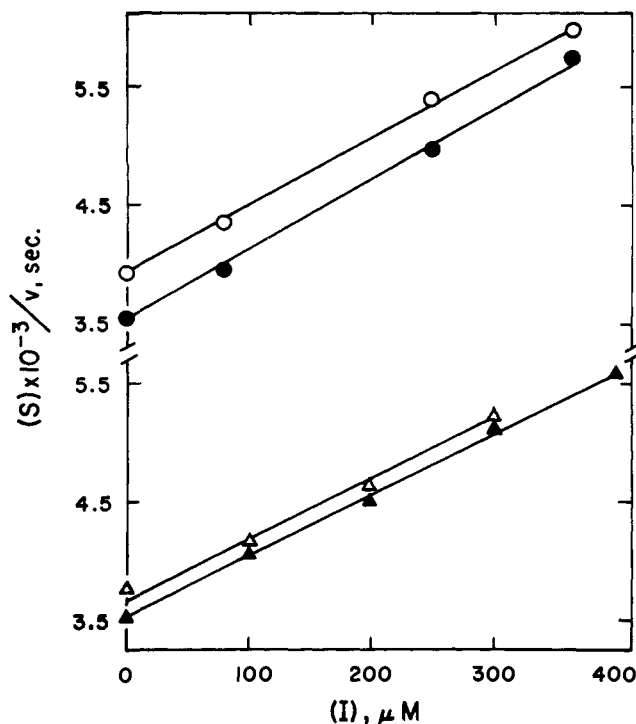
Fig. 2.—Four plots of $(S)/v$ vs. (I), determined with ribonuclease A in imidazole chloride buffer of 0.01 ionic strength and pH 7.0 at 25°. The experimental conditions were: O, 370 μM cytidine 2',3' cyclic phosphate with 5-fluorodeoxyuridine 3'-sulfate; ●, 280 μM cytidine 2',3' cyclic phosphate with 5-fluorodeoxyuridine 3'-sulfate; △, 345 μM cytidine 2',3'-cyclic phosphate with 5-fluorodeoxyuridine; ▲, 280 μM cytidine 2',3'-cyclic phosphate with 5-fluorodeoxyuridine.

(K_I) of 390 μM for the FUDR 3'-sulfate. The observation that the plots at two different substrate concentrations have the same slope indicates that this is an example of competitive inhibition. The inhibition of RNase with FUDR was tested for comparative purposes. It was found that FUDR was somewhat less effective than the sulfate derivative with a K_I for competitive inhibition of 480 μM. The finding of an affinity between the enzymatic active site of RNase and FUDR 3'-sulfate, suggests that the nucleoside sulfates are worthy of further tests as enzyme inhibitors. Additional experiments to ascertain the inhibition potency of FUDR 5'-sulfate with respect to thymidylate synthetase, may be of particular interest.

Experimental

Fractionating Systems.—Paper chromatographic separations of the synthetic products were performed on Whatman 3MM paper with solvent 1, 2-propanol–water (80:20); solvent 2, isobutyric acid–concentrated ammonium hydroxide–water (66:1: 33)[15]; solvent 3, saturated aqueous ammonium sulfate–1.0 M aqueous sodium acetate–2-propanol (80:18:2).[16] Solvents 1 and 2 were used in descending flow, but solvent 3 was used in ascending flow with the method of Drummond, et al.[17]

The Partial Reaction of Pyridine–Sulfur Trioxide and 5-Fluorodeoxyuridine.—The pyridine–sulfur trioxide (PST) used in these experiments was prepared by the method of Sisler and Audrieth,[18] the 5-fluorodeoxyuridine (FUDR) was a gift from Dr. R. Duschinsky of Hoffmann La Roche, Inc., and the pyridine (Fisher, reagent grade) was redistilled and stored over activated alumina.

(15) B. Magasanik, E. Vischer, R. Doniger, D. Elson, and E. Chargaff, J. Biol. Chem., **186**, 37 (1950).

(16) R. Markham and J. D. Smith, Biochem. J., **49**, 401 (1951).

(17) G. I. Drummond, N. T. Iyer, and J. Keith, J. Biol. Chem., **237**, 3538 (1962).

(18) H. H. Sisler and L. F. Audrieth, "Inorganic Syntheses," W. C. Fernelius, Ed., McGraw–Hill Book Co., Inc., New York, N. Y., 1946, p. 173.

The sulfates of FUDR were prepared by stirring 1.0 g. (4.0 mmoles) of FUDR and from 6.4 to 10.0 mmoles of PST in 60 ml. of dry pyridine at 28° for 24 or 48 hr. The solution was cooled in an ice bath, 60 ml. of water was added, and the solution was kept at 0° for several hours. The solvent was removed in vacuo, the resulting syrup was dissolved in 10 ml. of water, and 1.3 N NaOH was added to pH 7.0. The solvent was removed under vacuum; the residue was thoroughly dried and suspended in 75 ml. of anhydrous methanol at 64°. After slow cooling to 4°, the precipitate of Na₂SO₄ was filtered off, and the solution was dried.

The mixture was converted to the acid form with Rexyn AG-50 (H⁻ form), 0.2 to 0.5 mg. of the mixture was applied to Whatman 3MM paper, and the chromatogram was developed descending with solvent 1 in a sealed tank for 18 hr. The zones were located with an ultraviolet lamp, removed from the chromatogram, and the fractions were eluted with 0.1 M TRIS acetate buffer, pH 5.9. The absorbancy was determined at 2680 Å. with a Gilford Model 2000 spectrophotometer and the mole % of each fraction was calculated based on the assumption that the molar absorbancy of all the compounds is approximately equal (see Table I).

5-Fluorodeoxyuridine 3',5'-Disulfate.—FUDR (1.2 g., 5.0 mmoles) and 4.0 g. (25.1 mmoles) of PST in 90 ml. pyridine were stirred at 28° for 48 hr. The reaction was terminated with 90 ml. of water and the pH was adjusted to 10.5 with 1.3 N NaOH. The solvent was removed under vacuum, the residue was suspended in 100 ml. of hot methanol, and the suspension was cooled to 4°. The Na₂SO₄ was removed, and the filtrate was dried to a brownish solid. One crystallization from methanol and isopropyl alcohol gave 0.96 g. of the disulfate which was dissolved in water and converted to the acid form with Rexyn (H⁺). The resin was removed and the pH was adjusted to 6.9 with 1.0 N KOH. The solvent was removed under vacuum, and the residue was recrystallized twice from 60% aqueous ethanol; the ultraviolet absorption spectrum showed $\lambda_{max}^{pH\ 5.9}$ 2680 Å., a_M at 2680 Å. = 8700.

Anal. Calcd. for $C_9H_9FK_2N_2O_{11}S_2$: C, 22.40; H, 1.88; F, 3.94; N, 5.81; S, 13.29. Found: C, 22.19; H, 2.02; F, 4.14; N, 5.87; S, 13.16.

3'-O-Benzoyl-5-fluorodeoxyuridine.—The 5'-O-trityl-5-fluorodeoxyuridine, (0.9 g., 1.9 mmoles) prepared by a method similar to that of Fox and Miller,[13] was stirred with 1.0 ml. (8.6 mmoles) of benzoyl chloride (Baker and Adamson, reagent) and 6 ml. of dry pyridine for 2 hr. After 13 hr. at room temperature, 100 g. of ice was added, and the solution was extracted three times with 75 ml. of chloroform. The organic phase was dried with anhydrous Na₂SO₄ and the solvent was removed under vacuum. The product was recrystallized from 95% ethanol to yield 1.0 g. of 3'-O-benzoyl-5'-O-trityl-5-fluorodeoxyuridine.

Anal. Calcd. for $C_{35}H_{29}FN_2O_6$: C, 70.94; H, 4.93; F, 3.21; N, 4.73. Found: C, 70.83; H, 4.93; F, 3.08; N, 4.38.

3'-O-Benzoyl-5'-O-trityl-5-fluorodeoxyuridine (1 g.) was refluxed in 75 ml. of 80% aqueous acetic acid for 2 hr. The solvent was removed, the residue was suspended in 300 ml. of water at 100°, and insoluble triphenylcarbinol was removed by filtration of the hot suspension. Slow cooling of the aqueous solution to 4° led to crystal formation; the crystals were dried and extracted with 50 ml. of warm cyclohexane to dissolve traces of triphenylcarbinol. The product was dried to give 0.56 g. of 3'-O-benzoyl-5-fluorodeoxyuridine (monohydrate).

Anal. Calcd. for $C_{16}H_{15}FN_2O_6 \cdot H_2O$: C, 52.18; H, 4.65; F, 5.16; N, 7.61. Found: C, 52.64; H, 4.70; F, 5.09; N, 7.82.

3'-O-Acetyl-5'-fluorodeoxyuridine.—A 3.9-g. (7.8 mmoles) sample of 5'-O-trityl-5-fluorodeoxyuridine was dissolved in 40 ml. pyridine and placed in an ice bath. Acetic anhydride, 1.8 ml. (15.6 mmoles), was slowly added to the 0° solution with constant stirring. When the addition was completed, the temperature was permitted to rise and the solution was stirred an additional 24 hr. at room temperature. The solution was cooled again, 15 ml. of cold water was added, and the solvent was removed under vacuum. The pale yellow residue was dissolved in 100 ml. of 80% aqueous acetic acid and the solution was stirred for 54 hr. at 45°. The solution was cooled, 500 ml. of water was added, and the solution was stored at 4° for 12 hr. The solution was filtered cold to remove the triphenylcarbinol crystals, and the solvent was removed under vacuum. The product was dried to give 1.3 g.; recrystallization of 3'-O-acetyl-5-fluorodeoxyuridine, m.p. 205.5–206.5°, was accomplished from water.

Anal. Calcd. for $C_{11}H_{13}FN_2O_8$: C, 45.84; H, 4.55; F, 6.59; N, 9.72. Found: C, 45.65; H, 4.60; F, 6.40; N, 9.81.

5-Fluorodeoxyuridine 3'-Sulfate.—A 2.1-g. (4.3 mmoles) sample of 5'-O-trityl-5-fluorodeoxyuridine was dissolved in 60 ml. of dry pyridine, 5.1 g. (32.0 mmoles) of PST was added, and the solution was stirred at 28° for 3 days. The solvent was removed under vacuum, 25 ml. water was added, and the solvent was removed a second time. Upon addition of 25 ml. water, the pH was found to be 1.2. The acidic solution was stirred at 75° for 20 min. The solution was cooled to room temperature, and the pH was adjusted to 6.5 with 1.0 N KOH. Crystals of triphenylcarbinol formed at 4° when the suspension was stored for 20 hr. The crystals were removed, and the filtrate was thoroughly dried to yield a pale yellow powder. This product was extracted four times with 25-ml. portions of hot methanol, insoluble K_2SO_4 was discarded, and the solute was recrystallized from methanol and isopropyl alcohol to give 0.78 g. of white product. Recrystallization three times from the same solvent gave FUDR 3'-sulfate; its migration on paper chromatography was identical with fraction B, and the ultraviolet absorption showed $\lambda_{max}^{pH\ 5.9}$ 2680 Å., a_M at 2680 Å. = 8100.

Anal. Calcd. for $C_9H_{10}FKN_2O_8S$: C, 29.67; H, 2.77; F, 5.21; K, 10.73; N, 7.69; S, 8.80. Found: C, 29.49; H, 2.67; F, 5.46; K, 10.97; N, 7.49; S, 8.49.

Preparation and Partial Hydrolysis of 3'-O-Benzoyl-5-fluorodeoxyuridine 5'-Sulfate.—This compound was prepared from 550 mg. (1.6 mmoles) of 3'-O-benzoyl-5-fluorodeoxyuridine and 2.4 g. (15.0 mmoles) of PST in 60 ml. of dry pyridine. The solution was stirred for 40 hr. at 28° and 60 ml. of water was added; the solution was cooled and adjusted to pH 10.0 with 1.0 N NaOH. The solvent was removed under vacuum, and the dry residue was suspended in 100 ml. of hot methanol. The suspension was filtered to remove sodium sulfate, and the solvent was removed to yield the product. When this compound was treated with an excess of Rexyn (H^+), placed on a chromatogram, and developed with solvent 1, a single zone with an R_f value of 0.63 was observed.

The residue from the methanol solution was dissolved in 60 ml. of dioxane–concentrated ammonia–water (20:30:10). After 16 hr. at room temperature, the solvent was removed, and the residue was dissolved in 50 ml. water. The pH was adjusted to 3.0 with Rexyn (H^+), and the filtered solution was cooled to 0° until benzoic acid crystallized out. The crystals were removed by filtration and the solvent was removed under vacuum; a new zone with a migration identical with fraction C was observed on the paper chromatograms.

5-Fluorodeoxyuridine 5'-Sulfate.—To 0.96 g. (3.5 mmoles) of 3'-O-acetyl-5-fluorodeoxyuridine in 70 ml. pyridine, 2.8 g. (17.6 mmoles) of PST was added. The solution was stirred at 28° for 48 hr., and 35 ml. of 1.0 N KOH was added. The solvent

was removed, the residue was suspended in 50 ml. of hot absolute ethanol, and the suspension was cooled to room temperature. The ethanol solution was decanted and the K_2SO_4 precipitate was extracted three more times with 50-ml. portions of absolute ethanol. The ethanol extracts were pooled, and the solvent was removed under vacuum. The residue was dissolved in 50 ml. of water, and the pH was adjusted to 12.0 with 1.0 N KOH. The solution was heated to 89° and maintained at that temperature for 30 min. The solution was cooled and Rexyn (H^+) was added to adjust the pH to 4.0. The resin was removed, the filtrate was dried under vacuum, and the residue was suspended in 75 ml. of hot absolute ethanol. The suspension was cooled and filtered, and the precipitate was extracted a second time with 75 ml. of absolute ethanol. The precipitate was discarded, and the pooled ethanol filtrates were dried. The residue was dissolved in a hot solution of ethanol–methanol–water (75:25:10) and cooled slowly to 0°. The crystals of FUDR disulfate which formed were removed by filtration, and the solvent was removed under vacuum. The residue was recrystallized from methanol and isopropyl alcohol to yield 0.55 g. of FUDR 5'-sulfate The product was recrystallized twice from the same solvent; paper chromatography gives one zone with an R_f identical with fraction C; ultraviolet spectral analysis shows $\lambda_{max}^{pH\ 5.9}$ 2680 Å., a_M at 2680 Å. = 8700.

Anal. Calcd. for $C_9H_{10}FKN_2O_8S$: C, 29.67; H, 2.77; F, 5.21; K, 10.73; N, 7.69; S, 8.80. Found: C, 29.33; H, 2.99; F, 5.06; K, 10.56; N, 7.53; S, 8.48.

The spectra given in Fig. 1 were determined with a Perkin-Elmer Model 21 recording infrared spectrophotometer.

The steady-state initial velocity of bovine pancreatic ribonuclease A (Sigma Biochemical Corp.) was determined by the following procedure. Enzyme crystals were dissolved in 0.01 M KCl at 0° in a polyethylene bottle. A 0.2-ml. aliquot of the enzyme solution in a Cornwall pipettor was added to a 5.0-ml. solution of 280–370 μM cytidine 2',3'-cyclic phosphate (K^+ form, prepared by the method of Smith, Moffatt, and Khorana[19]) in 0.01 M imidazole hydrochloride and 0.01 M imidazole. The solution was mixed in a quartz cell of 20 mm. light path to give a final pH of 7.0, enzyme concentration of 1.6 mg./l., and temperature of 25°. The final inhibitor concentrations are given in Fig. 2. The absorbancy increase was determined at 2880 Å. and a slit width of 1.4 mm. with a Gilford Model 2000 recording spectrophotometer, which was set for a 0 to 0.1 absorbancy scale.
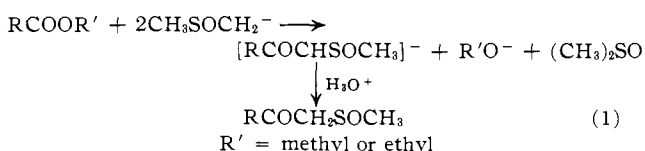
COMMUNICATIONS TO THE EDITOR

A New Synthesis of Ketones

Sir:

During the course of our studies on carbanions which are stabilized by sulfur-containing functional groups we have discovered a reaction sequence which opens a new and general route to ketones. In our opinion the method will prove a very useful one both for the development of carbon chains and for the formation of rings.

The methylsulfinyl carbanion[1] reacts with a wide variety of esters according to eq. 1 to give β-keto sulfoxides. This reaction, which was discovered independently

$$RCOOR' + 2CH_3SOCH_2^- \longrightarrow$$
$$[RCOCHSOCH_3]^- + R'O^- + (CH_3)_2SO$$
$$\downarrow H_3O^+$$
$$RCOCH_2SOCH_3 \qquad (1)$$
$$R' = \text{methyl or ethyl}$$

in our laboratories[2] and by Russell and co-workers,[3] is analogous to the well known reaction of esters with α-sulfonyl carbanions.[4] It proceeds exceptionally smoothly and is simply performed. The ester (neat if liquid, in dry tetrahydrofuran if solid) is added to a solution of the methylsulfinyl carbanion (2 equivalents, concentration *ca.* 1 M) in dimethyl sulfoxide–tetrahydrofuran at 0° under nitrogen with stirring. The reaction mixture is allowed to warm to room temperature over 30 min. and the product is isolated by addition of

(1) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(2) A discussion of our work on this reaction was presented in a seminar at the University of Illinois in Nov., 1962, and also in subsequent lectures at various places.

(3) H-D. Becker, G. J. Mikol, and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963); H-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963). These workers report only the reaction with aromatic esters, however.

(4) See for example (a) J. Tröger and E. Nolte, *J. Prakt. Chem.*, [2] **101**, 136 (1920); (b) L. Field, J. E. Lawson, and J. W. McFarland, *J. Am. Chem. Soc.*, **78**, 4389 (1956); (c) W. E. Truce and R. H. Knospe, *ibid.*, **77**, 5063 (1955).