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.

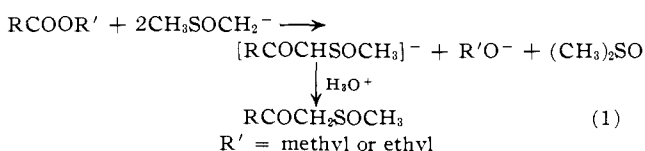(19) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

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

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

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

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

(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).

water, acidification, and extraction (chloroform). Table I records the yields of β-keto sulfoxides (all crystalline solids) obtained with a variety of esters.[5,6]
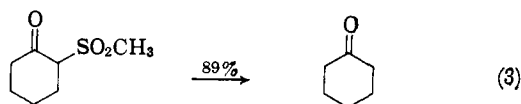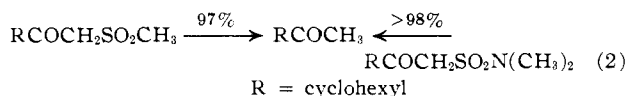
TABLE I

CONVERSION OF ESTERS ($RCOOC_2H_5$) TO β-KETO SULFOXIDES
($RCOCH_2SOCH_3$) AND METHYL KETONES ($RCOCH_3$)

R	% yield of β-keto sulfoxide	% yield of methyl ketone
Phenyl	79	>98
Anisyl	>98	>98
α-Naphthyl	>98	89
α-Furyl	71	70
Cyclohexyl	98	98
n-Pentyl	70	>98
n-Heptadecyl	>98	>98

These keto sulfoxides react rapidly and cleanly with aluminum amalgam[7] in 90% tetrahydrofuran–10% water mixture to give ketones[8]

$$RCOCH_2SOCH_3 + Al \cdot Hg + H_2O \longrightarrow RCOCH_3$$

The yields given in Table I are indicative of the high efficiency of this reduction process. The reductive cleavage is not limited to the formation of methyl ketones, but seems to be characteristic of β-keto sulfoxides in general. Furthermore β-keto sulfones and β-keto sulfonamides also undergo the reaction as shown by eq. 2 and 3. β-Keto sulfonamides can be prepared from esters in high yield using the highly reactive di-

$$RCOCH_2SO_2CH_3 \xrightarrow{97\%} RCOCH_3 \xleftarrow{>98\%}$$
$$RCOCH_2SO_2N(CH_3)_2 \quad (2)$$
$$R = \text{cyclohexyl}$$

$$(3)$$

methylaminosulfonyl carbanion.[9]

This ketone synthesis is also applicable to certain polyfunctional esters. For example, dimethyl azelaate was converted via the β-keto sulfoxide route to undecan-2,10-dione in 82% yield.

The reductive fission of β-keto sulfoxides by aluminum amalgam permits a new and very flexible approach to the synthesis of five- and six-membered carbocycles, which should be especially useful for fused-ring systems. In general this approach consists of the following elements: (1) introduction of a one, two, or three carbon chain containing an attached sulfur substituent, for example at $C\alpha$ starting with a ketone; (2) introduction of other carbons and a functional group which can be converted to a carboxylic ester group, for example at

(5) The examples in which the yields of β-keto sulfoxides are below 90% are generally those cases in which the product was quite soluble in the aqueous phase and not completely recovered by simple extraction with chloroform.

(6) Satisfactory analytical data were obtained for the compounds described herein.

(7) Prepared by immersing aluminum foil in 2% aqueous mercuric chloride solution for 10–15 sec. and rinsing the amalgamated foil quickly with alcohol and ether, and used immediately for the reductions.

(8) In the case of conjugated aromatic keto sulfoxides the reaction was carried out for 10 min. at 0° with stirring using 10 g.-atoms of aluminum per mole of keto sulfoxide and ca. 60 ml. of 10% aqueous tetrahydrofuran per gram of keto sulfoxide (extended reaction times and higher temperature allow pinacol formation by further reduction). In the case of nonconjugated keto sulfoxides the reactants (same proportions) were heated at reflux temperature for 60–90 min. with stirring.

(9) This carbanion can be prepared in tetrahydrofuran solution as the lithium salt from N,N-dimethylmethanesulfonamide and n-butyllithium. It reacts with dimethyl sulfoxide to form the methylsulfinyl carbanion.

the carbonyl carbon of a ketone; (3) cyclization of a sulfone ester to an α-sulfonyl ketone; and (4) reductive removal of the α-sulfonyl grouping. Another application of the aluminum reduction to carbocycle synthesis is discussed in the following paper.[10]

(10) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., **86**, 1640 (1964).

(11) National Institutes of Health Postdoctoral Fellow 1962–1964.

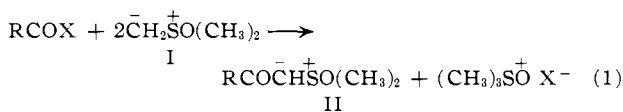DEPARTMENT OF CHEMISTRY E. J. COREY
HARVARD UNIVERSITY MICHAEL CHAYKOVSKY[11]
CABMRIDGE 38, MASSACHUSETTS

Formation and Photochemical Rearrangement of β'-Ketosulfoxonium Ylides

Sir:

Dimethylsulfoxonium methylide (I)[1] can be acylated by treatment with reactive carboxylic acid derivatives such as acid chlorides and phenyl esters to give stable β-ketosulfoxonium ylides according to eq. 1. Thus, with benzoyl chloride and 2 equivalents of I in tetra-

$$RCOX + 2\bar{C}H_2\overset{+}{S}O(CH_3)_2 \longrightarrow$$
$$I$$
$$RCO\bar{C}H\overset{+}{S}O(CH_3)_2 + (CH_3)_3\overset{+}{S}O \ X^- \quad (1)$$
$$II$$

hydrofuran at 25° for 1 hr. the ylide II, R = C_6H_5, m.p. 119–120°, ultraviolet maxima 229, 283 mμ (ϵ 9500, 11,300) is formed in 92% yield.[2] Similarly, the ylide II, R = cyclo-C_6H_{11}, m.p. 198–199°, ultraviolet maximum 252 mμ (ϵ 13,600), is obtained in 87% yield. Reaction of the phenyl esters of Δ^1-cyclohexenyl carboxylic acid and Δ^1-cyclopentenyl carboxylic acid with I (1 equiv.) in tetrahydrofuran at reflux for 4 hr. also proceeds according to eq. 1 to give the respective products II, R = Δ^1-cyclohexenyl, m.p. 168.5–169.5°, ultraviolet maxima 228, 279 mμ (ϵ 11,400, 16,400) (92%), and II, R = Δ^1-cyclopentenyl, m.p. 145–146.5°, ultraviolet maxima 235, 284 mμ (ϵ 7500, 10,900) (85%).

Under the conditions used to effect reaction 1 with more reactive acid derivatives nonconjugated ethyl esters are unchanged. However, α,β-unsaturated ethyl esters undergo conjugate addition followed by cyclization as depicted in eq. 2 for ethyl Δ^1-cyclohexenyl carboxylate which is transformed into III, m.p. 205–

$$(2)$$
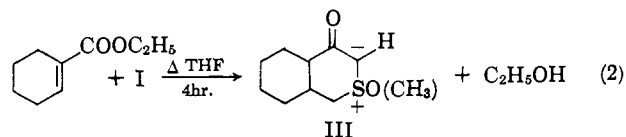
220° dec., ultraviolet maximum 245 mμ (ϵ 14,500). The structure III is assigned to this product on the basis of physical data and sequential conversion to IV, R = $SOCH_3$ (zinc–acetic acid, 0°), IV, R = SCH_3 (zinc–acetic acid, 110°), IV, R = $\overset{+}{S}(CH_3)_2$ (methyl iodide), and V (base). The last substance is identical with an authentic sample obtained from the methylene transfer reaction[1,3] of I with 1-acetylcyclohexene.

(1) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., **84**, 867 (1962).

(2) Satisfactory elemental analyses have been obtained for all new compounds reported herein. The β-ketosulfoxonium ylides studied all show carbonyl absorption in the infrared in the range 6.35–6.60 μ (chloroform solution); those derived from conjugated carbonyl systems, e.g., II, R = C_6H_5, absorb near the higher wave length. Ultraviolet data are for solutions in 95% ethanol.

(3) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., **84**, 3782 (1962).