(0.055 mole) of sodium cyanide in 100 ml of water was stirred for 4 hr at room temperature. Chloroform (ten 40-ml portions) was used to extract the product from the reaction mixture. Upon evaporation of the combined, dried chloroform extracts there was obtained 3.80 g (74.4%) of I, mp 80–82°.

**2-Aminoethyl 2-Aminethanethiolsulfinate Dihydrochloride (X 2HCl)**[31].—To an ice-cooled, stirred solution of 5.63 g (0.025 mole) of cystamine dihydrochloride in 200 ml of methanol was added dropwise 5.57 g of *m*-chloroperbenzoic acid (85+% assay) in 15 ml of isopropyl alcohol. The thiolsulfinate started to precipitate from solution as the addition approached completion. Stirring was continued for 1.5 hr. The precipitated product and two additional crops were collected and extracted with several portions of boiling ether to remove the *m*-chlorobenzoic acid contaminant. (The mother liquors were found to contain cystamine dihydrochloride, the corresponding thiolsulfonate and taurine.) The product, 4.48 g, darkened and softened at *ca.* 130° and melted at 150–152° dec. Recrystallization from water–ethanol afforded 3.35 g (55.5%) of X 2HCl as white crystals which darkened at *ca.* 135°, softened at *ca.* 140°, and melted at 154–155° dec. The thiolsulfinate oxidizes hydriodic acid to iodine.

*Anal.* Calcd for $C_4H_{14}Cl_2N_2OS_2$: C, 19.92; H, 5.85; N, 11.62; S, 26.58. Found: C, 20.11; H, 6.25; N, 11.69; S, 26.75.

**Preparation of I from X 2HCl.**—A solution of 2.47 g (0.01 mole) of X 2HCl, 0.80 g (0.02 mole) of sodium hydroxide, and 0.54 g (0.011 mole) of sodium cyanide in 20 ml of water was stirred for 4 hr at room temperature. Chloroform (five 30-ml portions) extracted 0.94 g (92.2%) of I, mp 80–82°, from solution.

(31) Procedure based upon that reported by A. Schöberl and H. Gräfje, *Ann.*, **617**, 71 (1958).

**Acknowledgment.**—We wish to thank Mr. Peter Merkel and Dr. Peter Coad (Walter Reed Army Institute of Research) for assistance in synthesizing some of the compounds used in this study.

# The Alkylation of β-Keto Sulfoxides. A General Route to Ketones

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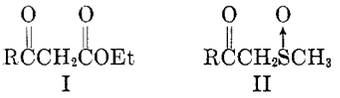
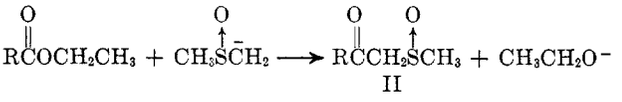
Procedures have been developed for the mono- and dialkylation of β-keto sulfoxides. Reductive cleavage of these alkylated β-keto sulfoxides with aluminum amalgam provides an attractive synthetic route to a wide variety of ketones.

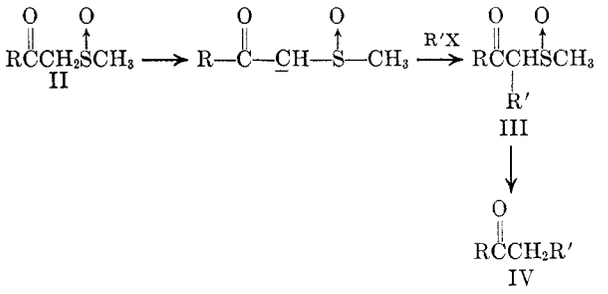
The classical acetoacetic ester synthesis is one of the most often quoted methods for the synthesis of ketones. A portion of most undergraduate texts is devoted to discussing this synthetic sequence. In practice, the acetoacetic ester type of synthesis is generally limited to the synthesis of methyl ketones. We wish to report a variation of this type of alkylation–cleavage procedure which permits the synthesis of a broad spectrum of ketones. Our method is based on the alkylation of β-keto sulfoxides followed by reductive cleavage of the carbon–sulfur bond with aluminum amalgam. The advantage of our method arises from the ease of preparation of β-keto sulfoxides compared with β-keto esters. Whereas β-keto esters (I), where R is other than methyl,



are not readily available, β-keto sulfoxides (II) can be prepared easily and in high yield with wide variation in the nature of the R group. Both Russell[2] and Corey[3]



have shown that esters react with dimethyl sulfoxide anion to produce β-keto sulfoxides in very high yield. In addition, it had been reported[3] that compounds such as II could be reductively cleaved to yield methyl ketones. Thus, the only completely unknown factors in the sequence shown below were whether II could be readily alkylated and whether substituted β-keto sulfoxides such as III could be cleaved reductively.



Addition of II (R = phenyl) to a solution of sodium ethoxide in ethanol gave little reaction. When sodium hydride or lithium hydride was used as base in tetrahydrofuran (THF) an immediate evolution of hydrogen gas occurred and the alkali metal salt of the β-keto sulfoxide precipitated. Numerous attempts to alkylate this salt were unsuccessful and only starting material was obtained when the reaction was worked up. The failure of these alkylation attempts was attributed to the insolubility of the salts of II. When dimethylformamide (DMF) was used as solvent and sodium hydride was the added base, II reacted vigorously to yield the *soluble* salt. Addition of methyl iodide to the DMF solution gave a high yield of crude monoalkylated β-keto sulfoxide, IIIa, where R is phenyl and R′ is methyl. These alkylated β-keto sulfoxides were very difficult to purify. As a result the yield of purified alkylation product when DMF was used as solvent was 30%. Carrying out the same alkylation using dimethyl sulfoxide (DMSO) as solvent gave a 70% yield of monoalkylation product. This increase in yield was due primarily to a different work-up of

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(2) G. A. Russell and H.-D. Becker, *J. Am. Chem. Soc.*, **85**, 3406 (1963); H.-D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963).

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TABLE I

ALKYLATION OF $C_6H_5\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\uparrow}SCH_3$ AND CLEAVAGE OF $C_6H_5\overset{O}{\overset{\|}{C}}-\underset{R}{\overset{R'}{\underset{|}{\overset{|}{C}}}}-\overset{O}{\uparrow}SCH_3$

| Alkylating agent | Product R | Product R' | Alkylation solvent | Ketone obtained | % yield | 2,4-Dinitrophenylhydrazone mp, °C | Lit. mp, °C |
|---|---|---|---|---|---|---|---|
| $CH_3I$ (1 mole) | $CH_3$ | H | DMF | Propiophenone | 64 | 191–192 | 191 |
| $CH_3I$ (2 moles)[a] | $CH_3$ | $CH_3$ | DMF | Isobutyrophenone | 54 | 160–161 | 161–162 |
| $CH_3I$ (2 moles)[b] | $CH_3$ | $CH_3$ | DMF | Isobutyrophenone | 50 | ... | ... |
| $CH_3CH_2I$ | $CH_3CH_2$ | H | DMF | Butyrophenone | 70 | 190–191 | 191–192 |
| $CH_3CH_2CH_2Br$ | $CH_3CH_2CH_2$ | H | DMF | Valerophenone | 44 | 164–165 | 165–166 |

[a] Stepwise carbanion formation and alkylation (see Experimental Section). [b] Two moles of sodium hydride was added, followed by 2 moles of alkylating agent.

TABLE II

ALKYLATION OF $CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\uparrow}SCH_3$ AND CLEAVAGE OF $CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}-\underset{R}{\overset{R'}{\underset{|}{\overset{|}{C}}}}-\overset{O}{\uparrow}SCH_3$

| Alkylating agent | Product R | Product R' | Alkylation solvent | Ketone obtained | % yield | 2,4-Dinitrophenylhydrazone mp, °C | Lit. mp, °C |
|---|---|---|---|---|---|---|---|
| $CH_3I$ (1 mole) | $CH_3$ | H | DMF | 3-Octanone | 62 | 65–66 | 64–65 |
| $CH_3I$ (2 moles) | $CH_3$ | $CH_3$ | DMF | 2-Methyl-3-octanone | 59 | 91–92 | 92.5 |
| $CH_3CH_2I$ | $CH_3CH_2$ | H | DMF | 4-Nonanone | 57 | ... | ... |
| $CH_3CH_2I$ | $CH_3CH_2$ | H | DMSO | 4-Nonanone | 69 | ... | ... |

the DMSO solution. The ease with which alkylated β-keto sulfoxides can be cleaved was demonstrated by the reduction of purified IIIa with aluminum amalgam which gave a 96% yield of propiophenone.

$$C_6H_5\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{CH}}\overset{O}{\uparrow}SCH_3 \xrightarrow{Al(Hg)} C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_3$$

IIIa

Since purification of the alkylated β-keto sulfoxides was a major obstacle in obtaining a high yield, the direct reductive cleavage of the crude alkylation products appeared attractive. Table I gives the yield of ketone based on starting ω-(methylsulfinyl)acetophenone for the combined alkylation and cleavage steps. The yields showed that purification of the alkylated β-keto sulfoxide intermediate was unnecessary. The general scope of this synthetic sequence was extended to aliphatic β-keto sulfoxides as illustrated by Table II, which lists the results obtained from alkylation and cleavage of methylsulfinylmethyl *n*-pentyl ketone.

From Tables I and II it is obvious that not only monoalkylation but also dialkylation was possible. This dialkylation can be achieved by either a two-step procedure or a one-step procedure where 2 equiv of sodium hydride was added followed by addition of 2 equiv of alkylating agent. The two-step procedure could be used to obtain alkylation with two different alkylating agents thereby allowing the synthesis of rather complex α-substituted ketones.

One alkylation was done both in DMSO and in DMF. In these experiments the yield of ketone was slightly higher in DMSO than in DMF. This slight increase in yield was not sufficient to merit the added problems of rigorously drying the DMSO and of a more complex reaction work-up.

Preliminary attempts to alkylate the β-keto sulfoxide anion with secondary halides gave extremely poor yields of alkylation product.

## Experimental Section

**Solvents.**—Dimethylformamide was distilled from calcium hydride before use. Dimethyl sulfoxide was distilled from calcium hydride and stored over Linde Type 13X Molecular Sieves. ω-(Methylsulfinyl)acetophenone and methylsulfinylmethyl *n*-pentyl ketone were prepared by the published procedure.[3]

**Methylation of ω-(Methylsulfinyl)acetophenone in DMF.**—Sodium hydride (0.264 g, 0.011 mole) was washed free of mineral oil with dry pentane under a nitrogen atmosphere. Dimethylformamide (30 ml) was added to the dry sodium hydride powder. To this stirred slurry was added a solution of 2.0 g (0.011 mole) of ω-(methylsulfinyl)acetophenone in 10 ml of DMF. Vigorous hydrogen evolution ensued and the reaction was controlled by cooling. When the conversion of the β-keto sulfoxide to the anion was complete, 1.56 g (0.011 mole) of methyl iodide was added dropwise with cooling. The reaction mixture was stirred for 0.5 hr at room temperature and diluted with 100 ml of water, and the aqueous solution was extracted with chloroform. The chloroform extracts were washed with water and dried over anhydrous magnesium sulfate. After removal of the drying agent, the chloroform was stripped off on a rotary evaporator and the residual yellow oil was triturated with a small amount of cold ether to yield a solid product. Recrystallization of this material from ethyl acetate yielded 0.65 g. (30%) of pure IIIa as colorless needles, mp 77–78°.

*Anal.* Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.49; H, 6.31; S, 16.51.

**Methylation of ω-(Methylsulfinyl)acetophenone in DMSO.**—Dry sodium hydride (0.66 g, 0.0275 mole) was prepared as described above and slurried with 40 ml of dry DMSO. While maintaining the reaction temperature at 20°, 5.0 g (0.0275 mole) of ω-(methylsulfinyl)acetophenone in 10 ml of DMSO was added. When hydrogen evolution ceased, 3.9 g (0.0275 moles) of methyl iodide was added and the reaction was stirred for 0.5 hr. The reaction mixture was diluted with 150 ml of water and extracted with chloroform, and the chloroform extracts were dried over anhydrous magnesium sulfate. The drying agent was filtered off and the chloroform was removed under vacuum. The residue was seeded and triturated with cold ether–pentane. Recrystallization from ethyl acetate yielded 3.77 g (70%) of α-(methylsulfinyl)propiophenone (IIIa), mp 77–78°.

**Propiophenone.**—α-(Methylsulfinyl)propiophenone (0.34 g, 1.73 mmoles) dissolved in 25 ml of 10% aqueous tetrahydrofuran (THF) was allowed to react with 0.47 g of freshly prepared amalgamated aluminum[3] for 10 min. The reaction mixture was filtered and the inorganic products were washed with THF. The THF was removed on a rotary evaporator. The residue was diluted with *ca.* 5 ml of water and extracted with ether. The

ethereal extracts were dried over anhydrous magnesium sulfate. Removal of the drying agent and solvent gave 0.225 g (96%) of propiophenone.

**General Procedure for Combined Alkylation and Cleavage Steps.**—The alkylations were carried out as described above for the methylation of ω-(methylsulfinyl)acetophenone except that no attempt was made to crystallize or purify the crude alkylation product obtained upon removal of the solvent. This crude alkylation product was dissolved in 10% aqueous THF and reduced as described above for the preparation of propiophenone with the exception that the resulting ketones were extracted with pentane rather than with ether. The pentane solution was washed with water and dried over anhydrous magnesium sulfate, and the pentane was removed on a rotary evaporator. The crude ketones were distilled and the purity of the distillation product was checked by vapor phase chromatography.

**Dialkylation. The Preparation of Isobutyrophenone. A. Two-Step Procedure.**—ω-(Methylsulfinyl)acetophenone (5.0 g, 0.0275 mole) was methylated in DMF as described above using sodium hydride (0.66 g, 0.0275 mole) and methyl iodide (3.9 g, 0.0275 mole). After *ca.* 0.5-hr reaction time, the reaction mixture was transferred *via* syringe to a second reaction flask containing 0.66 g (0.0275 mole) of sodium hydride. When evolution of hydrogen ceased, the second equivalent of alkylating agent was added (in this case 3.9 g of methyl iodide) and the reaction mixture was stirred for *ca.* 45 min. Reduction with aluminum amalgam and distillation of the product yielded 2.21 g (54%) of isobutyrophenone, bp 68–72° (1 mm). A 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol–ethyl acetate: mp 160–161° (lit.[4] mp 161–162°).

**B. One-Step Procedure.**—ω-(Methylsulfinyl)acetophenone (5.0 g, 0.0275 mole) was added to a slurry of sodium hydride (1.32 g, 0.055 mole) in 50 ml of DMF, and 3.9 g (0.0275 moles) of methyl iodide was added. After 0.5 hr an additional 3.9 g of methyl iodide in 50 ml of DMF was added and the reaction mixture was stirred for 40 min. Reduction and isolation were completed as described to yield 2.05 g (50%) of isobutyrophenone.

**Propiophenone.**—Propiophenone was prepared as outlined in the general procedure from 5.0 g (0.0275 moles) of ω-(methylsulfinyl)acetophenone. Distillation of the product yielded 2.37 g (64%) of propiophenone, bp 62–66° (1.5 mm), 2,4-dinitrophenylhydrazone mp 191–192° (lit.[5] mp 191°).

**Butyrophenone.**—Butyrophenone was prepared on the usual scale (0.0275 mole) as described in the general procedure using ethyl iodide as the alkylating agent and allowing the alkylation 1-hr reaction time. Distillation of the product gave 2.83 g (70%) of butyrophenone, bp 75–80° (1.5 mm), 2,4-dinitrophenylhydrazone mp 190–191° (lit.[4] mp 191–192°).

**Valerophenone.**—Valerophenone was prepared in the described manner except with *n*-propyl bromide as the alkylating agent and at reaction time of 22 hr at 55°. Distillation of the crude product gave 1.97 g (44%) of valerophenone, bp 82–86° (0.5 mm), 2,4-dinitrophenylhydrazone mp 164–165° (lit.[6] mp 165–166°).

**3-Octanone.**—3-Octanone was prepared by the general procedure described above except the reduction with aluminum amalgam required 1 hr in refluxing THF. Distillation of the crude product gave 62% of 3-octanone, bp 55–58° (1.5 mm), 2,4-dinitrophenylhydrazone mp 65–66° (lit.[7] mp 64–65°).

**2-Methyl-3-octanone.**—The procedure described for two-step dialkylation was followed in the preparation of this ketone. This procedure was modified to have a reduction time of 1 hr in refluxing THF. Distillation of the product gave 59% of ketone, bp 70–74° (1.5 mm), 2,4-dinitrophenylhydrazone mp 91–92° (lit.[8] mp 92.5°).

**4-Nonanone.**—The general procedure was followed, allowing an alkylation time of 1 hr and a reduction time of 1 hr in refluxing THF. Distillation gave 57% of product, bp 85–88° (2.0 mm).

**4-Nonanone.**—The same alkylation procedure was followed using DMSO as the solvent. The reaction mixture was poured into three times its volume of water and extracted with chloroform. The chloroform extracts were washed three times with water and the chloroform was evaporated. No attempt was made to isolate the intermediate keto sulfoxide. Reduction was completed as above. Methylsulfinylmethyl *n*-pentyl ketone (5 g, 0.0284 moles), sodium hydride (0.68 g, 0.0284 mole), and ethyl iodide (4.43 g, 0.0284 moles) yielded upon distillation 2.81 g (70%) of 4-nonanone.

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# A Study of Aliphatic Sulfonyl Compounds. VIII. The Thermal Decomposition of Trimethylmethanesulfonyl Chloride[1]

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Erroneous reports concerning trimethylmethanesulfonyl chloride and other tertiary aliphatic sulfonyl chlorides are discussed. Authentic trimethylmethanesulfonyl chloride has been synthesized and its instability examined, and conclusions regarding the mechanism of decomposition are presented. The extremely low activation energy and the complete ineffectiveness of free radical inhibitors and scavengers on the rates and product ratios for the vapor phase decomposition support the view that the reaction proceeds by either a cyclic, intramolecular mechanism or a radical nonchain mechanism which may be heterogeneous. The same conclusions are made for the mechanism of decomposition in solution, except for heterogeneity. The activation energies and A factors, while still remarkably low, are larger than the vapor phase counterparts.

The thermal vapor phase decomposition of some simple aliphatic primary and secondary sulfonyl chlorides and bromides has been studied carefully by Geiseler, *et al.*,[3a–c] In addition, Naumann[3d] studied the vapor phase decomposition of methanesulfonyl chloride. These studies leave little doubt that the

(1) Taken in part from the dissertation of R. T. van Aller presented in partial fulfillment of the requirements for the Ph.D. degree at the University of Alabama in 1965. This research, which was initiated at the University of Alabama, was completed at The University of Mississippi.

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