The Preparation of β-Keto Sulfones by the Thorpe Reaction. The Acidity of β-Keto Sulfones[1,2]

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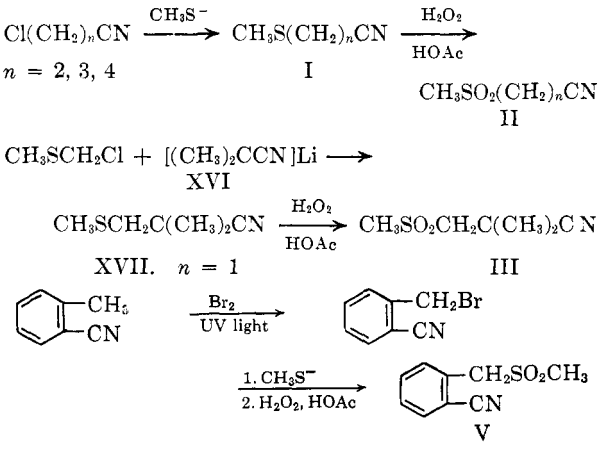
The Thorpe cyclization has been extended to ω-cyano sulfones, $CH_3SO_2(CH_2)_nC(CH_3)_2CN$, where n = 1, 3, and 4. Cyclization fails when n = 2 and 11, and with compounds of the type $CH_3SO_2(CH_2)_nCN$. Cyclization to 2,3-dihydrothianaphthene-3-one 1,1-dioxide occurs with *o*-methylsulfonylbenzonitrile, although Claisen condensation of the corresponding ester is not successful. Acidity constants of various cyclic and acyclic β-keto sulfones have been measured and discussed.

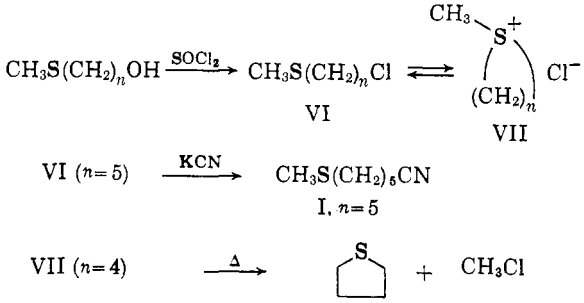
Preparation of β-Keto Sulfones by the Thorpe Reaction

Truce and Knospe[2] previously had employed mixed Claisen (Dieckmann) condensations to prepare various acyclic and cyclic β-keto sulfones. To explore further the usefulness of such mixed condensations, this work was extended to the Thorpe reaction, particularly in view of its advantages in preparing large ring systems.

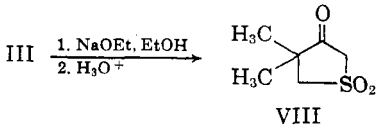
The homologous series of cyano sulfones, $CH_3SO_2(CH_2)_nCN$ (II. n = 2–6), was prepared. Anticipating that 3-methylsulfonylpropionitrile (II. n = 2) would undergo beta elimination of methanesulfinic acid, as was true of ethyl 3-methylsulfonylpropionate,[2] 2,2-dimethyl-3-methylsulfonylpropionitrile (III) was prepared by alkylation of isobutyronitrile with chloromethyl methyl sulfide followed by oxidation to the sulfone. Also prepared were *o*-methylsulfonylbenzonitrile (IV),[4] for possible cyclization to 2,3-dihydrothianaphthene-3-one 1,1-dioxide (IX), the synthesis of which had failed in a Dieckmann approach,[2] and α-methylsulfonyl-*o*-tolunitrile (V) for possible cyclization to 2-thiachroman-4-one 2-dioxide.



In attempts to prepare 1-chloro-4-methylthiobutane and 1-chloro-5-methylthiopentane (VI. n = 4 and 5) from the corresponding alcohols with thionyl chloride, for later conversion to the nitriles, the sulfonium chlorides (VII) were obtained, with no sulfide found when n = 4, and a mixture of VI and VII when n = 5, from which the sulfide could be distilled. Compounds VII were unreactive toward potassium cyanide, but VI (n = 5) reacted normally to afford the cyano sulfide (I. n = 5). On pyrolysis[5] of VII (n = 4) tetrahydrothiophene was obtained, but with n = 5, no appreciable amount of tetrahydrothiapyran could be obtained.



Treatment of the cyano sulfones (II. n = 2–6, III, IV, and V) with sodium ethoxide in ethanol, using Thorpe's conditions[6] in all instances, resulted in the formation of a red-brown color (presumably due to anion formation). With II (n = 2) beta elimination of methanesulfinic acid[7] resulted, and with III a 91% yield to 4,4-dimethyltetrahydrothiophene-3-one 1,1-dioxide (VIII)[2] resulted after acid hydrolysis. With the remaining compounds (II. n = 3–6, IV, and V) starting materials were returned almost quantitatively.



(1) Abstracted from portions of the Ph.D. theses of William W. Bannister and Robert H. Knospe.

(2) For the preceding paper in this series see W. E. Truce and R. H. Knospe, *J. Am. Chem. Soc.*, **77**, 5063 (1955).

(3) Standard Oil Company (Ohio) Fellow, 1959–1960.

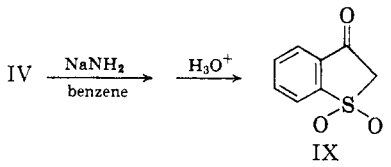
(4) P. Oxley, N. W. Partridge, T. D. Robson, and W. F. Short, *J. Chem. Soc.*, 763 (1946).

(5) C. S. Davis, A. M. Knevel, and G. L. Jenkins, *J. Org. Chem.*, *in press*.

(6) J. F. Thorpe, *J. Chem. Soc.*, 1901 (1909).

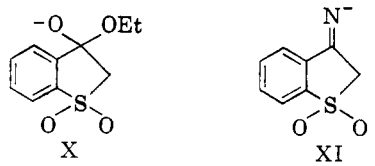
(7) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3127 (1928); 2338 (1929); 705 (1930).

On the basis of Thompson's work[8] indicating the need in Thorpe cyclizations for stronger bases than sodium ethoxide, the reactions were repeated using sodium amide in refluxing benzene. Using this method an 81% yield of IV to IX was realized after acid hydrolysis. This preparation is novel in view of the failure of methyl *o*-methylsulfonylbenzoate to



IX

cyclize under Claisen conditions.[2] This difference may be due to the fact that the intermediate X expected from the ester would suffer from more eclipsing strain[9] than would the intermediate XI from the nitrile:



X XI

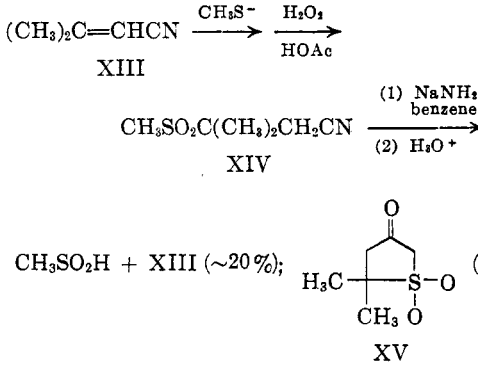
With the other cyano sulfones (II. n = 3–6; V) a highly insoluble red-brown sludge precipitated during the course of reaction, and ammonia was evolved practically quantitatively. On acidification, the starting sulfones were recovered almost quantitatively.

Solvents other than benzene were used with II (n = 4). This sulfone was treated with sodium amide in monoglyme, diglyme, and tetrahydrofuran, and with potassium *t*-butoxide in diglyme. With either base in diglyme (as well as after prolonged refluxing in benzene) a small amount of polymeric material was obtained along with starting material, after acidification. Presumably, insolubility of the metalated intermediates in the solvents employed accounted for the lack of much cyclization. Treatment of the starting material with sodium amide in refluxing benzene, followed by reaction with benzyl chloride afforded a 72% yield to the benzylated product XII. On the basis of n.m.r. comparisons with isobutyronitrile and with methyl isopropyl sulfone, alkylation is believed to have occurred alpha to the nitrile:

$$CH_3SO_2(CH_2)_3CH(CH_2C_6H_5)CN$$

XII

These results contrast with the cyclizations of carbethoxy sulfones, where metalations alpha to the sulfone *were* achieved.[2] Although Pearson and Dillon[10] suggest the order $SO_2 > COOR > CN$ for the pseudoacidifying effects of these groups, this order applies for equilibrium situations which may be upset by formation of insoluble carbanions, stabilized in this instance by the nitrile rather than the sulfone group. Supporting this suggestion is the fact that when metalation alpha to the nitrile is not possible, it does occur alpha to the sulfone (evinced by cyclization of III and IV). The possibility that III cyclizes (whereas compounds II do not) simply because of a *gem*-dimethyl stabilizing effect on the ring structure seems remote in view of the fact that IV also cyclizes readily. Furthermore, 3,3-dimethyl-3-methylsulfonylpropionitrile (XIV) was prepared and treated with sodium amide in benzene. That no cyclized product XV was found, and 80% of starting material was recovered, indicates the position of the *gem*-dimethyl groups alpha to the nitrile to be critical; in a beta elimination methanesulfinic acid and XIII were formed in low yield. The same conditions with isomeric III affords 93% cyclization to VIII.



There are several examples analogous to this system where dimethyl groups substituted alpha to one of the acidifying groups are necessary for condensation to occur, although in these instances the effect appears to have been ascribed only to the *gem*-dimethyl principle.[11] It appears that if the *gem*-dimethyl effect is operative, it is so to an auxiliary extent, and that some other factor, assumed to be the absence of hydrogens alpha to the nitrile, permits cyclization of cyanosulfones.

To test this further, a series of cyano sulfones, all with two methyl groups alpha to the nitrile, was synthesized.

Alkylations of isobutyronitrile were achieved using Ziegler conditions,[12] *i.e.*, addition of a catalytic amount of diethylamine to an equivalent amount of phenyllithium, followed by equivalent amounts of isobutyronitrile and then alkyl halide [in almost all cases low (*ca.* 10%) yields of isopropyl phenyl ketone were obtained from condensation of phenyllithium with isobutyronitrile[13]].

(8) Q. E. Thompson, *J. Am. Chem. Soc.*, **80**, 5483 (1958).

(9) H. C. Brown, J. H. Brewster, and H. Schechter, *ibid.*, **76**, 467 (1954).

(10) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953).

(11) (a) C. Le Peletier de Rosanbo, *Ann. Chim.* (Paris), **19**, 327 (1923). (b) N. J. Toivensen, *Ann. Acad. Sci. Fennicae, Ser. A., II*, 28 (1929).

(12) K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

(13) C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *J. Am. Chem. Soc.*, **70**, 426 (1948).

$CH_3S(CH_2)_nBr + [(CH_3)_2CCN]Li \longrightarrow$ (n = 2, 3; XVI)

$CH_3S(CH_2)_nC(CH_3)_2CN \xrightarrow[HOAc]{H_2O_2}$ (XVII)

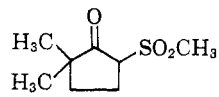
$CH_3SO_2(CH_2)_2C(CH_3)_2CN$ (XVIII) $\quad CH_3SO_2(CH_2)_3C(CH_3)_2CN$ (XIX)

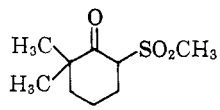
$Cl(CH_2)_4Cl + XVI \longrightarrow Cl(CH_2)_4C(CH_3)_2CN \xrightarrow{CH_3S^-} \xrightarrow[HOAc]{H_2O_2} CH_3SO_2(CH_2)_4C(CH_3)CN_2$ (XX)

$CH_2{=}CH(CH_2)_9Br + XVI \longrightarrow CH_2{=}CH(CH_2)_9C(CH_3)_2CN \xrightarrow[UV\ light]{CH_3SH}$

$CH_3S(CH_2)_{11}C(CH_3)_2CN \xrightarrow[HOAc]{H_2O_2} CH_3SO_2(CH_2)_{11}C(CH_3)_2CN$ (XXI)

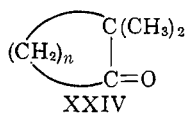
The dimethyl-substituted cyano sulfones were treated with excess sodium amide in refluxing benzene for three hours. An equivalent amount of ammonia was evolved and a red-brown precipitate formed in all cases. The mixtures were then refluxed with dilute hydrochloric acid. Cyclizations to 2,2-dimethyl-5-methylsulfonylcyclopentanone (XXII) and 2,2-dimethyl-6-methylsulfonylcyclohexanone (XXIII) were thus achieved with XIX and XX in 77% and 92% yields, respectively:

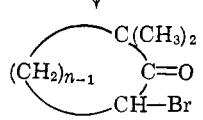
XIX $\xrightarrow[2.\ H_3O^+]{1.\ NaNH_2,\ benzene}$  (XXII)

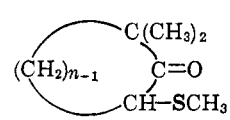
XX $\xrightarrow{''}$  (XXIII)

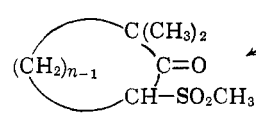
These structures were confirmed by independent syntheses:

$Cl(CH_2)_nBr + XVI \longrightarrow Cl(CH_2)_nC(CH_3)_2CN \xrightarrow{KCN} NC(CH_2)_nC(CH_3)_2CN$

$\xrightarrow[2.\ H_3O^+;\ \Delta,\ -CO_2]{1.\ NaNH_2}$  (XXIV)

$\xrightarrow{Br_2}$  (XXV)

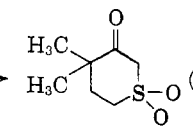
$\xrightarrow{CH_3S^-}$  (XXVI)

$\xrightarrow[HOAc]{H_2O_2}$ 

XXII (n=3)
XXIII (n=4)

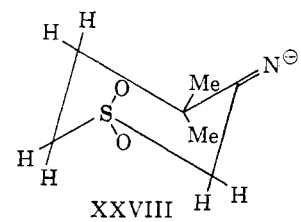
Moreover, the infrared spectrum of XXII indicates a cyclopentanone structure with the carbonyl shift from 5.82 to 5.73 μ.[14] The same is true to a lesser extent for IX; the decreased shift in this compound is probably due to conjugative effects with the aromatic ring. It is interesting to note that VIII also shows the same full shift to 5.73 μ, indicating that substitution of the sulfonyl group for a beta methylene group in cyclopentanone has little effect on this shift. The six-membered rings (XXIII), tetrahydrothiapyran-3-one 1,1-dioxide (XXXVI),[2] and 2-methylsulfonylcyclohexanone (XXXVII)[2] are all normal in showing no shift in carbonyl absorption frequency.

With XVIII no cyclization to the expected 4,4-dimethyltetrahydrothiapyran-3-one 1,1-dioxide (XXVII) could be achieved. Use of diglyme re-

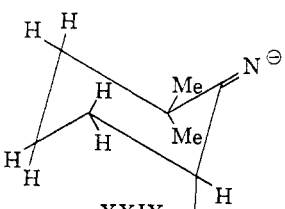
XVIII $\xrightarrow[benzene]{NaNH_2}$ $\xrightarrow{H_3O^\oplus}$  (not found)

XXVII

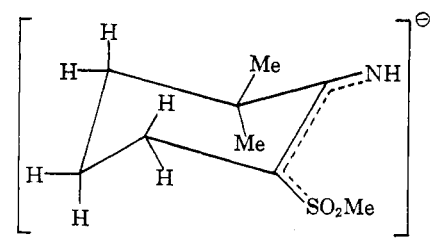
sulted in a small amount of poorly defined polymer and recovery of most of the starting material. It is difficult to reconcile the inability of XVIII to undergo intramolecular condensation with the behavior of XX which readily cyclizes to XXIII, presumably *via* intermediates XXVIII (from XVIII) and XXIX (from XX).[15]



XXVIII



XXIX



XXX

High dilution cyclization techniques[16] were unsuccessfully employed with XXI, using sodium amide in refluxing benzene or diglyme and high

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, 1959, p. 133ff.

(15) *Cf.*, F. G. Bordwell, C. E. Osborne, and R. D. Chapman, *J. Am. Chem. Soc.*, **81**, 2698 (1959). In both XXVIII and XXIX, as with all the β-keto sulfone anions and their imido intermediates, tautomerization to resonance-stabilized structures such as XXX should be considered likely.

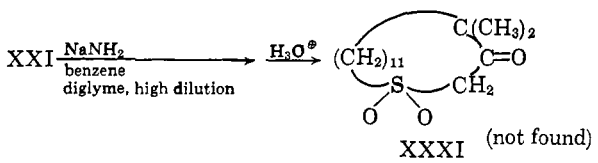
(16) (a) K. Ziegler, H. Eberle, and H. Ohlinger, *Ann.*, **504**, 84 (1933). (b) R. Adams and N. Kornblum, *J. Am. Chem. Soc.*, **63**, 195 (1941).

TABLE I
ACIDITIES OF ACYCLIC β-KETO SULFONES

$C_6H_5SO_2CH_2COC_6H_6$	$CH_3SO_2CH_2COC_6H_5$	$C_6H_5SO_2CH_2COCH_3$	$CH_3SO_2CH_2COCH_3$
XXXII	XXXIII	XXXIV	XXXV
pK_a 9.83 ± 0.02[a]	10.01 ± 0.02[a]	10.09 ± 0.02[a]	10.48 ± 0.01[a]
			9.90 ± 0.02[b]

[a] Measured in 50% ethanol–50% water; consequently, these are apparent acidities. [b] Measured in water.

speed stirring. No cyclization product XXXI was found; rather, an undetermined quantity of ill-defined polymer resulted.



XXXI (not found)

As might be expected, from the decreased acidifying effect of sulfide as compared to sulfone, none of the α,α-dimethyl-α-cyano ω-sulfides (XVII. n = 1–4) afforded any isolable condensation products when refluxed with sodium amide in benzene.

The Acidity of β-Keto Sulfones

The acidities of various acyclic and cyclic β-diketo compounds have been determined and compared by a number of workers, and several interesting correlations brought to light.[10,17] However, with the exception of some pK_D measurements of dioxane–water solutions of several acyclic β-keto sulfones,[18] quantitative measurements on many of these compounds have been lacking. No attempt appears to have been made to determine structural and substitutent effects on the acidities of β-keto sulfones. Therefore, dissociation constants of the following acyclic (Table I) and cyclic (Table II) β-keto sulfones were measured by potentiometric titration: ω-phenylsulfonylacetophenone (XXXII)[2]; ω-methylsulfonylacetophenone (XXXIII)[2]; phenyl sulfonylacetone (XXXIV)[19]; methylsulfonylacetone (XXXV)[20]; 4-4-dimethyltetrahydrothiophene-3-one 1,1-dioxide (VIII); tetrahydrothiapyran-3-one 1-dioxide (XXXVI)[2]; 2,2-dimethyl-5-methylsulfonylcyclopentanone (XXII); 2-methylsulfonylcyclohexanone (XXXVII)[2]; 2,2-dimethyl-6-methylsulfonylcyclohexanone (XXIII); and 2,3-dihydrothianaphthene-3-one 1,1-dioxide (IX). As previously reported,[2] 2-methylsulfonylcyclopentanone (XXXVIII) has been prepared but has resisted purification; indications are that it is relatively unstable.

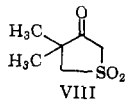
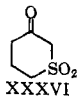
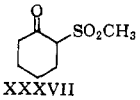
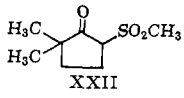
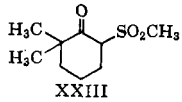
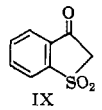
The relative electronic effect of the methyl versus the phenyl group could provide a qualitative correlation of the acidity differences shown in Table I: By replacing the methyl group with a phenyl group the acidity of the β-keto sulfone linkage would be expected to increase. Also, in comparing the acidity of methylsulfonylacetone with that of acetylacetone (pK = 8.94[17a]) and bis(methylsulfonyl)methane (pK = 14[17b]), the keto sulfone falls between the diketone and disulfone, as might be expected.

In comparing the acidities of the cyclic β-keto sulfones, the following need to be considered:

(1) Compounds VIII and XXXVI afford secondary carbanions, whereas XXII, XXIII, and XXXVII give tertiary carbanions on treatment with base. Secondary carbanions are more stable than are tertiary,[21] in small part explaining why VIII and XXXVI are more acidic.

(2) If present at all, enolizing influences (such

TABLE II
ACIDITIES OF CYCLIC β-KETO SULFONES (IN WATER)

	pK_a
 VIII	5.83 ± 0.04
 XXXVI	9.01 ± 0.02
 XXXVII	10.46 ± 0.02[a]
 XXII	10.70 ± 0.03
 XXIII	11.62 ± 0.03
 IX	7.65[17b]

[a] Possibly erroneous, since in determining the pK_a it was noted that the pH tended to drop steadily after each increment of base. The acidity determination was therefore made by adding aliquots of equal amounts of XXXVII to varying known amounts of base and immediately determining the pH. A value approximating the true acidity was probably achieved, but it is likely that the pK_a could be significantly higher. The drop in pH may have been due to decomposition.

(17) (a) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940). (b) G. Schwarzenbach and E. Felder, *ibid.*, **27**, 1701 (1944). (c) B. Eistert and W. Reiss, *Ber.*, **87**, 92 (1954).

(18) E. H. Holst and W. C. Fernelius, *J. Org. Chem.*, **23**, 1881 (1958).

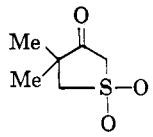
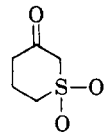
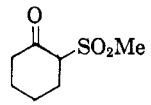
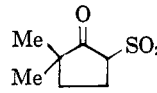
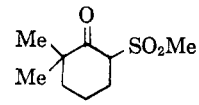
(19) R. Otto and W. Otto, *J. prakt. Chem.* [2], **36**, 401 (1887).

(20) D. W. Coure and D. T. Gibson, *J. Chem. Soc.*, 48 (1934).

(21) (a) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, 1956, p. 184ff. (b) A. A. Morton, *Chem. Rev.*, **35**, 1 (1944).

TABLE III

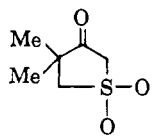
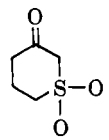
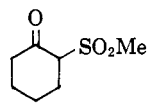
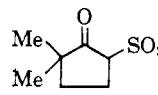
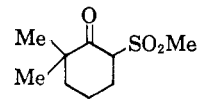
ULTRAVIOLET SPECTRA OF β-KETO SULFONES[a,b]

$MeSO_2CH_2COMe$						
	XXXV	VIII	XXXVI	XXXVII	XXII	XXIII
λ, mμ	285	296	290	297	302	294
ϵ_{max}	48	30	21	29	50	30

[a] Samples dissolved in ethanol. [b] Ultraviolet spectra of compounds IX, XXXII, XXXIII, and XXXIV suffered from strong interfering absorptions in this region because of the aromatic moieties.

TABLE IV

ULTRAVIOLET SPECTRA OF β-KETO SULFONYL ANIONS[a,b]

$MeSO_2CH_2COMe$						
	XXXV	VIII	XXXVI	XXXVII	XXII	XXIII
λ, mμ	242	227	236	252	248	253
ϵ_{max}	14,400	7,450	11,500	8,600	8,150	5,850

[a] Keto sulfone samples were run in quadruplet, in concentration ranges of 1.5 to 7.8 × 10^{-5} *N*, in 0.01 *N* NaOMe in methanol. Spectra were all run within one minute of preparation of each sample solution. Results are reported as averages of the λ_{max} and ϵ_{max} values thus observed and calculated; deviations in ϵ_{max} did not exceed 3% for a given set of samples, and in λ_{max} variations of more than 1 mμ were not observed. [b] Ultraviolet spectra of the compounds IX, XXXII, XXXIII, and XXXIV suffered from strong interfering absorptions in this region because of aromatic moieties.

as those suggested for the β-diketo analogs[17c]) among the cyclic β-keto sulfones could account for some of the acidity differences. That enol content is not appreciable for keto sulfones is evidenced by the complete lack of carbonyl frequency shifts in their infrared spectra, and by the lack of absorptions attributable to enol in the ultraviolet spectra (*e.g.*, ethyl acetoacetate in the enol form absorbs at 245 mμ with an ϵ_{max} of 18,000, and the keto form absorbs at 300 mμ with a much lower ϵ_{max} of 50[22]). The keto sulfones show no absorptions in the region of 245 mμ but do show a keto absorption near 300 mμ (Table III). This bears out the previous observations[18] that β-keto sulfones do not tautomerize.[23,24]

Ultraviolet spectra of the β-keto sulfonyl anions were obtained using the techniques of Fehnel and Carmack.[25] The results are summarized in Table IV.

Two sets of factors may be considered to influence the extinction coefficient values: the relative concentration of the anions (the more acidic compounds afford higher equilibrium concentrations of the anions, hence higher ϵ_{max} values); and the relative polarities of the anions—*e.g.*, because of sulfonyl–carbonyl oxygen interactions (the more polar anions being identified with increased extinction coefficients[26]).

(3) Solvation effects could presumably be invoked in considering stability of anions of β-keto sulfones. As indicated in Table IV deviations of up to 3% were encountered in the extinction coefficients over a moderately wide range of concentrations; it is possible these small departures from the Beer law might be ascribed to such solvation effects. However, this type of deviation is often encountered with bases, acids, and salts[27] and hence is no real evidence for this phenomenon.

It is difficult at this time to explain the high acidity of VIII. There is the possibility that this material is undergoing decomposition in base; however, no drop of pH was noted for this compound as was observed for XXXVII (Table II).

As can be seen from Tables I and II, there are interesting variations in the acidities of open chain and ring β-keto sulfones. It would be interesting to pursue further the variety of factors which cause these variations.

(22) A. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy." Edward Arnold Publishers, London, 1954, p. 223ff.

(23) Kurt Meyer titrations were performed on several of the compounds using modifications of A. Gero (*J. Org. Chem.*, **19**, 1960 (1954)). Per cent enols were thus determined for the following: VIII, 0.308; XXII, 0.205; XXV, 0.10; XXXVI, 0.5. The last two were used in such small quantity that the titrations were probably not as accurate as for the first two, where 0.1 *M* quantities were used in duplicate runs.

(24) M. Prochazka, *Coll. Czech. Chem. Comm.*, **25**, 465 (1960), has reported the preparation and strong enolic character of tetrahydrothiophene-3-one 1,1-dioxide, the only evidence for this being *O*-methylation with diazomethane.

(25) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 231 (1949).

(26) F. A. Miller, in H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, 1953, p. 163.

(27) A. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy." Edward Arnold Publishers, London, 1954, p. 8.

Experimental[28]

Methyltetramethylenesulfonium Chloride (VII. $n = 4$).—To an aqueous solution of sodium methylmercaptide (prepared by passing an excess of methyl mercaptan into a solution of 30.0 g. (0.75 mole) of sodium hydroxide in 300 ml. of water) was added with stirring and cooling 72.1 g. (0.65 mole) of 4-chloro-1-butanol. After chloroform extraction, drying over potassium carbonate, and stripping off volatiles, the residue was distilled to yield 73.5 g. (0.50 mole, 78%) of 4-methylthiobutanol, b.p. 88–90°/4.4 mm., $n^{20}D$ 1.4885. This was dissolved in 150 ml. of dry chloroform at 60° and to this solution was added slowly with stirring 83.5 g. (0.70 mole) of thionyl chloride. After addition the mixture was refluxed for 30 min., water slowly added, and the chloroform layer separated and combined with chloroform extracts. The combined extracts were dried and stripped of chloroform, leaving essentially no residue. The water phase was evaporated to dryness affording 56.8 g. (0.41 mole, 82.5%) of methyl tetramethylenesulfonium chloride. On heating to 225°, decomposition to tetrahydrothiophene ($HgCl_2$ adduct: m.p. 126–128°[29]) and methyl chloride was observed. After refluxing 13.8 g. (0.20 mole) of the sulfonium chloride with 16.3 g. (0.25 mole) of potassium cyanide in 300 ml. of aqueous ethanol, stripping, and crystallization from water, all of the sulfonium chloride was recovered; no reaction product was found.

6-Methylthiocapronitrile (I. $n = 5$).—Similarly, 199.5 g. (1.63 moles) of 5-chloropentanol[30] was treated with excess sodium methylmercaptide, affording 145.5 g. (1.19 moles, 73%) of 5-methylthiopentanol, b.p. 102–104°/2.8 mm., $n^{20}D$ 1.4847. Using thionyl chloride 93.0 g. (0.61 mole) of 1-chloro-5-methylthiopentane was obtained, b.p. 89–91°/9.5 mm., $n^{20}D$ 1.4855. A large amount of crystalline material was obtained which on recrystallization from aqueous ethanol afforded 16.7 g. (0.11 mole) of methylpentamethylenesulfonium chloride. On pyrolysis at 250° no tetrahydrothiapyran was formed, although extensive decomposition was noted. No reaction was observed on treatment of the sulfonium chloride with excess potassium cyanide. On refluxing a solution of 60.0 g. (0.40 mole) of 1-chloro-5-methylthiopentane, 38.5 g. (0.60 mole) of potassium cyanide, and 5.0 g. of potassium iodide in aqueous ethanol for 4 hr. a yield of 40.6 g. (0.28 mole, 71%) of 6-methylthiocapronitrile, b.p. 96–98°/1.5 mm, $n^{20}D$ 1.4780, was obtained.

Other α,ω-Cyano Sulfides.—The following halonitriles were treated with sodium methylmercaptide in alcoholic solutions: $X(CH_2)_nCN$: $n = 2$–4; 6[31]; and α-bromo-*o*-tolunitrile.[32] The product cyano sulfides are listed in Table V.

2,2-Dimethyl-3-methylthiopropionitrile (XVII. $n = 1$).—Using Ziegler conditions,[12] phenyllithium reagent was prepared from 6.1 g. (0.88 g.-atom) of lithium metal and 70.6 g. (0.45 mole) of dry bromobenzene in 200 ml. of dry ether. Diethylamine (15 g., 0.2 mole) was added, followed by 29.0 g. (0.42 mole) of isobutyronitrile. Chloromethyl methyl sulfide[34] was slowly added, and after an additional hour of refluxing, water was carefully added and the water layer extracted with ether, and this combined with the original organic layer. After drying and stripping, the residue was distilled to give 37.3 g. (0.29 mole, 65%) of product; b.p. 78–79°/10 mm., $n^{19.5}D$ 1.4680.

TABLE V

Cyano Sulfide	B.p.	n_D (temp.)	Yield	Lit. ref.
I. $n = 2$	94/95°/15 mm.	1.4839 (22°)	89	33a
3	103–105°/13 mm.	1.4805 (20°)	56	33b
4	92–94°/2.9 mm.	1.4800 (20°)	61	33c
5	119–122°/14.5 mm.	...	72	..
6	135–138°/7.5 mm.	1.4779 (20°)	..	33d

α-Methylthio-*o*-tolunitrile (oxidized directly to sulfone without isolation).

α,ω-Cyano Sulfones (II. $n = 2$–6; III; IV; V).—The cyano sulfides were oxidized to the sulfones using a fourfold excess of 30% hydrogen peroxide added slowly with cooling to an equal volume of acetic acid and acetic anhydride, in which the sulfide had been dissolved. After addition the mixture was heated at 100° for 1 hr., then catalytically deoxygenated until starch iodide tests were negative. After stripping, the residues were crystallized from aqueous ethanol. (IV was prepared by the method of Oxley, *et al.*[4]). Sulfones are listed in Table VI.

With I ($n = 3$) oxidation resulted in varying amounts (10–30%) of the following products in addition to the expected sulfone: ammonium methanesulfonate (m.p. 192–192.5°); 4-methylsulfonylbutyramide (m.p. 102–105°); and 1,3-bis(methylsulfonyl)propane (m.p. 155–156°). Gases evolved from the reaction were bubbled into lime water with precipitation of calcium carbonate. From the odor of the vapors it is believed that methanesulfinic acid was also a product, but attempts to isolate it were unsuccessful.

Reactions of Cyano Sulfones with Ethanolic Sodium Ethoxide.—Using Thorpe's conditions[6] the cyano sulfones II ($n = 2$–6); III, IV, and V were dissolved in ethanol (dry) in which a slight excess of sodium had been dissolved and the reaction mixture refluxed 3 hrs. Excess dilute hydrochloric acid was then added, the mixture refluxed 30 min., and the volatiles stripped off. With III, a 91% yield to VIII, m.p. 130–131° was noted, which gave no m.p. depression with an authentic sample.[2] In all other instances greater than 90% of the starting materials were returned, except with II, $n = 2$, in which case extensive decomposition occurred.

Reactions of Cyano Sulfones with Sodium Amide in Benzene.—The cyano sulfones II ($n = 3$–6), IV, and V were dissolved in benzene containing 10% excess sodium amide, and the reaction mixtures refluxed with stirring for three hours. With II, $n = 4$, the effluent gases were absorbed in dilute hydrochloric acid and the ammonium chloride so trapped determined by back titration, indicating 101% of the theoretical amount of ammonia had been evolved. With IV, a yield of 81% to IX, m.p. 132–134°,[35] was realized.

Anal. Calcd. for $C_8H_6O_3S$: C, 52.73; H, 3.32. Found, C, 52.99; H, 3.60.

In all other instances starting materials were returned almost quantitatively. With II ($n = 4$) the reaction was repeated in diglyme and tetrahydrofuran using sodium amide, and in diglyme using potassium *t*-butoxide. In the first and third cases after 3-hr. refluxing and acidification a polymeric residue was obtained in small yields. Treatment of 16.1 g. (0.1 mole) of II ($n = 4$) in refluxing benzene with 3.9 g. (0.1 mole) of sodium amide followed by addition of 12.7 g. (0.1 mole) of benzyl chloride gave 18.1 g. (0.072 mole, 72%) of XII, m.p. 79–81°.

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.81; N, 5.57. Found: C, 61.89; H, 6.48; N, 5.72.

The n.m.r. spectrum of this compound was compared to

(28) All boiling and melting points are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 21 spectrophotometer; ultraviolet spectra were obtained using a Cary recording spectrophotometer; n.m.r. studies were made using a Varian Associates n.m.r. spectrometer (60 megacycle high resolution). A glass electrode, saturated calomel half cell and a Perkin-Elmer "Zeromatic" pH meter were used to determine pK_a values.

(29) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

(30) M. S. Newman and J. H. Wotiz, *ibid.*, **71**, 1294 (1949).

(31) C. H. Andrews, H. King, and J. Walker, *Proc. Roy. Soc.* (London), **B133**, 20 (1946).

(32) R. C. Fuson, *J. Am. Chem. Soc.*, **48**, 830 (1926).

(33) (a) A. Kjaer, F. Marcus, and J. Conti, *Acta Chem. Scand.*, **7**, 1370 (1953). (b) A. Kjaer and J. Conti, *ibid.*, **8**, 295 (1954). (c) A. Kjaer, I. Larsen, and R. Gmelin, *ibid.*, **9**, 1311 (1955). (d) A. Kjaer and B. Christensen, *ibid.*, **11**, 1298 (1957).

(34) W. E. Truce, B. H. Birum, and E. T. McBee, *J. Am. Chem. Soc.*, **74**, 3594 (1952).

(35) M. M. Lanfrey, *Compt. rend.*, **155**, 1517 (1912).

TABLE VI

Cyano-sulfone	M.P.	Yield	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Lit.
II, n = 2	73.5–75.5°	72	36.02	5.30	10.56	36.24	5.50	10.27	33a
3	44.5–45.5°	30	40.80	6.17	9.52	40.54	6.45	9.50	
4	38.5–40°	68	44.70	6.88	8.69	44.59	6.99	8.44	
5	39–40°	..	...	...	...	...	...	...	
6	33–35°	..	50.76	7.99	7.40	50.26	7.60	7.05	
III	44.5–45.5°	86	44.70	6.88	8.69	44.70	6.63	8.54	
IV	103–105°	80	...	...	...	...	...	...	4
V	129–130.5°	25 (overall)	55.36	4.65	7.17	55.48	4.71	7.07	

those of isopropyl methyl sulfone[29] and isobutyronitrile, indicating benzylation had occurred alpha to the nitrile group (see Table VII):

TABLE VII

(J in c.p.s.)

	J_{HH}-$MeSO_2$	J_{HH}-R_2CHCN	J_{HH}—SO_2CH-$(CH_2R)_2$
XII	4.12	5.00	...
$(CH_3)_2CHSO_2CH_3$	4.10	...	3.42
$(CH_3)_2CHCN$	...	5.06	...

3,3-Dimethyl-3-methylsulfonylpropionitrile (XIV) and Attempted Cyclization.—A solution of 33.0 g. (0.40 mole) of 3-methyl-3-butenenitrile (XIII)[36] in 100 ml. of benzene was treated with 50 g. (1 mole) of methyl mercaptan and 1.0 g. of sodium ethoxide and allowed to stand overnight at 0°. Water was added, volatiles stripped off, and the organic layer distilled, affording 28.4 g. (0.22 mole, 55%) of 3,3-dimethyl-3-methylthiopropionitrile, b.p. 117–117.5°/25 mm., $n^{25.5}D$ 1.4733. Slow addition of excess hydrogen peroxide with cooling to an acetic acid–acetic anhydride solution of the sulfide gave 22.5 g. (0.15 mole, 68%) of 3,3-dimethyl-3-methylsulfonylpropionitrile, m.p. 61.5–63.5°.

Anal. Calcd. for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.92; H, 6.92; N, 8.71.

The sulfone was dissolved in benzene and treated with an excess of sodium amide at reflux for 3 hr.; 20.0 g. of starting material was returned after acidification (80%). No cyclized product XV was found but traces of XIII were detected by vapor phase chromatography and a faint odor of methanesulfinic acid was noted.

Other α,α-Dimethyl-ω-methylthio- and Methylsulfonylnitriles.—Compounds XVII (n = 2–4, 11) were prepared using various techniques depending on the value of n. When n = 2 and 3, 0.5 molar quantities of 2-bromoethyl methyl sulfide[37] and 3-bromopropyl methyl sulfide[38] were treated with 0.6 M quantities of the lithium salt of isobutyronitrile (XVI)[12] in 200 ml. of dry ether, followed by 3 hr. of refluxing, water washing, ether extraction, stripping of solvent, and distillation of the residue. When n = 4, 1.00 mole of XVI in 500 ml. of dry ether was added slowly with stirring to 650 g. (*ca.* 5 moles) of 1,4-dichlorobutane in 500 ml. of dry ether, followed by similar work-up, to yield 54.0 g. (0.34 mole, 34%) of 6-chloro-2,2-dimethylcapronitrile, b.p. 77–82°/1.32 mm., $n^{23.5}D$ 1.4758. The latter was treated in turn with excess sodium methylmercaptide in aqueous alcohol. When n = 11, 0.5 mole of XVI was treated with 63.0 g. (0.27 mole) of 11-bromo-1-undecene,[39] which after similar work-up gave 42.5 g. (0.19 mole, 71%) of 2,2-dimethyl-12-tridecenenitrile, b.p. 117–118°/0.8 mm. The latter was treated with 36.0 g. (0.75 mole) of methylmercaptan in carbon tetrachloride at Dry Ice temperature for 4 hr. with broad spectrum ultraviolet irradiation, affording the cyano sulfide. The α,α-dimethyl-ω-methylthionitriles are described in Table VIII. (In all alkylations with XVI, varying low yields of phenyl isopropyl ketone were isolated as a result of condensation of phenyllithium with isobutyronitrile.) No condensation were obtained on refluxing benzene solutions of XVII (n = 1–4), with excess sodium amide; starting materials were returned almost quantitatively.

TABLE VIII

Sulfide	B.p.	n_D (temp.)	Yield
XVII. n = 2	77–78° (3.2 mm.)	1.4873 (20°)	75
3	85–88° (2.5 mm.)	1.4793 (22°)	76
4	88–90° (0.8 mm.)	1.4715 (22.5°)	85
11	37–39° (m.p.)	...	67

The sulfides were subjected to oxidation in acetic acid–acetic anhydride solution using excess hydrogen peroxide, and were crystallized from aqueous ethanol. The resulting sulfones are described in Table IX.

Condensations to Cyclic β-Keto Sulfones.—Using techniques similar to the condensation of III and IV to VIII and IX, the above α,α-dimethyl-ω-methylsulfonylnitriles were treated with excess sodium amide in refluxing benzene for 3 hr. The resultant yields to cyclic β-keto sulfones are listed in Table X.

[Using high dilution techniques[16] for compound XXI, a solution of 10 g. (3.32×10^{-3} mole) of XXI in 500 ml. of distilled diglyme was forced slowly by nitrogen pressure through a capillary onto the sides of a condenser. The latter was constantly being washed with refluxing benzene from a distilling pot containing 250 ml. of diglyme, 200 ml. of benzene, and 1 g. (0.025 mole) of sodium amide. The entire addition required 2 days, whereupon the system was hydrolyzed with dilute hydrochloric acid, refluxed for 2 hr., and all solvents stripped *in vacuo*. The remaining material was a viscous sludge which defied crystallization.]

Structure Proof of 2,2-Dimethyl-5-methylsulfonylcyclopentanone (XXII).—A 1.11-*M* quantity of XVI in 500 ml. of dry ether was added with cooling to 236 g. (1.5 moles) of 1-bromo-3-chloropropane in 400 ml. of dry ether, followed by work-up as described above, to afford 75.6 g. (0.52 mole, 47%) of 2,2-dimethyl-5-chlorovaleronitrile, b.p. 80.5–85°/5 mm., $n^{18.5}D$ 1.4692. Potassium cyanide (49.0 g., 0.75 mole) was dissolved in 250 ml. of ethylene glycol and to this was added, at 100°, the chloronitrile.[40] After 2 hr. of stirring and heating, water was added and the products extracted, affording 40.0 g. (0.29 mole, 56.5%) of 2,2-dimethyladiponitrile, b.p. 106–108°/1.5 mm., $n^{19.0}D$ 1.4384. This was dissolved in 200 ml. of dry ether with 13.0 g. (0.33 mole) of sodium amide, and refluxed overnight under nitrogen. The product was acidified with dilute hydrochloric acid, the ether layer and extracts stripped off, and the residue dissolved in 350 ml. of acetic acid with 20 ml. of concentrated sulfuric acid and stirred at 100° overnight. The product was

(36) M. M. Shemyakin and D. M. Trakhtenberg, *Compt. rend. acad. sci. U.R.S.S.*, **24**, 763 (1939).

(37) S. Akabori, T. Kaneko, and S. Matizuki, *Nippon Kagaku Zashi*, **59**, 1135 (1938).

(38) F. K. Kirchner, A. E. Soria, and C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 4599 (1955).

(39) N. A. Sorensen and J. Mehlum, *Acta Chem. Scand.*, **2**, 140 (1948).

(40) F. B. La Forge, *et al.*, *J. Am. Chem. Soc.*, **70**, 3709 (1948).

TABLE IX

Sulfone	M.P.	Yield	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XVIII	108–109°	65	47.97	7.94	7.99	48.00	7.47	7.95
XIX	51.8–53.8°	80	...	...	...	...	...	...
XX	49–50°	70	53.17	8.43	6.89	53.25	8.30	6.92
XXI	58.5–59.5°	79	63.74	10.37	4.65	63.68	10.64	4.61

TABLE X

Cyanosulfone	β-Keto Sulfone	M.P.	Yield	Calcd. C	Calcd. H	Found C	Found H
XVIII	XXVII	...	0	...	...	...	...
XIX	XXII	95–96.5°	58	50.50	7.41	50.47	7.43
XX	XXIII	92–94°	90	52.86	7.90	53.18	7.69
XXI	XXXI	...	0	...	...	...	...

washed with water and the ether stripped. The residue was distilled, giving 22.0 g. (0.20 mole, 67%), b.p. 69–70°/60 mm. of XXIV (n = 3); oxime, m.p. 66–68°. Bromine (12.0 g., 0.075 mole) was added to sufficient ether, with cooling, to form a solution, and the etherate dripped into 8.4 g. (0.075 mole) of XXIV, n = 3, in 75 ml. ether, with stirring. The resulting product was stripped of ether and 0.15 mole of potassium methylmercaptide in methanol was added with stirring and ice cooling, to give after distillation, 4.8 g. (0.03 mole, 40%) of XXVI (n = 3), b.p. 81–84°/8 mm., $n^{25.3}$D 1.4843. On oxidation with 30% hydrogen peroxide in acetic acid solution a 1.2 g. yield of XXII was obtained which gave no mixed m.p. depression with the previously prepared sample.

Structure Proof of 2,2-Dimethyl-6-methylsulfonylcyclohexanone (XXIII).—To 54 g. (0.26 mole) of 6-bromo-2,2-dimethylcyclohexanone (XXV, n = 4)[41] was added excess potassium methylmercaptide in methanol. After extraction, stripping of solvents, and distillation, 41.2 g. (0.24 mole, 90%) of XXVI (n = 4), b.p. 73–75°/1.0 mm., n^{22}D 1.5012 was obtained. On oxidation to the sulfone a product was obtained which gave no depression of the m.p. when mixed with the previously prepared sample.

Determination of Acidities (pK_a's) of β-Keto Sulfones.—With the exception of XXXVII (described previously), stock solutions of the β-keto sulfones (0.001 M) were prepared by dissolving a weighed portion of the compound in carbon dioxide–free water (or in a 50:50 ethanol-water solution) in a volumetric flask. One hundred-milliliter portions of the stock solution were partially neutralized with freshly prepared carbonate-free sodium hydroxide solution, made up from the same solvent as the stock solutions. The pH of the solution was measured at different stages of neutralization at 25°. The pK_a values were calculated from the simple Henderson equation[42] when the pH was below 10; above this value the more accurate form[42] was used.[43] The average of five to seven determinations from 20–80% neutralization for each compound is given in Tables I and II; the spread in pK_a values was generally 0.01 to 0.03.

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(42) S. Glasstone, "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., New York, 1946, p. 1002.

(43) In the case of 50% ethanol solutions above a pH of 10, the K_w for the solvent was taken to be 1.5 × 10^{-15}, as given by D. L. Tabroff, G. E. K. Branch, and B. Betlman, *J. Am. Chem. Soc.*, **56**, 1850 (1934).

Synthesis of Cyclic Sulfides from Cyclic Carbonate Esters. I. Thietanes[1]

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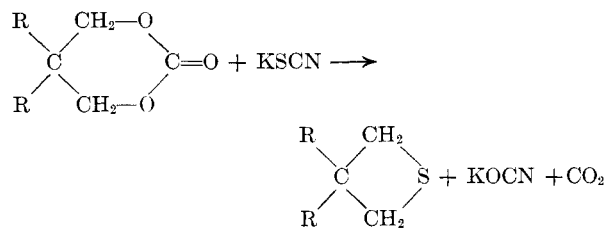
A new synthesis of thietanes by the reaction of a thiocyanate salt with the cyclic carbonate esters of 1,3-diols is described. The scope of the reaction and the nature of side reactions has been investigated.

The thermal decomposition of carbonate esters of 1,3-diols, forming oxetanes or allylic alcohols, with loss of carbon dioxide, has been observed to be markedly catalyzed by bases and by certain salts.[2,3] During the course of that study it was observed that the action of potassium thiocyanate led to a different type of reaction, in which a thietane, rather than an oxetane, was produced.[4] Potassium thiocyanate was consumed in equimolar quantities, and potassium cyanate was identified as a product:



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(3) D. B. Pattison, U. S. Patent 2,924,607 (February 9, 1960).