574. *Oxidation of Organic Sulphides. Part XII.*[1] *Inhibition of Squalene Autoxidation by Keto-sulphides and Keto-sulphoxides.*

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In a series of aliphatic keto-sulphides $R\cdot CO\cdot[CH_2]_n\cdot SR'$, where $n = 0$—4, only those homologues having $n = 2$ inhibit the thermal oxidation of squalene at 75°. The inhibitory action is really associated with the corresponding γ-keto-sulphoxides which are formed *in situ* after the absorption of a very small amount of oxygen. Factors bearing on this structural specificity are discussed.

AN earlier paper in this series [2] dealt with the effects of organic mono- and di-sulphides on the thermal autoxidation of olefins, mainly squalene; this work has now been extended to aliphatic keto-sulphides, $R\cdot CO\cdot[CH_2]_n\cdot SR'$. γ-Keto-sulphides have been claimed [3] as autoxidation inhibitors for edible fats and oils and other materials, but the reported structural dependence shows considerable difference from that observed with other sulphur compounds. Thus, keto-sulphides prepared from benzene- or tertiary alkane-thiols were less effective than those obtained from normal alkanethiols,[4] whereas, among dialkyl monosulphides, only di-t-butyl sulphide is an antioxidant and t-butyl or phenyl groups give maximum effects in a series of alkenyl alkyl (or aryl) monosulphides.[2] The antioxidant action of monosulphides has been shown to be due to the formation *in situ* of the corresponding sulphoxides,[2] and the generality of this behaviour has been investigated in the present system.

RESULTS

Antioxidant efficiencies are compared by using an arbitrary standard,[2] the retardation ratio, which is defined as the ratio of the times for squalene to absorb 1% w/w of oxygen with and without the additive, and thus the larger this ratio the more effective is the antioxidant. Autoxidations were carried out at 75° and 760 mm. oxygen pressure.

Variation in Position of Carbonyl Group.—The effect of the relative positions of carbonyl group and sulphur atom on the inhibition by keto-sulphides of squalene autoxidation is shown in Table 1.

TABLE 1.

Retardation ratios showing the effect of the position of the keto-group.

Keto-sulphide	0·25M	0·05M	Keto-sulphide	0·25M	0·05M
$Me\cdot CO\cdot SMe$	1·1	—	$Bu^t\cdot CO\cdot SBu^t$	1·1	—
$Me\cdot CO\cdot CH_2\cdot SMe$	0·8	1·1	$Bu^t\cdot CO\cdot CH_2\cdot SBu^t$	0·6	1·0
$Me\cdot CO\cdot[CH_2]_2\cdot SMe$	27	34	$Bu^t\cdot CO\cdot[CH_2]_2\cdot SBu^t$	330	160
$Me\cdot CO\cdot[CH_2]_3\cdot SMe$	1·4	1·1	$Bu^t\cdot CO\cdot[CH_2]_3\cdot SBu^t$	1·8	1·2
$Me\cdot CO\cdot[CH_2]_4\cdot SMe$	1·6	1·2	$Bu^t\cdot CO\cdot[CH_2]_4\cdot SBu^t$	2·0	1·2

Variation of Structure of γ-Keto-sulphides.—The antioxidant efficiencies of γ-keto-sulphides containing various alkyl groups are compared in Table 2. To minimise the time of each experiment the retardation ratios were measured at a keto-sulphide concentration of 0·01M. At this concentration autocatalytic autoxidation is resumed before the absorption of 1% of oxygen.

TABLE 2.

Retardation ratios showing the effect of the alkyl group.

$Me\cdot CO\cdot[CH_2]_2\cdot SMe$	26	$Me\cdot CO\cdot[CH_2]_2\cdot SBu^t$	42
$Me\cdot CO\cdot[CH_2]_2\cdot SEt$	70	$Bu^t\cdot CO\cdot[CH_2]_2\cdot SMe$	59
$Me\cdot CO\cdot[CH_2]_2\cdot SPr^i$	90	$Bu^t\cdot CO\cdot[CH_2]_2\cdot SBu^t$	42

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[1] Part XI, Barnard and Percy, *J.*, 1962, 1667.

[2] Barnard, Bateman, Cain, Colclough, and Cunneen, *J.*, 1961, 5339.

[3] U.S.P. 2,492,334—6.

[4] Thompson, *Ind. Eng. Chem.*, 1951, **43**, 1638; Thompson and Chenicek, *ibid.*, 1952, **44**, 1659.

Effect of Keto-sulphoxides on the Autoxidation of Squalene.—Antioxidant efficiencies of keto-sulphoxides are compared in Table 3, the retardation ratios being calculated from the times for absorption of 0·1% w/w of oxygen.

TABLE 3.

Retardation ratios of keto-sulphoxides (0·01M).

$\mathrm{Me{\cdot}CO{\cdot}CH_2{\cdot}SO{\cdot}Me}$	1·2	$\mathrm{Bu^t{\cdot}CO{\cdot}[CH_2]_2{\cdot}SO{\cdot}Bu^t}$	90
$\mathrm{Bu^t{\cdot}CO{\cdot}CH_2{\cdot}SO{\cdot}Bu^t}$	86	$\mathrm{Me{\cdot}CO{\cdot}[CH_2]_3{\cdot}SO{\cdot}Me}$	1·2
$\mathrm{Me{\cdot}CO{\cdot}[CH_2]_2{\cdot}SO{\cdot}Me}$	120	$\mathrm{Bu^t{\cdot}CO[CH_2]_3{\cdot}SO{\cdot}Bu^t}$	1·0

Effect of Concentration on the Antioxidant Action of Sulphur Compounds.—The higher efficiency of a γ-keto-sulphide, but not the corresponding sulphoxide, at low concentration in squalene at 75° is shown in Table 4.

TABLE 4.

Retardation ratios showing the effect of concentration.

Compound	$\mathrm{Bu_2{}^tS}$	$\mathrm{Bu_2{}^tSO}$	$\mathrm{Bu^t{\cdot}CO{\cdot}[CH_2]_2{\cdot}SBu^t}$	$\mathrm{Bu^t{\cdot}CO{\cdot}[CH_2]_2{\cdot}SO{\cdot}Bu^t}$
Ratio at 0·25M	256	—	330	—
,, 0·01M	1·5	24	42	28

Rates of Oxidation of Sulphides by t-Butyl Hydroperoxide.—Bimolecular velocity constants for the oxidation of di-t-butyl sulphide and 4-t-butylthiobutan-2-one in two solvents at 50° are compared in Table 5.

TABLE 5.

Bimolecular velocity constants for oxidation.

Sulphide	$\mathrm{Bu_2{}^tS}$		$\mathrm{Me{\cdot}CO{\cdot}[CH_2]_2{\cdot}SBu^t}$	
Solvent	MeOH	n-Heptane	MeOH	n-Heptane
10^5k_2 (l. mole^{-1} sec.$^{-1}$)	5·0 *	32	8·3	110

* From ref. 5.

DISCUSSION

The results confirm the view that among keto-sulphides only the γ-homologues have inhibitory action, and that structural changes in these compounds produce large changes in their efficiency (Tables 1 and 2). Thompson[4] suggested that this structural specificity may be due either to a special steric requirement, involving close approach of the sulphur atom to the carbonyl group, or to activation of the sulphur atom by the carbonyl group. The suggested steric requirement, although providing a plausible explanation for the lower efficiency of t-alkylthio-compounds, cannot account for the higher efficiency of the s-alkylthio-compound or, adequately, for the inertness of δ- and ε-keto-sulphides since examination of Stuart molecular models suggests that quasi-ring formation should be easier with the last compounds. The second suggestion is not supported by the work of Fehnel and Carmack,[6] who found that ultraviolet spectra of keto-sulphides show no evidence of electronic interaction between a sulphur atom and a carbonyl group separated by more than one methylene group.

Initial absorption of small amounts of oxygen by squalene–γ-keto-sulphide mixtures (Fig. 1) indicates that the effective antioxidant is formed from the γ-keto-sulphide during this period, and by analogy with the behaviour of alkyl monosulphides this would be expected to be the corresponding sulphoxide.[2] The presence of sulphoxides in the co-oxidation products was indicated by infrared absorption bands observed near 1050 cm.$^{-1}$ by a difference spectrum technique, and oxidation experiments with keto-sulphoxides prepared separately showed that in general only the γ-homologues are antioxidants (Table 3), no initial oxygen absorption then being necessary for this to be realised (Fig. 2).

[5] Barnard and Woodbridge, *Chem. and Ind.*, 1959, 1603.

[6] Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 84.

The apparent specific inhibition by γ-keto-sulphides is therefore due solely to the activity of the corresponding γ-keto-sulphoxides, this system thus conforming to the pattern established for other sulphides.[2] One exception is the β-keto-sulphoxide, $Bu^t\cdot CO\cdot CH_2\cdot SO\cdot Bu^t$ (Table 3), although it is derived from an inactive sulphide (Table 1). This probably reflects the special activating influence of the t-butyl groups, as found in alkyl sulphides.

The structural effects shown in Table 2 are probably due to differences in stability [7] and reactivity of the γ-keto-sulphoxides, while the extent of the initial oxygen absorption appears to depend on the alkylthio-group (Fig. 1) and may reflect differences in the rate of oxidation of the sulphur atom. It is noteworthy that other antioxidant sulphides are ineffective at concentrations as low as 0·01M, but the derived sulphoxides do not show similar differences (Table 4). The greater efficiency of γ-keto-sulphides at these low concentrations is probably due to their more rapid conversion into sulphoxide in a non-polar medium, although rates of oxidation do not differ appreciably in a polar solvent such as methanol (Table 5). This enhanced reaction rate may be explained by preliminary association of hydroperoxide and carbonyl compound in the non-polar solvent, whereas such association is not possible with di-t-butyl sulphide.

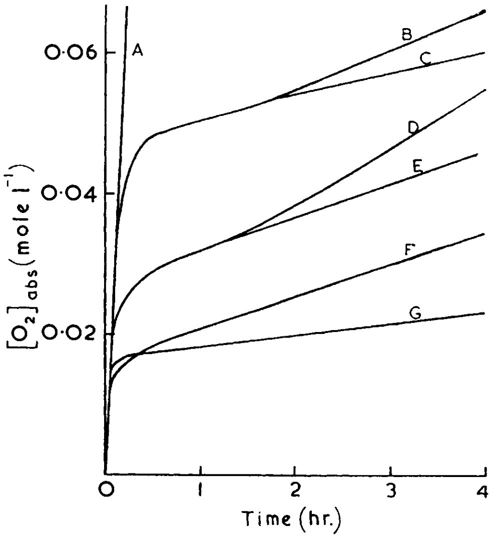

FIG. 1.

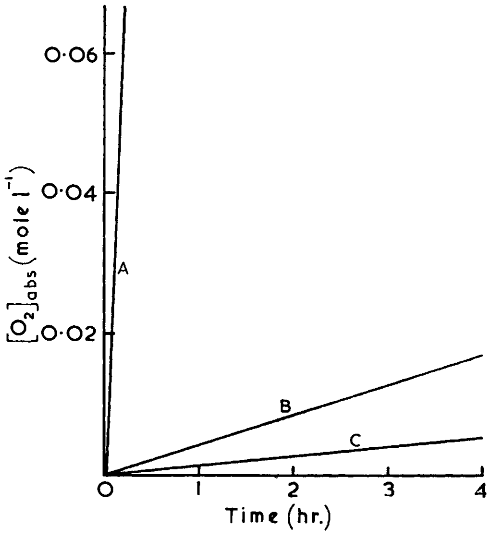

FIG. 2.

FIG. 1. Autoxidation of squalene containing γ-keto-sulphides (0·01M) at 75°/760 mm.
(A) No addition. (B) $Bu^t\cdot CO\cdot[CH_2]_2\cdot SBu^t$. (C) $Me\cdot CO\cdot[CH_2]_2\cdot SBu^t$. (D) $Me\cdot CO\cdot[CH_2]_2\cdot SMe$. (E) $Bu^t\cdot CO\cdot[CH_2]_2\cdot SMe$. (F) $Me\cdot CO\cdot[CH_2]_2\cdot SEt$. (G) $Me\cdot CO\cdot[CH_2]_2\cdot SPr^i$.

FIG. 2. Autoxidation of squalene containing keto-sulphoxides (0·01M) at 75°/760 mm.
(A) No addition, or $Me\cdot CO\cdot CH_2\cdot SO\cdot Me$, or $Me\cdot CO\cdot[CH_2]_3\cdot SO\cdot Me$, or $Bu^t\cdot CO\cdot[CH_2]_3\cdot SO\cdot Bu^t$. (B) $Bu^t\cdot CO\cdot[CH_2]_2\cdot SO\cdot Bu^t$. (C) $Me\cdot CO\cdot[CH_2]_2\cdot SO\cdot Me$.

EXPERIMENTAL

The oxidation apparatus was essentially that of Bateman and Cunneen,[8] and, together with the technique, is fully described elsewhere.[9]

Infrared spectra were recorded on a Hilger H.800 double-beam spectrometer.

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[7] Cain, Colclough, and Cunneen, unpublished work.
[8] Bateman and Cunneen, *J.*, 1955, 1596.
[9] Cain, M.Sc. Thesis, London, 1959.

Kinetics of Sulphide Oxidation by t-Butyl Hydroperoxide.—The rate constant in methanol was obtained by following the concentration of t-butyl hydroperoxide (initially 0·1M) in the presence of an excess of 4-t-butylthiobutan-2-one (0·5M) in methanol at 50° by Barnard and Hargrave's method.[10] A different technique was used for reactions in n-heptane, as follows. Aliquot parts (3—5 ml.) of a solution of the sulphide (0·05M) and t-butyl hydroperoxide (0·25M) at 50° were removed and washed once with saturated sodium hydrogen carbonate solution (10 ml.). Sulphide concentrations in the resulting sulphoxide- and hydroperoxide-free heptane solutions were determined by infrared spectroscopy, by using the carbonyl band (for 4-t-butylthiobutan-2-one), or by gas–liquid chromatography (for di-t-butyl sulphide) with n-decane as an internal standard.[11]

Storage and Treatment of Materials.—Compounds used in oxidation experiments were stored under nitrogen in sealed tubes, except squalene, which was stored *in vacuo*, and the keto-sulphoxides, which were kept in stoppered flasks at −20°. The last compounds, being hygroscopic, were handled in a dry-box. Immediately before use all liquids were freed from possible peroxidised material by passage through small columns of chromatographic alumina.

Materials.—Squalene was obtained as previously described.[2] 5-Bromopentan-2-one [12] had b. p. 71·5—73°/10 mm., n_D^{20} 1·4684 (Found: C, 36·5; H, 5·45. Calc. for C_5H_9BrO: C, 36·4; H, 5·5%). 6-Bromohexan-2-one [13] had b. p. 100—105°/15 mm., n_D^{20} 1·4668 (Found: Br, 41·8. Calc. for $C_6H_{11}BrO$: Br, 44·2%). Pivaloyl chloride, prepared by Brown's method,[14] had b. p. 102—104°. 1-Bromo-3,3-dimethylbutan-2-one, b. p. 58°/4 mm., and 1-chloro-4,4-dimethylpentan-3-one, b. p. 67—69°/11 mm., n_D^{20} 1·4408 (Found: C, 56·8; H, 9·0; Cl, 23·5. Calc. for $C_7H_{13}ClO$: C, 56·6; H, 8·8; Cl, 23·9%), were prepared from pinacolone by the methods of Boyer and Straw [15] and Cologne,[16] respectively. 2-Chloroethyl t-butyl sulphide, b. p. 79—80°/26 mm., n_D^{20} 1·4782 (Found: Cl, 23·3; S, 21·0. Calc. for $C_6H_{13}ClS$: Cl, 23·3; S, 21·0%), was obtained by Dawson's method.[17] 2,2-Dimethylhept-6-en-3-one [18] had b. p. 69—70°/15 mm., n_D^{20} 1·4324 (Found: C, 75·7; H, 10·8. Calc. for $C_9H_{16}O$: C, 77·1; H, 11·5%).

Keto-sulphides.—Most of these compounds were obtained by one of two general methods, which are each illustrated by one example. Other methods are described individually. The purified keto-sulphides were characterised by elemental and spectroscopic analysis, and, where possible, by the preparation and analysis of their 2,4-dinitrophenylhydrazones (Tables 6 and 7). The purity of all the compounds was checked by analysis, but these data are given for the new compounds only.

TABLE 6.

			Found (%)				Required (%)		
Keto-sulphide	B. p./mm.	n_D^{20}	C	H	S	Formula	C	H	S
$Me\cdot CO\cdot SMe$	98°/760	1·4624	—	—	—	—	—	—	—
$Bu^t\cdot CO\cdot SBu^t$	174°/760	1·4538	62·3	10·5	18·4	$C_9H_{18}OS$	62·0	10·4	18·4
$Me\cdot CO\cdot CH_2\cdot SMe$	153°/760	1·4738	—	—	—	—	—	—	—
$Bu^t\cdot CO\cdot CH_2\cdot SBu^t$	100°/11	1·4635	63·4	10·9	17·1	$C_{10}H_{20}OS$	63·8	10·7	17·0
$Me\cdot CO\cdot[CH_2]_2\cdot SMe$	70°/9	1·4742	—	—	—	—	—	—	—
$Me\cdot CO\cdot[CH_2]_2\cdot SEt$	84°/14	1·4724	—	—	—	—	—	—	—
$Me\cdot CO\cdot[CH_2]_2\cdot SPr^i$	89°/10	1·4663	57·2	9·8	21·6	$C_7H_{14}OS$	57·5	9·65	21·9
$Me\cdot CO\cdot[CH_2]_2\cdot SBu^t$	112°/18	1·4655	60·0	10·0	19·8	$C_8H_{16}OS$	59·9	10·1	20·0
$Bu^t\cdot CO\cdot[CH_2]_2\cdot SMe$	97°/11	1·4680	60·2	10·1	19·9	,,	,,	,,	,,
$Bu^t\cdot CO\cdot[CH_2]_2\cdot SBu^t$	124°/15	1·4627	65·3	10·7	16·1	$C_{11}H_{22}OS$	65·3	11·0	15·8
$Me\cdot CO\cdot[CH_2]_3\cdot SMe$	88°/10	1·4730	—	—	—	—	—	—	—
$Bu^t\cdot CO\cdot[CH_2]_3\cdot SBu^t$	137°/14	1·4657	66·8	11·0	15·3	$C_{12}H_{24}OS$	66·6	11·2	14·8
$Me\cdot CO\cdot[CH_2]_4\cdot SMe$	112°/14	1·4742	57·6	9·7	21·9	$C_7H_{14}OS$	57·5	9·65	21·9
$Bu^t\cdot CO\cdot[CH_2]_4\cdot SBu^t$	154°/12	1·4655	67·9	11·4	13·9	$C_{13}H_{26}OS$	67·8	11·4	13·9

(1) *From halogeno-ketone and sodium mercaptide:* 3,3-*dimethyl*-1-*t-butylthiobutan*-2-*one*. 2-Methylpropane-2-thiol (0·12 mole) was added rapidly with vigorous stirring to sodium

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[10] Barnard and Hargrave, *Analyt. Chim. Acta*, 1951, **5**, 576.

[11] Cain, Evans, and Lee, *J.*, 1962, 1694.

[12] Bacchetti and Fiecchi, *Gazzetta*, 1953, **83**, 1037.

[13] Anderson, Crawford, and Sherrill, *J. Amer. Chem. Soc.*, 1946, **68**, 1294.

[14] Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325.

[15] Boyer and Straw, *J. Amer. Chem. Soc.*, 1952, **74**, 4506.

[16] Cologne, *Bull. Soc. chim. France*, 1936, **3**, 2116.

[17] Dawson, *J. Amer. Chem. Soc.*, 1947, **69**, 1211.

[18] Haller and Bauer, *Compt. rend.*, 1910, **150**, 582.

TABLE 7.

2,4-Dinitrophenylhydrazones of keto-sulphides.

		Found (%)					Required (%)			
Keto-sulphide	M. p.	C	H	N	S	Formula	C	H	N	S
Me·CO·CH_2·SMe	111—112°	42·2	4·3	20·2	11·5	$C_{10}H_{12}N_4O_4S$	42·2	4·25	19·7	11·3
Bu^t·CO·CH_2·SBu^t	160—162	52·5	6·9	—	8·7	$C_{16}H_{24}N_4O_4S$	52·2	6·6	—	8·75
Me·CO·$[CH_2]_2$·SMe	100—101	—	—	—	—	—	—	—	—	—
Me·CO·$[CH_2]_2$·SEt	90—91	—	—	—	—	—	—	—	—	—
Me·CO·$[CH_2]_2$·SPr^i	80—82	47·8	5·6	—	9·6	$C_{13}H_{18}N_4O_4S$	47·8	5·6	—	9·8
Me·CO·$[CH_2]_2$·SBu^t	92—93	49·2	5·8	—	9·0	$C_{14}H_{20}N_4O_4S$	49·4	5·9	—	9·4
Bu^t·CO·$[CH_2]_2$·SMe	124—125	49·3	6·0	—	9·5	,,	,,	,,	—	,,
Bu^t·CO·$[CH_2]_2$·SBu^t	117—118	53·7	7·1	14·6	9·0	$C_{17}H_{26}N_4O_4S$	53·4	6·85	14·7	8·4
Me·CO·$[CH_2]_3$·SMe	93—94	—	—	—	—	—	—	—	—	—
Bu^t·CO·$[CH_2]_3$·SBu^t	138—139	54·5	7·2	—	8·1	$C_{18}H_{28}N_4O_4S$	54·5	7·1	—	8·1
Me·CO·$[CH_2]_4$·SMe	64—65	47·8	5·6	—	9·85	$C_{13}H_{18}N_4O_4S$	47·8	5·6	—	9·8
Bu^t·CO·$[CH_2]_4$·SBu^t	92—93	55·6	7·3	—	7·8	$C_{19}H_{30}N_4O_4S$	55·6	7·4	—	7·8

(0·11 g.-atom) in ethanol (85 ml.), the mixture boiled under reflux for 20 min. and then cooled to room temperature, and 1-bromo-3,3-dimethylbutan-2-one (0·11 mole) added slowly. After boiling under reflux for a further 20 min., the mixture was cooled and poured into water (100 ml.), the layers were separated, and the aqueous layer was saturated with salt and extracted with ether (3 × 50 ml.). The combined organic layer and ether extracts were washed once with brine, dried, and distilled.

(2) *From methyl vinyl ketone and thiol:* 4-*isopropylthiobutan*-2-*one.* Methyl vinyl ketone (0·28 mole), propane-2-thiol (0·28 mole), and pyridine (4 drops) were mixed and warmed to 60°, the vigorous reaction maintaining this temperature for *ca.* 30 min. After cooling, the mixture was washed twice with 0·5% sulphuric acid (10 ml.), dried, and distilled.

S-*Methyl thioacetate.* This was prepared from methanethiol and acetic anhydride by Wenzel and Reid's method,[19] the product being worked up as in method (1).

2,2-*Dimethyl*-6-*t-butylthiohexan*-3-*one.* Finely powdered sodamide (0·15 mole) was added slowly to pinacolone (0·15 mole) in refluxing anhydrous ether (100 ml.), and heating continued for a further 2½ hr. Addition of 2-chloroethyl-t-butyl sulphide gave no precipitate. The ether was replaced by benzene (distillation), and the benzene solution boiled under reflux for 1½ hr. during which a precipitate appeared. The mixture was worked up as in method (1).

2,2-*Dimethyl*-7-*t-butylthioheptan*-3-*one.* A mixture of 2,2-dimethylhept-6-en-3-one (0·046 mole), 2-methyl-2-propanethiol (0·067 mole), 8-*p*-menthyl hydroperoxide (3 drops), and tetraethylenepentamine (1 drop) was boiled under reflux for 4 hr. Distillation gave unchanged thiol (3 g.) and ketone (4 g.), and a fraction (4·5 g.) of b. p. 138—156°/14 mm. The last was combined with a similar fraction obtained by treating the recovered ketone with more thiol, as above, and distilled.

Keto-sulphoxides.—These were prepared by oxidation of the corresponding keto-sulphides with hydrogen peroxide in acetone.[20] They were purified by distillation at room temperature from a pot still at 10^{-3} mm., or by recrystallisation from light petroleum, as appropriate, and were characterised by elemental, titrimetric,[20] and spectroscopic analysis (Table 8).

TABLE 8.

Sulphoxides.

Keto-sulphoxide	M. p.	Found: S (%)	Formula	Reqd.: S (%)	SO content (%), Found
Bu^t·CO·CH_2·SO·Bu^t	62—63°	15·6	$C_{10}H_{20}O_2S$	15·7	100
Me·CO·CH_2·SO·Me *	—	—	—	—	75
Me·CO·$[CH_2]_2$·SO·Me	28—29	23·7	$C_5H_{10}O_2S$	23·9	100
Bu^t·CO·$[CH_2]_2$·SO·Bu^t	84—85	14·7	$C_{11}H_{22}O_2S$	14·7	98
Me·CO·$[CH_2]_3$·SO·Me	30—31	21·7	$C_6H_{12}O_2S$	21·6	100
Bu^t·CO·$[CH_2]_3$·SO·Bu^t	64—65	14·5	$C_{12}H_{24}O_2S$	13·8	100

* Could not be purified.

THE NATURAL RUBBER PRODUCERS' RESEARCH ASSOCIATION,
48—56, TEWIN ROAD, WELWYN GARDEN CITY, HERTS.

[*Received, January* 22*nd*, 1962.]

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[19] Wenzel and Reid, *J. Amer. Chem. Soc.*, 1937, **59**, 1089.

[20] Barnard and Hargrave, *Analyt. Chim. Acta*, 1951, **5**, 536.