as an ether-insoluble residue. From the ether solution 118 mg. (48%) of VIIa crystallized after evaporation of the solvent.

VIIa. Reaction 7c.—Compound Va (50 mg., 0.13 mmole) and 100 mg. of potassium *t*-butoxide were dissolved in 0.4 ml. of *t*-butyl alcohol and 1.6 ml. of DMSO. The reaction mixture was kept under nitrogen at 75° for 2 hr. Addition of 10 ml. of water yielded an emulsion which was shaken with 3 ml. of ether. The crystalline product which separated from the ether–water mixture was separated after 2 days. Recrystallization from hot ethanol gave 19 mg. (48%) of VIIa, m.p. 103°. The infrared spectrum was identical with that of compounds prepared in reactions 7, 7a, and 7b.

VIIb and IVb (R' = R = C_6H_5). Reactions 4a and 7a.—Diphenylmethane (1.68 g., 10 mmoles) and 1.12 g. of potassium *t*-butoxide were dissolved under nitrogen at 60° in 15 ml. of DMSO. Benzaldehyde (1.0 g., 10 mmoles) in 5 ml. of DMSO was added over a period of 15 min. The color of the solution changed from red to green during the addition. The mixture was kept at room temperature for 30 min. after which time 100 ml. of ice–water was added. The mixture was extracted with 300 ml. of ether. Separation and evaporation of the ether layer yielded a yellow oil which contained colorless crystals. The oily residue was treated with few cc. of ether and filtered, yielding 155 mg. of IVb (5%). The m.p. after recrystallization from a chloroform–methanol mixture was 195–196°.

Anal. Calcd. for $C_{22}H_{22}OS$ (334.40): C, 79.01; H, 6.63; S, 9.52. Found: C, 78.98; H, 6.72; S, 9.21.

The oil obtained after evaporation of the filtrate was heated with ethanol, yielding 430 mg. of VIIb (15.8%), m.p. 88–90°; lit.[20] m.p. 87–89°; 92–93°.

Anal. Calcd. for $C_{21}H_{18}$ (270.35): C, 93.29; H, 6.71. Found: C, 93.39; H, 6.94; mol. wt. (dioxane), 294.

VIIc (R' = C_6H_5, R = 3,4-$CH_2O_2C_6H_3$). Reaction 7a.—Diphenylmethane (1.68 g., 10 mmoles) and 1.12 g. of potassium *t*-butoxide were dissolved in 15 ml. of DMSO and 60°. From a buret 1.5 g. of piperonal (10 mmoles) in 5 ml. of DMSO was added over a period of 13 min. The reaction mixture, which turned red and finally green-brown, was kept at room temperature for 30 min. After addition of 100 ml. of ice–water the mixture was extracted with 600 ml. of ether. Evaporation of the ether layer yielded an oil which upon treatment with ethanol gave 600 mg. of crude VIIc (19%). The substance was recrystallized from a hot ethanol–chloroform mixture to give VIIc, m.p. 123–125°.

Anal. Calcd. for $C_{22}H_{18}O_2$ (314.6): C, 84.05; H, 5.77. Found: C, 83.87; H, 5.89.

Condensation between *p*-Anisaldehyde, DMSO, and Cyclohexanone. (VIII).—*p*-Anisaldehyde (2.8 ml., 20 mmoles) was added to a solution of 2.75 g. of potassium *t*-butoxide in 15 ml. of DMSO at 60° under nitrogen. After 5 min. at 60°, 2 ml. of cyclohexanone (20 mmoles) was added to the brown solution. After 30 min. at 60°, 100 g. of ice was added to the reaction mixture and the mixture extracted with 200 ml. of ether. From the ether solution 380 mg. of VIII separated (6.5%), m.p. 275°. Recrystallization from ethanol by the addition of a little chloroform gave a compound, m.p. 275–276°. The infrared and n.m.r. spectra were consistent with structure VIII. The n.m.r. spectrum failed to show a methyl group other than that of the *p*-methoxy group.

Anal. Calcd. $C_{15}H_{22}O_3S$ (294.34): C, 65.29; H, 7.53; S, 10.82. Found: C, 65.31; H, 7.69; S, 11.00.

Di-9-fluorenylphenylmethane.—Benzaldehyde (0.3 ml., 3 mmoles) was added to a solution of 499 mg. of fluorene (3 mmoles) in 7.5 ml. of DMSO containing 0.37 g. of sublimed potassium *t*-butoxide under a nitrogen atmosphere. The red solution turned blue after 6 min. at room temperature. At this time 100 ml. of water was added and the resulting solution extracted with 600 ml. of ether. Evaporation of the ether solution gave crystals which after recrystallization from a mixture of ethanol and chloroform yielded 74 mg. (9%) of di-9-fluorenylphenylmethane, m.p. 230°, lit.[13] 239°. The n.m.r. shows an A_2B pattern of methine protons with the benzylic proton absorbing as a triplet (J_{AB} = 7.6 c.p.s. at 60 Mc./sec.) at τ = 6.8 and the 9-fluorenyl protons absorbing as a doublet at τ = 5.0.

Di-9-fluorenyl-*p*-methoxyphenylmethane.—*p*-Anisaldehyde (0.4 ml., 3 mmoles) was added to 499 mg. (3 mmoles) of fluorene dissolved in 7.5 ml. of DMSO under nitrogen. The addition of 366 mg. of potassium *t*-butoxide resulting in warming and the development of a red color which turned to a blue (reminiscent of fluorenyl ketyl) after 15 min. When the blue color developed, 100 ml. of water was added to give a yellow emulsion which was extracted with 200 ml. of ether. Evaporation of the ether extract to 30 ml. yielded 400 mg. (70%) of di-9-fluorenyl-*p*-methoxyphenylmethane, m.p. 230–232°. The n.m.r. spectrum appears unequivocal for this structure since it shows an A_2B pattern for the three methine hydrogens. The *p*-methoxybenzyl hydrogen appeared as a triplet at τ = 6.8, J_{AB} = 6.9 c.p.s. at 60 Mc./sec., area = 1.0; the 9-fluorenyl hydrogens absorbed as a doublet at τ = 5.05, area = 2.0; methoxy protons at τ = 6.4, area = 3.0; *p*-methoxyphenyl protons (A_2B_2) at τ = 3.6, area = 4.0; and fluorenyl ring protons as a complex absorption between 420 and 480 c.p.s. relative to tetramethylsilane, area = 16.

1-Benzoyl-2-phenyl-3-(methylsulfonyl)-propane.—To 0.53 g. of benzaldehyde (5 mmoles) in 15 ml. of DMSO, 1.12 g. of potassium *t*-butoxide and 0.54 g. (5 mmoles) of acetophenone were added. After 1 hr. at 30–35°, 100 ml. of water was added and the resulting emulsions extracted with 300 ml. of ether. The ether was evaporated to yield an oil which did not readily crystallize. After 10 days in an open vessel, the oil crystallized to give 70 mg. (15%) of 1-benzoyl-2-phenyl-3-(methylsulfonyl)-propane, m.p. 125–126°, recrystallized from ethanol. The infrared showed sulfone and carbonyl absorptions. The n.m.r. (60 Mc./sec.) showed one methyl group (τ = 7.5), area 3.0 units; aromatic protons 438 to 480 c.p.s. relative to tetramethylsilane, area 10.1 units; and a complicated 5-proton absorption (area = 5.1 units) between 155 and 266 c.p.s. relative to tetramethylsilane. The complexity of the 5-proton area is undoubtedly due to the presence of two methylene groups attached to an asymmetric methine group.

Anal. Calcd. $C_{17}H_{18}O_3S$ (302.37): C, 67.54; H, 6.00; S, 10.60. Found: C, 67.78; H, 5.94; S, 10.30.

(20) W. Schlenk and E. Bergmann, *Ann.*, **463**, 1 (1928); K. Ziegler, H. Grabbe, and F. Ulrich, *Ber.*, **57**, 1983 (1924).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY, AMES, IOWA]

Preparation and Pummerer Rearrangement of β-Ketosulfoxides[1,2]

BY HANS-DIETER BECKER, GERARD J. MIKOL, AND GLEN A. RUSSELL[3]

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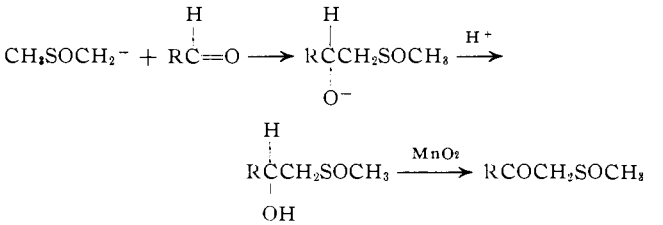
The preparation of β-ketosulfoxides from aromatic esters and dimethyl sulfoxide is described. Acid-catalyzed rearrangement of these β-ketosulfoxides leads to the formation of methyl hemimercaptals of α-ketoaldehydes. The mechanism of this rearrangement is discussed.

Introduction

The carbanion formed in solutions of dimethyl sulfoxide (DMSO) containing bases such as sodium hydride or alkali metal alkoxides, undergoes reaction with carbonyl compounds such as aldehydes or ketones.[4] β-Hydroxysulfoxides formed in this manner can be oxidized to β-ketosulfoxides by active manganese dioxide.[5] We have found that β-ketosulfoxides can



(1) Reactions of Resonance Stabilized Anions. X.

(2) This work was supported by grants from the Alfred P. Sloan Foundation and the Air Force Office of Scientific Research.

(3) Alfred P. Sloan Foundation Fellow, 1959–1963.

(4) (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962); (b) G. A. Russell, E. G. Janzen, H.-D. Becker, and F. S. Smentowski, *ibid.*, **84**, 2652 (1962).

(5) G. A. Russell and H.-D. Becker, *ibid.*, **85**, 3406 (1963).

be more conveniently prepared by the reaction of the methylsulfinyl carbanion with an aromatic ester in DMSO solution.

$$CH_3SOCH_2^- + RCO_2R' \xrightarrow{DMSO} \underset{I}{CH_3SOCH_2COR} + R'O^-$$

β-Ketosulfoxides are intermediates for the formation of glyoxals *via* the Pummerer rearrangement.[6] The resulting hemimercaptals of glyoxals (II) in aqueous

$$RCOCH_2SOCH_3 \xrightarrow{H^+} \underset{OH\ \ II}{RCOCHSCH_3}$$

solution give reactions typical of glyoxals such as osazone formation. This condensation followed by the Pummerer rearrangement furnishes a convenient route to ninhydrin.[7]

Results

Ethyl benzoate reacts with a mixture of potassium *t*-butoxide and DMSO to form the β-ketosulfoxide Ia (R = phenyl), isolated in 72% yield by extraction after careful acidification of the reaction mixture to a pH of 5–6. On the other hand, when the reaction mixture was acidified to pH 1, the methyl hemimercaptal of phenylglyoxal (IIa, R = phenyl) crystallized directly from the solution in a high state of purity and in good yield. Acidification of the reaction solution was necessary in any case since β-ketosulfoxides are ionized in basic solution and cannot be extracted by organic solvents.

Starting from methyl *p*-anisate the β-ketosulfoxide Ib (R = *p*-methoxyphenyl) was formed in 74% yield. The methyl hemimercaptal of *p*-methoxyphenylglyoxal (IIb, R = *p*-methoxyphenyl) was obtained in 82% yield by the acid-catalyzed rearrangement of Ib in DMSO solution. Treatment of Ib with strong aqueous hydrochloric acid resulted in the formation of the hemihydrate of *p*-methoxyphenylglyoxal.[8]

Methyl *p*-toluate reacts to give the expected ketosulfoxide Ic (R = *p*-tolyl) or its acid-catalyzed rearrangement product, the methyl hemimercaptal IIc, (R = *p*-tolyl). The yields are good and there is no evidence of side reactions involving the methyl *p*-toluate anion ($CH_3O_2CC_6H_4CH_2^-$) which could have condensed with methyl *p*-toluate to give a polyketone. The self-condensation of methyl *p*-toluate was carefully studied because of possible implications in the autoxidation of this substance in basic solution.[4b] No evidence of self-condensation or of β-ketosulfoxide formation could be found in DMSO (80%)–*t*-butyl alcohol (20%) solution at 70° whereas in 100% DMSO only the β-ketosulfoxide (Ic) was formed. In DMSO (95%)–*t*-butyl alcohol (5%) at 70° for 6 hr. a 9% yield of *p*-carbomethoxybenzyl *p*-tolyl ketone

$$2CH_3C_6H_4CO_2CH_3 \xrightarrow[-(CH_3OH)]{OR^-} CH_3C_6H_4COCH_2C_6H_4CO_2CH_3$$

and a 40% yield of Ic were obtained. No polyketone was formed, probably because the first ketoester forms a very stable anion due to the acidic methylene group, and the probability of ionization of the methyl protons is hence quite low. This ionization must also stabilize the ketone against forming an adduct with dimethyl sulfoxide.[4] In other aprotic, polar solvents, such as dimethylformamide and hexamethylphosphoramide, yields of the ketoester in excess of 50% have been achieved (see Experimental section).

(6) (a) R. Pummerer, *Ber.*, **42**, 2282 (1909); (b) *ibid.*, **43**, 1401 (1910).
(7) H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963).
(8) H.-D. Becker and G. A. Russell, *ibid.*, **28**, 1895 (1963).

The β-ketosulfoxide Id (R = *o*-hydroxyphenyl) was prepared in low yield from methyl salicylate. Although when recrystallized Id is completely stable at room temperature, impure samples (filtered directly from the acidified solution and washed with ethanol) in sealed containers form a brown oil after several months of storage. The methyl mercaptal of *o*-hydroxyphenylglyoxal (IIId) was isolated in 60% yield from such a product. The methyl mercaptal of phenylglyoxal (IIIa) is easily prepared in 70% yield by treatment of Ia with

$$R\text{–}CO\text{–}CH(SCH_3)_2$$

IIIa, R = phenyl
d, R = *o*-hydroxyphenyl

strong hydrochloric acid. The phenylosazones of phenylglyoxal, *p*-methoxyphenylglyoxal, and *p*-methylphenylglyoxal were formed in high yields (90%) by treatment of IIa, IIb, or IIc with phenylhydrazine in boiling ethanol containing a trace of hydrochloric acid.

Discussion

The rearrangement and cleavage of sulfoxides containing a β-carbonyl function was first recognized by Pummerer[6a] who discovered that phenylsulfinylacetic acid forms thiophenol and glyoxylic acid under the influence of warm dilute mineral acids, while treatment with anhydrous hydrogen chloride gives α-chloro-S-phenylthioglycolic acid. An intramolecular rearrangement mechanism proposed by Pummerer has recently been supported by Walker and Leib.[9] The reaction of ethyl phenylsulfinylacetate with acetic anhydride leading to α-acetoxy-S-phenylthioglycolic acid was first discovered by Pummerer.[6b] Horner and Kaiser later studied the scope of this reaction between sulfoxides and acid anhydrides.[10]

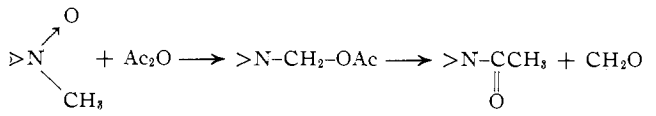
A mechanism for the acid-catalyzed rearrangement of ketosulfoxides, involving a primary cleavage into ketoaldehyde and mercaptan, was proposed recently.[11] However, the rearrangement of sulfoxides of pyrimidothiazines reported by Schroeder and Dodson[12] makes the cleavage–recombination mechanism unlikely. Some of the earlier rearrangement experiments[6a,11] were carried out under rather drastic conditions, for example boiling in acetic acid or 6 *N* sulfuric acid for 1 or 2 days. In these cases the different compounds obtained (cleavage products, mercaptals) might be used to support the cleavage–recombination mechanism. However, we have shown that the rearrangement of I into II occurs under mild conditions at room temperature, and that the formation of the mercaptals III is due to an acid-catalyzed decomposition reaction of initially formed II. In our hands no evidence was found for a free arylglyoxal during rearrangement.

The Pummerer rearrangement seems to be related to the rearrangement of chlorosulfonium chlorides,[13] as

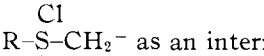
$$RSCH_3 + Cl_2 \text{ (or } SO_2Cl_2, SOCl_2) \longrightarrow \left[\begin{matrix} & Cl & \\ R & | & CH_3 \\ & S & \end{matrix}\right]^+ Cl^- \longrightarrow \underset{RSCH_2Cl + HCl}{}$$

well as the reaction of amine oxides with acid anhydrides.[14] In the first case the Böhme mechanism in-

(9) D. Walker and J. Leib, *Can. J. Chem.*, **40**, 1242 (1962).
(10) L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959); see also, W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961); W. R. Sorenson, *J. Org. Chem.*, **24**, 978 (1959).
(11) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961).
(12) E. F. Schroeder and R. M. Dodson, *ibid.*, **84**, 1904 (1962).
(13) (a) H. Böhme, H. Fischer, and R. Frank, *Ann.*, **563**, 54 (1949); H. Böhme and H.-J. Gran, *ibid.*, **577**, 68 (1952); (b) W. E. Truce, G. H. Birum, and E. T. McBee, *J. Am. Chem. Soc.*, **74**, 3594 (1952); (c) F. G. Bordwell and B. M. Pitt, *ibid.*, **77**, 572 (1955).
(14) M. and M. Polonovski, *Compt. rend.*, **184**, 331 (1927); *Bull. soc. chim. France*, **41**, 1190 (1927).

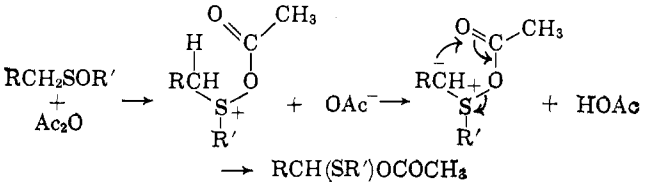


volving an intramolecular rearrangement of the chlorine atom seems well substantiated since Truce, Birum, and McBee found that in the presence of molecular bromine that the rearrangement to give the α-chlorosulfide proceeded normally.[13b] The rearrangement of the chlorosulfonium chloride has been pictured as involving

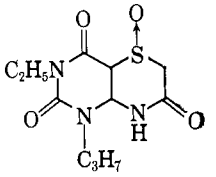


as an intermediate followed by a "downhill ride of the chloronium ion from sulfur to carbon on an electron cloud."[13c]

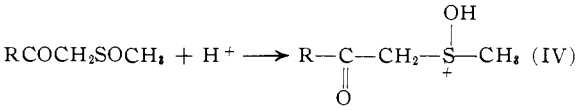
In the case of rearrangements involving the use of acetic anhydride the Pummerer rearrangement seems to present no mechanistic problems and can be readily formulated as involving a cyclic intermediate.[13c] How-



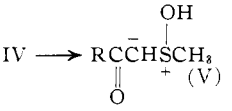
ever, the rearrangements of sulfoxides directly to hemimercaptals under the mild conditions employed in this work, as well as the analogous rearrangements observed in the recrystallization of 1-propyl-3-ethyl-1*H*-pyrimido[5,4-b][1,4]thiazine-2,4,7-(3*H*,6*H*,8*H*)-trione 5-oxide



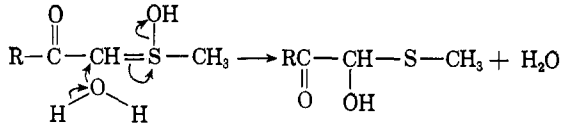
from methanol, ethanol, acetic acid, or water with the formation of α-methoxy, α-ethoxy, α-acetoxy, and α-hydroxy derivatives,[12] is not as easily understood. In our work the need for catalysis by a mineral acid certainly suggests protonation prior to rearrangement. The fact that Ia rearranges readily under conditions



where Ib is stable, strongly suggests the loss of a proton from the methylene group prior or during rearrangement. In fact, Schroeder and Dodson have reported

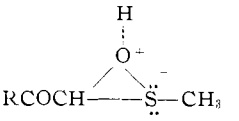


examples of base-catalyzed "rearrangements" in the pyrimidothiazines.[12] Intermediate V could rearrange directly to the α-hydroxysulfide by the migration of the HO^+ moiety. Alternately, V could ionize to $RCO-CH{=}SCH_3^+$ as suggested by Schroeder and Dodson.[12] A third alternative is that V undergoes nucleophilic attack by the solvent. We are currently attempting

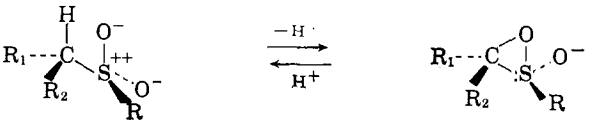


to ascertain the source of the hydroxy group in the final product by isotopic labeling.

If the conversion of ketosulfoxides to hemimercaptals does indeed involve a true intramolecular rearrangement without participation by the solvent, an intermediate or transition state of the type would be in-



dicated. This would seem to have considerable implication in regard to the stereochemistry of carbanions α to the sulfone group. The observation that such carbanions can maintain the stereochemistry of the original alkyl substituent[15] could be explained if the carbanion has the cyclic structure.



Experimental[16]

Reagents.—Dimethyl sulfoxide (Crown Zellerbach Corp.) was dried over calcium hydride and distilled at 1 mm. (bath temperature 60°, b.p. 35°) immediately before use. Ethyl benzoate and methyl salicylate were distilled and methyl *p*-anisate was recrystallized before use. The potassium *t*-butoxide was vacuum sublimed.

ω-(Methylsulfinyl)-acetophenone (Ia).—Potassium (2 g., 51 mg.-atoms) was dissolved in 50 ml. of refluxing *t*-butyl alcohol. After cooling to room temperature, 50 ml. of DMSO was added and the solution vacuum distilled (pressure about 2 mm., bath temperature 65–70°) using a Vigreux column until pure DMSO started distilling (b.p. 43°). Approximately 50 ml. of distillate was collected. To the partially solid residue ethyl benzoate (7.5 g., 50 mmoles) was added dropwise at room temperature. The reaction mixture was agitated by a stream of dry, oxygen-free nitrogen for a total of 4 hr. The solvent was then removed by vacuum distillation (~1 mm. pressure, bath temperature 75°) during 1.5 hr. Ether (100 ml.) and water (50 ml.) were added to the oily yellowish residue at room temperature. The aqueous layer was separated and acidified to pH 5–6 (indicator paper) with a mixture of 5 ml. of concentrated hydrochloric acid and 20 ml. of water. The aqueous solution was extracted with five 200-ml. portions of chloroform. Evaporation of the chloroform yielded a slightly yellow-colored oil from which solvent was removed under vacuum at 2 mm. The solid residue obtained was washed with 100 ml. of ether, filtered, and dried to give 6.55 g. of Ia as colorless crystals (yield 72%), m.p. 85°.

Anal. Calcd. for $C_9H_{10}O_2S$ (182.17): C, 59.33; H, 5.53; S, 17.56. Found: C, 59.62; H, 5.76; S, 17.45.

ω-(Methylsulfinyl)-*p*-methoxyacetophenone (Ib).—The solution of potassium *t*-butoxide was prepared as described for the preparation of Ia. To this mixture (containing 51 mmoles of potassium *t*-butoxide) 4.78 g. of methyl *p*-anisate (28.8 mmoles) was added. The reaction mixture as agitated by a stream of nitrogen for 4 hr. at room temperature. Removal of the solvent as described in the preparations of Ia yielded a yellow mass which was shaken with 100 ml. of ether and 50 ml. of water at room temperature. The yellow aqueous layer was covered with an additional 100 ml. of ether and acidified with a mixture of 6 ml. of concentrated hydrochloric acid and 24 ml. of water. Precipitated Ib, 220 mg., m.p. 101°, was removed by filtration. Evaporation of the ether layer gave 670 mg. (15.3%) of *p*-anisic acid. The remaining aqueous layer was extracted six times with 200-ml. portions of chloroform. Evaporation of the combined chloroform extracts yielded an almost colorless oil which solidified upon treatment with ether to give 3.43 g. of Ib, m.p. 101°. The mother liquor was evaporated (50° at 3 mm. for 3 hr.). The oily residue crystallized at room temperature, yielding additional crude Ib, m.p. 95–100°. The total yield of Ib was 5.01 g., 71%. Upon recrystallized from a chloroform–ether mixture, Ib melted at 101°.

Anal. Calcd. for $C_{10}H_{12}O_3S$ (212.20): C, 56.60; H, 5.70; S, 15.08. Found: C, 56.72; H, 5.65; S, 15.31.

(15) E. J. Corey, H. König, and T. H. Lowry, *Tetrahedron Letters*, 515 (1962); E. J. Corey and E. T. Kaiser, *J. Am. Chem. Soc.*, **83**, 490 (1961); D. J. Cram, W. D. Nielsen, and B. Rickborn, *ibid.*, **82**, 6415 (1960); D. J. Cram, D. A. Scott, and W. D. Nielsen, *ibid.*, **83**, 3696 (1961); H. L. Goering, D. L. Towns, and B. Dittmar, *J. Org. Chem.*, **27**, 736 (1962).

(16) All m.p.'s are uncorrected and were determined using a Fisher–Johns m.p. apparatus. All new compounds gave infrared and integrated n.m.r. spectra consistent with the assigned structure.

ω-(Methylsulfinyl)-p-methylacetophenone (Ic).—Potassium (1.6 g., 41 mg.-atoms) was dissolved in 70 ml. of refluxing *t*-butyl alcohol. The excess alcohol was removed by vacuum distillation (pressure approximately 1 mm., bath temperature 65–70°) until the alkoxide residue was nearly dry. Dimethyl sulfoxide (30 ml.) was added and the resultant solution was concentrated by vacuum distillation until approximately 10 ml. of distillate had been collected. To the partially solid residue, methyl *p*-toluate (3.03 g., 20 mmoles) was added dropwise, and the mixture was allowed to cool to room temperature. The reaction mixture was agitated by mechanical stirring under a stream of dry, oxygen-free nitrogen for a total of 4 hr. The solvent was then removed by vacuum distillation (1 mm., bath temperature 65–70°) over a period of 2 hr. The residue was dissolved in 50 ml. of water and acidified to pH 6–7 with dilute hydrochloric acid. The aqueous solution was extracted with three 25-ml. portions of chloroform. Evaporation of the chloroform yielded a yellow solid which was washed with 60 ml. of ether, filtered, and dried, yielding 2.82 g. of Ic (72%) as pale yellow to white crystals, m.p. 105–106°.

Anal. Calcd. for $C_{10}H_{12}O_2S$ (196.27): C, 61.20; H, 6.16; S, 16.34. Found: C, 61.35; H, 6.12; S, 16.50.

p-Carbomethoxybenzyl p-Tolyl Ketone.—In 75 ml. of DMSO (80%)—*t*-butyl alcohol (20%) containing 30 mmoles of potassium *t*-butoxide, 30 mmoles of methyl *p*-toluate failed to produce either the ketoester by self-condensation or the ketosulfoxide during 6 hr. at 70°, irrespective of the order of addition of the reagents. If the reaction mixture was distilled to dryness under vacuum at 60° approximately 11% of the ketoester and 45% of the β-ketosulfoxide could be isolated after acidification. However, in pure DMSO as solvent only the ketosulfoxide could be detected as a reaction product. The maximum yield of the ketone was produced in DMSO containing 5% *t*-butyl alcohol but even here the ketosulfoxide was the main reaction product.

Potassium (1.25 g., 32 mg.-atoms) was dissolved in 50 ml. of refluxing *t*-butyl alcohol and the excess alcohol removed by vacuum distillation to give a dry residue. A solution (60 ml.) of DMSO (95%)–*t*-butyl alcohol (5%) was added and the mixture heated to 50°. Ethyl acetate (1.4 g., 16 mmoles) was added to destroy hydroxide ion and methyl *p*-toluate (4.83 g., 32 mmoles) added 10 min. later. The yield of the ketoester and ketosulfoxide were both improved by the use of the ethyl acetate. The reaction mixture was held at 70° for 6 hr. after which it was added to 500 ml. of ice and water. The aqueous solution was saturated with sodium chloride and extracted thrice with 100 ml. of ether. Evaporation of the ether gave 0.4 g. of a yellow solid which was washed with pentane and recrystallized from ethanol to give *p*-carbomethoxybenzyl *p*-tolyl ketone, m.p. 126–127°, 9.3%.

Anal. Calcd. for $C_{17}H_{16}O_3$ (268.3): C, 76.10; H, 6.01. Found: C, 76.02; H, 6.15.

Acidification of the aqueous layer followed by extraction with ether gave 2.31 g. (40%) of Ic.

A suitable synthetic preparation of the ketoester involves the use of dimethylformamide or hexamethylphosphoramide (HMPA) at 100°. Potassium *t*-butoxide (3.58 g.) was dissolved in 50 ml. HMPA and the mixture heated to 60°. Ethyl acetate (0.7 g., 8 mmoles) was added to destroy hydroxide ion and after 10 min. the temperature raised to 100° and methyl *p*-toluate (3.62 g., 24 mmoles) added dropwise. The mixture was stirred under dry, oxygen-free nitrogen for 6 hr. at 95–100°. The reaction mixture was cooled and poured into 500 ml. of ice–water and the aqueous solution saturated with sodium chloride and extracted four times with 100-ml. volumes of ether. Evaporation of the ether yielded 2.6 g. of a white solid which was dissolved in benzene, and the benzene solution was extracted with 100 ml. of water to remove residual HMPA. The benzene layer was dried and evaporated at room temperature to give 1.6 g. (50%) of pure *p*-carbomethoxybenzyl *p*-tolyl ketone, m.p. 126–127°. Slightly lower yields were obtained when dimethylformamide was substituted for HMPA.

ω-(Methylsulfinyl)-o-hydroxyacetophenone (Id).—Potassium *t*-butoxide (3.36 g.) was dissolved in 20 ml. of DMSO under a nitrogen atmosphere. Methyl salicylate (1.5 g., 10 mmoles) was added slowly at room temperature. The cloudy solution was agitated by a stream of nitrogen for 1 hr. Most of the solvent was then removed within 10 min. as described in the preparation of Ia. To the remaining residue 5 ml. of water was added followed by a mixture of 4.5 ml. of water and 3 ml. of concentrated hydrochloric acid. Extraction with 100 ml. of ether resulted in the formation of colorless needle-shaped crystals in the ether layer. The crystalline substance was separated by filtration, washed with ethanol, and finally with ether to yield Id, 286 mg. (18%), m.p. 152°. Recrystallization from a hot ethanol–chloroform mixture raised the m.p. to 153°

Anal. Calcd. for $C_9H_{10}O_3S$ (198.17): C, 54.54; H, 5.09; S, 16.15. Found: C, 54.77; H, 5.29; S, 16.30.

Methyl Hemimercaptal of Phenylglyoxal (IIa).—A solution of potassium *t*-butoxide was prepared as described in the preparation of Ia, starting from 4 g. of potassium (100 mg.-atoms), 100 ml. *t*-butyl alcohol, and 100 ml. of DMSO. After removal of the excess *t*-butyl alcohol under vacuum, 15 g. of ethyl benzoate (100 mmoles) was added dropwise from a buret to the partially solid mixture of base and DMSO at room temperature with agitation from a stream of nitrogen. After the 40 min. required for the addition of the ester, the reaction mixture was kept at room temperature for an additional 60 min. It was then heated for 60 min. at 60° under a vacuum of about 3 mm. during which time 20 ml. of the solvent distilled. Water (100 ml.) was added to the reaction mixture and the resulting aqueous solution extracted with 100 ml. of ether. The aqueous layer was acidified with a mixture of 30 ml. of concentrated hydrochloric acid and 30 ml. of water. After 1 hr., colorless needle-shaped crystals started to form. After 2 days the crystals were removed by filtration, washed with water, and dried in a desiccator to yield 15 g. of IIa (82%), m.p. 99–100°. Recrystallization from hot ethanol raised the m.p. to 101°.

Anal. Calcd. for $C_9H_{10}O_2S$ (182.17): C, 59.33; H, 5.53; 17.56. Found: C, 59.48; H, 5.62; S, 17.60.

Methyl Hemimercaptal of p-Methoxyphenylglyoxal (IIb).—Repetition of the procedure used to prepare IIa yielded the ketosulfoxide Ib (60%) instead of the rearranged hemimercaptal. When Ib (400 mg., 1.8 mmoles) was dissolved in a solution of 2 ml. of DMSO, 2 ml. of water, and 2 ml. of 5 *N* hydrochloric acid, the solution turned cloudy after about 30 min. at room temperature and crystals started to separate. After 2 days, 330 mg. of IIb (82%) as colorless crystals, m.p. 85–90°, were isolated by filtration. Recrystallization from hot ethanol containing a little water raised the m.p. to 89–91°.

Anal. Calcd. for $C_{10}H_{12}O_3S$ (212.2): C, 56.6; H, 5.70; S, 15.1. Found: C, 56.3; H, 5.78; S, 14.8.

Methyl Hemimercaptal of p-Methylphenylglyoxal (IIc).—The base was prepared and treated with the ester as in the preparation of Ic. After removal of the solvent by vacuum distillation, the residue was dissolved in 15 ml. of water and acidified with a solution of 10 ml. of concentrated hydrochloric acid diluted to 20 ml. with water. The yellow oil which formed solidified upon standing in the aqueous solution for 4 hr. The pale yellow solid was removed by filtration and air dried to yield 2.81 g. (72%) of IIc, m.p. 89–91°. Upon recrystallization from ethanol–water, colorless needles, m.p. 90–91°, were obtained.

Anal. Calcd. for $C_{10}H_{12}O_2S$ (196.27): C, 61.20; H, 6.16; S, 16.34. Found: C, 61.58; H, 5.95; S, 16.32.

The ketosulfoxide Ic (1.42 g.) was dissolved in 30 ml. of a 1:1 mixture of water and dimethyl sulfoxide. A hydrochloric acid solution (10 ml. of concentrated hydrochloric acid plus 10 ml. of water) was added and the cloudy solution which formed immediately was allowed to stand at room temperature for 75 min. The precipitate which formed was filtered, washed with water (50 ml.), and air dried. The filtrates were combined and after standing at room temperature for 18 hr. more precipitate formed. The total yield of IIc, m.p. 89–91°, was 1.05 g. (74%).

Methyl Mercaptal of Phenylglyoxal (IIIa).—The hemimercaptal IIa (1 g., 5.48 mmoles) was suspended in a mixture of 6 ml. of concentrated hydrochloric acid and 3 ml. of water and kept on a steam bath for 10 min. Ethanol was added to the solution until the yellow oil which had separated went into solution. On cooling to room temperature, IIIa precipitated in the form of fine colorless needle-shaped crystals. These were filtered and dried to give 415 mg. of IIIa (71%), m.p. 66°. Recrystallization from hot ethanol raised the m.p. to 66–67°.

Anal. Calcd. for $C_{10}H_{12}OS_2$ (212.2): C, 56.60; H, 5.70; S, 30.20. Found: C, 56.31; H, 5.64; S, 28.98.

Methyl Mercaptal of o-Hydroxyphenylglyoxal (IIId).—A sample of IId (116 mg.) in the form of colorless crystals which had not been recrystallized turned into a brown oil during 2 months of storage. Treatment of this oil with a little ether resulted in the formation of 40 mg. of IIId (60%) as colorless crystals, m.p. 119–120°.

Anal. Calcd. for $C_{10}H_{12}O_2S_2$ (228.2): C, 52.62; H, 5.30; S, 28.02. Found: C, 52.45; H, 5.43; S, 27.80.

Formation of Phenylosazones from IIa, IIb, IIc, and Id.—The hemimercaptal IIa (50 mg.) was dissolved in 1 ml. of ethanol and 0.5 ml. of water. The solution was refluxed for 1 hr. after addition of 0.2 ml. of phenylhydrazine and 2 drops of concentrated hydrochloric acid. The yellow-colored crystals which separated from the solution were filtered and dried to give 80 mg. (93%) of the phenylosazone of phenylglyoxal, m.p. 148–149°, lit.[17] m.p. 152°. The osazone of *p*-methoxyphenylglyoxal was prepared in a similar manner from IIb in 91% yield, m.p. 188–189°, lit.[18] m.p. 190°. The osazone of *o*-hydroxyphenylglyoxal was prepared by the same method but directly from Id in 27% yield, m.p. 205–206°, lit.[19] m.p. 202°.

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TABLE I

N.M.R. SPECTRA OF COMPOUNDS IIa, IIb, IIc

Compound	Aromatic protons	>C–H_a	–OH_b	–CH_3
IIa	Multiplet, intensities 2 and 3	Doublet, intens. 1	Doublet, intens. 1	Singlet, intens. 3
		τ = 3.87	τ = 5.62	τ = 8.00
			J_{ab} 8.4 c.p.s.	
IIb	a_2b_2 pattern, intensities 2 and 2	Broad doublet, intens. 1	Broad doublet, intens. 1	Singlets, intens. 3
		τ = 4.40	τ = 5.49	τ = 8.00, 6.14
			J_{ab} 6.9 c.p.s.	
IIc	a_2b_2 pattern, intensities 2 and 2	Broad doublet, intens. 1	Broad doublet, intens. 1	Singlets, intens. 3
		τ = 3.69	τ = 5.50	τ = 8.05, 7.60
			J_{ab} 5.5 c.p.s.	

Anal. Calcd. for $C_{20}H_{18}N_4O$ (330.38): C, 72.70; H, 5.49; N, 16.96. Found: C, 72.60; H, 5.32; N, 16.66.

The osazone of *p*-methylphenylglyoxal was prepared in the same manner as IIa in 90% yield, m.p. 136–137°; lit.[20] α-form m.p. 145°, β-form m.p. 167–168°.

Anal. Calcd. for $C_{21}H_{20}N_4$ (328.21): C, 76.79; H, 6.14; N, 17.07. Found: C, 76.91; H, 5.95; N, 16.97.

Proton Resonance Spectra.—The structures of the new compounds described in this work have been confirmed by integrated n.m.r. spectra.[21] β-Ketosulfones[22] exhibit a singlet representing the methylene hydrogen atoms in the $-CO-CH_2-SO_2-$ grouping. However, for the methylene group in the β-ketosulfoxides Ia–d ($-CO-CH_2-SO-$) an ab pattern is observed for the methylene protons due to the asymmetry caused by the sulfoxide group. In the spectrum of IIa there is in addition to the aromatic protons (multiplet, intensity 5, *ortho* and *meta–para* hydrogens separated), a pair of doublets (total intensity 2) for the methylene group at τ = 5.55 and 5.72 (J_{ab} 14 c.p.s.; relative intensities 0.18 and 1.82),[23] as well as a singlet at τ = 7.34 (intensity 3) for the methyl group. Similarly, Ib gives the following absorptions in addition to the aromatic protons (a_2b_2 pattern, intensity 4); a pair of doublets total (intensity 2) at τ = 5.57 and 5.77 (J_{ab} 14 c.p.s., relative intensities 0.28 and 1.72) for the methylene group, a singlet at τ = 6.12 (intensity 3) for the methoxy group and a singlet at τ = 7.27 (intensity 3) for the methyl group. Compound Ic shows an a_2b_2 pattern for the aromatic hydrogen atoms; a pair of doublets, τ = 5.50 and 5.81, J_{AB} 15.5 c.p.s. for the methylene group, and singlets at τ = 7.25 and 7.58 for the methylsulfinyl groups and *p*-methyl groups. In Id the center peaks of the ab system for the methylene group are only slightly separated.

The n.m.r. spectra of the hemimercaptals IIa, IIb, and IIc exhibit a pair of doublets for the $H_a-\overset{|}{\underset{|}{C}}-OH_b$ grouping. Deuterium exchange in deuterium oxide solution allowed the assignment of one doublet to the $-OH_b$ group. Further n.m.r. data are listed in Table I.

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Molecular and Crystal Structure of the Di-*p*-bromobenzoate of the Methyl Ester of Gibberellic Acid

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The complete molecular structure and stereochemistry, except for absolute configuration, have been determined by a single crystal X-ray diffraction study of the di-*p*-bromobenzoate of the methyl ester of gibberellic acid. The lactone ring is shown to be *trans* to the two-carbon bridge. The space group is C2, and there are four molecules of $C_{34}O_8Br_2$ in a unit cell having parameters a = 28.22, b = 7.69, c = 17.63 Å., and β = 125° 12′. The value of $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ is 0.13 for the 1978 observed diffraction maxima. The 30 H atoms of the molecule were not located in this study.

The gibberellins are active metabolites which have been isolated for about forty years from culture filtrates of the fungus *gibberella fujikuroi*. Plants which have been subjected to an excess of a gibberellin grow abnormally rapidly in their early stages but then wilt and die before reaching maturity. On the other hand, gibberellins have also been isolated from healthy plants.[1] Therefore, these natural products are thought to be normal plant growth hormones which cause disease when present in excess.

At least ten different, but similar, such compounds have been characterized. One of these compounds, gibberellic acid, has been most widely studied by chemists because its isolation[2] from fungal cultures is well defined, reproducible, and of high yield. The chemical evidence, reviewed by Grove,[3] for the molecular structure leaves some doubt as to the configuration of the lactone ring; but we shall show that contrary to chemical expectations the lactone bridge is in an α-orientation. Preliminary results of an independent X-ray diffraction study by McCapra, Scott, Sim, and Young[4] on methyl bromogibberellate appeared after our study was well under way. These authors[4] deduced the correct chemical structure of gibberellic acid from the stereospecificity of the bromination reaction which changes the molecular conformation.

The present X-ray diffraction study of single crystals of the di-*p*-bromobenzoate of the methyl ester of gibberellic acid confirms the chemical structure, shows that the lactone ring is indeed *trans* to the two-carbon bridge and yields for the first time detailed bond distances and angles in the essentially unaltered ring structures of the molecule.

Experimental

The di-*p*-bromobenzoate of the methyl ester of gibberellic acid was prepared by E. J. Corey and S. Barcza. Colorless, irregularly shaped single crystals were obtained from solutions in ethyl acetate. All crystals which were photographed were less than 0.08 mm. in cross section, and hence absorption and extinction corrections were not made. Reciprocal lattice symmetry of C_{2h}, the systematic extinction of reflections for

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