[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

The Relative Acidifying Influence of Oxygen and Sulfur Atoms on α-Hydrogen Atoms[1]

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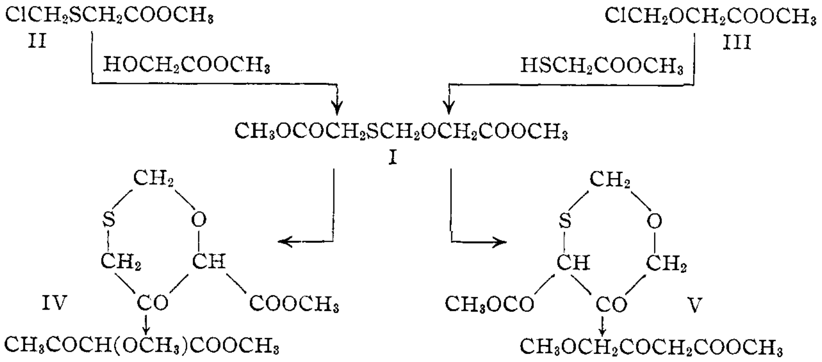
Bis-carbomethoxymethyl monothioformal has been prepared and subjected to Dieckmann cyclization. The product of the reaction has been proven to be 4-carbomethoxy-5-oxo-1,3-oxathiane. Comments are made concerning the significance of this fact on some of the fundamental aspects of sulfur chemistry.

The slight interest in monothioformals has been centered upon compounds containing a five-membered ring—readily prepared from a carbonyl compound and mercaptoethanol. Other examples of this type of compound can be prepared by the method of Böhme[3] but only with difficulty and in low yields. There has been no report of a compound containing the monothioformal system in a six-membered ring. We set about filling this gap by synthesizing such a product.

It was decided to synthesize the six-membered monothioformal by a Dieckmann condensation of the open chain compound I. There are two possible products of such a reaction. The paths to these two products differ only in the placement of an oxygen or sulfur atom adjacent to the initial reaction site. Since the first step of such a condensation is the removal of an acidic proton by the basic catalyst, the products of the reaction should offer a measure of the relative acidifying tendencies of oxygen and sulfur atoms.

Bis-carbomethoxymethyl monothioformal (I), b.p. 98° (0.14 mm.), was prepared by treating methyl S-chloromethylmercaptoacetate (II) with methyl glycolate or, in very poor yield, by treating methyl O-chloromethylglycolate (III) with methyl mercaptoacetate. In anything other than a very strongly basic medium either of these condensations produced appreciable amounts of the symmetrical dithioformal. The crystalline diamide, m.p. 180.5–181°, characterized I.



Dieckmann cyclization of I was effected by treatment with sodium methoxide. At 0° in ether or at 80° in toluene the only pure compounds isolated from the reaction mixture were starting material and a white crystalline solid, m.p. 70.5–72°. This solid gave an intense color with ferric chloride and had an analysis and molecular weight corresponding to either 6-carbomethoxy-5-oxo-1,3-oxathiane (IV) or 4-carbomethoxy-5-oxo-1,3-oxathiane (V). Its oxidation with ferric chloride or iodine is so convenient that these reagents may be used in the quantitative determination of the compound. Amide formation failed as a means of characterization since treatment with ammonia resulted in ring fission and the production of the diamide of I. The *p*-nitrophenylhydrazone could be prepared in two interconvertible forms, m.p. 165–166° and m.p. 214–216°.

To distinguish between the structures IV and V the material was desulfurized with Raney nickel. From IV there would be expected methyl α-methoxyacetoacetate; from V the product would be methyl γ-methoxyacetoacetate. At room temperature the reaction led to the complete destruction of all ketonic material. At 5° there was isolated a 2,4-dinitrophenylhydrazone, m.p. 125–127°, which was identical with the same derivative of methyl γ-methoxyacetoacetate. To evaluate the possibility that initially formed α-isomer might have rearranged to the γ-isomer, methyl α-methoxyacetoacetate was prepared and treated with Raney nickel under the same conditions. It gave none of the derivative described above but was degraded to methoxyacetone (isolated as its 2,4-dinitrophenylhydrazone). In fact, this same derivative was obtained merely upon treatment with 2,4-dinitrophenylhydrazine without any use of Raney nickel. This series of reactions proves that the product of the Dieckmann ring closure of I is V and not IV.

The acidifying influence of sulfones and sulfoxides upon α-hydrogen atoms is a well established fact. Whether this behavior is due to the expansion of the valence shell of the sulfur atom to include more than eight electrons is complicated by the possibility of simple inductive stabilization of the resulting carbanion by the formal positive charge(s) on the attached sulfur atom. In the data reported herein, the *uncharged* sulfur atom seems to have a greater acidifying effect on α-hydrogen atoms than does an oxygen atom. This is contrary to the order expected by a consideration of simple inductive effects based upon the position of the atoms in the periodic table.

In the past there have been several suggestions[4]

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(1) Abstracted from the dissertation submitted by T. Levenson in partial fulfillment for the Ph.D. degree at New York University.

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(3) H. Böhme, *Ber.*, **69**, 1610 (1936).

(4) Among others: E. Rothstein, *J. Chem. Soc.*, 1556, 1558, 1561 (1940); R. B. Woodward and R. H. Eastman, THIS JOURNAL, **68**, 2229 (1946).

that the sulfur atom in a sulfide linkage might be able to expand its valence shell to accommodate ten electrons. Here, too, the isolation of V without any IV suggests that forms such as $\mathrm{C{=}\overset{\ominus}{S}{-}}$reversed the normal order of electronegativities. The meager yields and lack of complete material balance prohibit further elaboration of this postulate.[5]

Experimental

Methyl S-Chloromethylmercaptoacetate (II).—In a procedure essentially that of Böhme,[3] a stream of dry hydrogen chloride was passed into a stirred mixture of 40.5 g. of paraformaldehyde and 159 g. of methyl mercaptoacetate. The last reagent was prepared by the method of Baker, *et al.*[6] The mixture was kept at 0° by means of an ice-salt-bath, and in about 3.5 hours saturation and homogeneity were attained. The solution was diluted with 700 ml. of ether, transferred to a separatory funnel and washed with ice-water (once with 120 ml., three times with 80 ml.). The aqueous extracts were combined and washed with 200 ml. of ether which was then rewashed with two 25-ml. portions of water. The ether solutions were combined, dried over 75 g. of phosphorus pentoxide and fractionated under vacuum. There was collected 92.2 g. (45% of theory) of product, b.p. 98° (14 mm.). When carefully redistilled a pure sample boiled at 55° (0.3 mm.).

Anal. Calcd. for $C_4H_7O_2SCl$: C, 31.1; H, 4.57; S, 20.7; Cl, 22.9. Found: C, 31.3; H, 4.78; S, 20.7; Cl, 23.0.

Bis-carbomethoxymethyl Monothioformal (I).—A solution of 12.61 g. of sodium metal in 150 ml. of methanol was treated with 80 ml. of methyl glycolate. The solution was placed in a water-bath at 50° and concentrated under vacuum until the thick sludge made stirring difficult. About 90 ml. of methanol was recovered. After cooling in an ice-bath at 0°, 83.43 g. of methyl S-chloromethylmercaptoacetate was dropped in with continued stirring over a one-hour period. There was a rapid reaction and a loosening of the sludge. After stirring for 45 minutes at room temperature 300 ml. of anhydrous ether was added and the mixture cooled in ice for 30 minutes. The suspension was filtered through Hiflo Supercel and the filtrate fractionated. There was obtained 30 g., b.p. 118–120° (0.8 mm.) and 8 g., b.p. 120–125° (0.8 mm.). An analytical sample boiled at 98° (0.14 mm.); yield was 31%.

Anal. Calcd. for $C_7H_{12}O_5S$: C, 40.4; H, 5.77; S, 15.4. Found: C, 40.3; H, 5.78; S, 15.2.

A solution of 250 mg. of I in 1.0 ml. of methanol was saturated with dry ammonia and on prolonged cooling there was obtained 204 mg. of the **diamide**, m.p. 179–181°. Recrystallization from methanol or water gave pure material, m.p. 180.5–181°.

Anal. Calcd. for $C_5H_{10}O_3N_2S$: C, 33.7; H, 5.62; N, 15.7; S, 18.1. Found: C, 34.0; H, 5.78; N, 15.7; S, 17.9.

To confirm the assigned structure an alternate synthesis was developed. A stirred mixture of 2.7 g. of paraformaldehyde and 8.1 g. of methyl glycolate[6] was saturated with dry hydrogen chloride. Complete solution resulted in about two hours. After adding 5.5 g. of freshly dehydrated calcium chloride the reaction mixture was let stand at room temperature overnight. The next morning, there were two liquid phases present above the drying agent. The larger, heavier, more viscous phase was ether insoluble and was discarded. The lighter, ether-soluble phase was separated by decantation. A stream of dry carbon dioxide was used to remove hydrogen chloride. Fractionation of the material resulted in considerable loss and the isolation of 0.35 g., b.p. 27° (0.4 mm.).

This product was added slowly to a solution prepared by dissolving 0.07 g. of sodium in 2.0 ml. of methanol followed by the addition of 0.24 g. of methyl mercaptoacetate. The addition, which was run at room temperature, was complete in 20 minutes. A white precipitate was formed immediately. The reaction mixture was diluted with dry ether and filtered. The ether was evaporated and the residue dissolved in 0.5 ml. of methanol. The solution was saturated with ammonia at 0° and allowed to stand overnight. The white crystalline product was recrystallized from methanol, m.p. 173–175.5°. This figure was not depressed by addition of authentic diamide (m.p. 180.5–181°). It was depressed markedly by addition of the diamide of the symmetrical dithioformal.

4-Carbomethoxy-5-oxo-1,3-oxathiane (V). Low Temperature Reaction.—Metallic sodium (4.16 g.) was powdered under xylene and then suspended in 50 ml. of ether. The suspension was treated with 7.59 ml. of methanol, stirred for 5 hours and then let stand overnight. The next morning 24.06 g. of I was slowly dropped into the suspension of sodium methoxide in ether at ice-bath temperature. The addition was complete in 50 minutes by which time stirring was difficult. Stirring was continued for 5 hours. Then an ice-cold solution of 10.56 ml. of glacial acetic acid in 50 ml. of water was added rapidly to the cold reaction mixture. The water layer was extracted three times with ether until it no longer gave a blue color with ferric chloride. The ether was distilled off to leave 17.3 g. of an oil which soon crystallized. All but 1.7 g. of this material was soluble in hot ligroin. The ligroin solution was made up to 500 ml. in a volumetric flask. The product was isolated by chromatography on 200-mesh silica gel (60 g. of silica in a column of 15 mm. diameter). A 200-ml. aliquot of the solution was passed through the column and adsorption was complete. Washing with 1% ether in ligroin removed essentially nothing. However, using 2% ether in ligroin there was obtained, after removal of the solvents, 4.85 g. of slightly oily, white crystalline material. This was dissolved in 25 ml. of methanol and by cooling and concentrating a quantity of white solid was obtained; this was augmented by fractional distillation of the mother liquor. There was obtained 3.53 g. of white solid, m.p. 69–71°. This is equivalent to a total yield of 8.83 g. (43% of theory) from the entire product. Note that some 73% of the product isolated from the chromatographic column is crystalline product. This figure is confirmed by titrating an aliquot of the methanol solution with standard 0.1 *N* iodine in the presence of sodium bicarbonate. This indicates a figure of 70% purity. Similarly a comparison of the infrared scan[7] of pure product with that from the chromatographic column indicates 60–65% (±5%) as a purity index. Further recrystallizations from ligroin and from methanol raised the melting point of the pure product to 70.5–72°.

Anal. Calcd. for $C_6H_8O_4S$: C, 40.9; H, 4.58; S, 18.2. Found: C, 40.96; H, 4.86; S, 18.3.

Two types of molecular weight determinations were performed. The first, according to the procedure of Signer[8] and Clark,[9] involved isothermal equilibration of an ethereal solution of V against a similar solution of azobenzene as a standard. Equilibrium was attained after 53 hours at room temperature to give a molecular weight of 176 (calcd. 176). For a second method the acidic β-keto ester was titrated with standard sodium hydroxide using phenolphthalein as an indicator. This gave a neutral equivalent of 186.

That there was a good recovery of product from the chromatographic purification step was proven by dissolving 303 mg. of pure V in 60 ml. of ligroin and adsorbing on a 10-g. column of silica gel. Elution with 2% ether in ligroin resulted in a quantitative recovery of pure product.

When a solution of 250 mg. of pure V was dissolved in 2 ml. of methanol and 0.25 ml. of benzene and the solution saturated with ammonia at 0° there was obtained 243 mg. of white crystals, m.p. 180–181°. This proved to be the diamide of I and did not depress the melting point of an authentic sample.

In order to prepare a **_p_-nitrophenylhydrazone**, a solution of 176 mg. of V and 200 mg. of *p*-nitrophenylhydrazine in 4 ml. of methanol containing one drop of glacial acetic acid was warmed slightly and left to stand overnight. The

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(5) Although there has been reported [E. Fischer, *Ber.*, **27**, 673 (1894)] the isolation of metallic salts from the treatment of various glucose mercaptal derivatives with alkali, the acidifying effect of even two such sulfur atoms must be considered a minor one. The diethylmercaptals of isobutyraldehyde and even of benzaldehyde fail to yield any hydrocarbon when treated with Grignard reagent.

(6) B. R. Baker, M. V. Querry, S. R. Safir and S. Bernstein, *J. Org. Chem.*, **12**, 138 (1947).

(7) The scans were made on a Perkin–Elmer model 12C single beam instrument by Mr. Paul Pemsler of Washington Square College, New York University and interpreted by Dr. Robert Kitson of the Polychemicals Department, E. I. du Pont de Nemours & Co., Inc.

(8) R. Signer, *Ann.*, **478**, 246 (1930).

(9) E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941).

yield was 218 mg. of solid product, m.p. 160–161°. This was separated into two portions. An acetone-soluble fraction melted at 165–166° after recrystallizations from methanol and from acetone water. A small acetone-"insoluble" fraction melted at 214–216° when purified from excess acetone. Repetition of the preparation using glacial acetic acid as solvent gave 184 mg., m.p. 203–206° dec., containing only a small amount of the low-melting isomer. Recrystallization of the isomer, m.p. 165–166°, from glacial acetic acid gave the higher melting product.

Anal. Calcd. for $C_{12}H_{13}O_5N_3S$: C, 46.28; H, 4.21; N, 13.51. Found (low-melting isomer): C, 45.88; H, 4.21; N, 12.77. Found (high-melting isomer): C, 45.94; H, 4.04; N, 13.47.

High Temperature Dieckmann Reaction.—Metallic sodium (1.443 g.) was dissolved in 2.6 ml. of absolute methanol and 156 ml. of dry toluene by heating and stirring under reflux for 2 hours. After standing overnight the mixture was heated to 80° with an oil-bath and 10.816 g. of I was added. Half the material was added rapidly producing an orange color and a precipitate. The rest was added over a period of 20 minutes. With continued stirring the temperature of the oil-bath was raised so that distillation began. Starting at 95° in 3.25 hours 100 ml. of distillate was collected and the temperature of the distilling material rose to 109.5°. The reaction mixture was cooled in an ice-bath and treated with 3.59 ml. of glacial acetic acid in 16 ml. of ice-water. The whole was thoroughly extracted with ether. The combined extracts were washed with water, dried with magnesium sulfate and the ether distilled off. The residue weighed 8.066 g. and partially crystallized on seeding with V. Extraction with hot ligroin dissolved all but 0.562 g. of oil. As before an aliquot of the ligroin solution containing 3.00 g. of crude product was chromatographed on silica gel. Elution with 2% ether in ligroin gave 0.796 g. (21.7% yield) of V, m.p. 66–69°, and 2.11 g. of an oil which had a refractive index, a boiling point and an infrared spectrum identical with those of the starting material I.

Methyl α-Methoxyacetate.—According to the procedure of Pratt and Robinson[10] a solution of 23 g. of sodium in 200 ml. of methanol was treated with 108 g. of methyl α-chloroacetate and the mixture refluxed for 2 hours. The mixture was neutralized with glacial acetic acid. The salt was filtered off and the filtrate fractionated to give 81 g. of product (78% of theory), b.p. 129°.

Methyl γ-Methoxyacetoacetate.—Following the general procedure of Sommelet,[11] a three-necked, 300-ml. flask was equipped with a stirrer, condenser and an adapter for two dropping funnels. In the flask there was placed 21.7 g. of granular zinc (30 mesh), 10 g. of methyl α-methoxyacetate, 8 g. of methyl α-bromoacetate and 10 ml. of benzene. The mixture was heated until vigorous reaction set in (controlled with an ice-bath). Then there was dropped in an additional 24.7 g. of methyl α-methoxyacetate and 40.3 g. of methyl α-bromoacetate, each in 20 ml. of benzene, at such a rate that the reaction mixture was maintained at reflux and the bromo compound was always in excess. Addition was complete in about one hour and the mixture was kept at reflux until only a small amount of zinc remained. The mixture was poured into ice-water, made acidic with dilute sulfuric acid and then extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate and fractionated. The bulk of the product was collected at 86–88° (8.5 mm.). Two more distillations gave an analytical sample, b.p. 89° (8.5 mm.). The product gave an intense red color with ferric chloride.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.3; H, 6.85. Found: C, 49.0; H, 7.13.

A solution of 300 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of methanol and 7 drops of concentrated hydrochloric acid was added to 230 mg. of the keto-ester. Very rapidly there was obtained 365 mg. of yellow **2,4-dinitrophenylhydrazone**, m.p. 121–123°. Recrystallization from methanol raised the melting point to 127.5–129°. This material is soluble in methanol at 30° to the extent of 4 mg./ml.

Anal. Calcd. for $C_{12}H_{14}O_7N_4$: C, 44.2; H, 4.30; N, 17.2. Found: C, 44.3; H, 4.40; N, 17.1.

Desulfurization of V with Raney Nickel.—A solution of 250 mg. of V in 5 ml. of methanol was cooled in an ice-bath and stirred with $^1/_4$ teaspoonful of Raney nickel for five minutes. The material was quickly filtered and washed with methanol. (Titration of an aliquot with ferric chloride or iodine indicated desulfurization to be 80% complete). The filtrate was treated with 250 mg. of 2,4-dinitrophenylhydrazine in 3 ml. of methanol containing 6 drops of concentrated hydrochloric acid. No precipitate formed in an ice-bath, but on cooling in Dry Ice–acetone there was obtained 46 mg. of yellow solid, m.p. 113–117°. Two recrystallizations from methanol raised the melting point to 125–127° which was not depressed when mixed with the authentic derivative of methyl γ-methoxyacetoacetate.

Methyl α-Diazoacetoacetate.—Following the procedure of Schroeter,[12] 200 g. of 20% sodium nitrite solution was dropped into an agitated solution of 88 g. of methyl acetoacetate in 120 g. of glacial acetic acid. The temperature was maintained at 25–30°. When addition was complete the mixture was diluted with 800 ml. of ice-water and placed in the ice-box overnight. The next morning 2400 ml. of 15% sulfuric acid was added followed by 160 g. of zinc shavings in the course of one hour. The temperature was kept at 18° during this addition. After cooling again in the ice-box overnight there was added 1.3 kg. of ice, the whole mixture cooled to 0° in an ice–salt-bath and 120 ml. of 29% sodium nitrite solution dropped in. After standing for $^1/_2$ hour the mixture was extracted with three 1-l. portions of ether. Fractionation of the combined extracts gave 38 g. of yellow oil (36% of theory), b.p. 75–76° (9 mm.).

Methyl α-Methoxyacetoacetate.—Following the work of Yates[13] and Newman and Beal,[14] a mixture of 7.1 g. of methyl α-diazoacetoacetate, 70 ml. of methanol and 1 g. of copper–bronze was treated with 2 drops of boron trifluoride etherate. With stirring the mixture was warmed to 50°. At this point a brisk evolution of nitrogen occurred, and the heat of reaction was sufficient to maintain the temperature. In 20 minutes most of the nitrogen had been evolved; in 45 minutes the theoretical amount had been reached and the reaction mixture was filtered through Hyflo Super-cel. The filtrate was fractionated to give a small yield of product, b.p. 40° (0.2 mm.). Redistillation gave a pure sample, b.p. 44–48° (1 mm.). When freshly distilled the material is yellow and gives no color with ferric chloride in the cold. When the mixture reaches room temperature an intense blue color is produced. The pure ester becomes colorless on standing.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.3; H, 6.85. Found: C, 48.8; H, 6.91.

A solution of 300 mg. of 2,4-dinitrophenylhydrazine in 12 ml. of methanol and 0.5 ml. of concentrated hydrochloric acid was added to 220 mg. of this ester. An oil precipitated immediately and slowly a reddish solid formed. After two days at room temperature there was obtained 250 mg. of solid melting over a wide range. Recrystallization from methanol gave beautiful yellow crystals, m.p. 163–165°.

Anal. Calcd. for $C_{12}H_{14}O_7N_4$: C, 44.2; H, 4.30; N, 17.2. Found: C, 44.0; H, 4.27; N, 20.7. Calcd. for $C_{10}H_{12}O_5N_4$: C, 44.7; H, 4.47; N, 20.9.

This material had the correct analysis and melting point for the 2,4-dinitrophenylhydrazone of methoxyacetone (*cf.* Marrielo and Leech[15]). The melting point was not depressed by admixture of a genuine sample. This same derivative of methoxyacetone was all that could be isolated when the α-methoxy ester was treated with Raney nickel following the same procedure as that recorded above for the desulfurization reaction.

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(10) D. D. Pratt and R. Robinson, *J. Chem. Soc.*, **127**, 166 (1925).

(11) M. Sommelet, *Bull. soc. chim.*, [4] **29**, 553 (1921).

(12) G. Schroeter, *Ber.*, **49**, 2697 (1916).

(13) P. Yates, THIS JOURNAL, **74**, 5376 (1952).

(14) M. S. Newman and P. F. Beal, *ibid.*, **72**, 5161 (1950).

(15) R. P. Mariella and J. L. Leech, *ibid.*, **71**, 3558 (1949).