

181. *Selenium Dioxide. A New Oxidising Agent. Part IV. The Preparation and Properties of Ethyl Ketohydroxysuccinate.*

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SELENIUM dioxide oxidises a variety of organic compounds, giving, in many instances, excellent yields of compounds difficult to prepare by other methods. In the majority of cases studied, the organic compounds contain, closely associated with a negative group, a methylene group which is oxidised to carbonyl by the dioxide : *e.g.*, aldehydes and ketones give 1 : 2-keto-aldehydes and 1 : 2-diketones respectively (Riley, Morley, and Friend, J., 1932, 1875; Evans, Ridgion, and Simonsen, this vol., p. 137); malonic ester gives mesoxalic ester (Astin, Newman, and Riley, J., 1933, 391; Müller, *Ber.*, 1933, **66**, 1668); acetoacetic ester gives $\alpha\beta$ -diketobutyric ester (Müller, *loc. cit.*); methylbenzanthrones and allied compounds give the corresponding aldehydes (I. G. Farb. A.G., B.P., 1931, 347, 743). Besides this extensive type of reaction, examples are known in which the dioxide behaves differently : *e.g.*, the group $\cdot\text{CH}:\text{CH}\cdot$ in ethylene and propylene is oxidised to $\cdot\text{CO}\cdot\text{CO}\cdot$ (Riley and Friend, J., 1932, 2342); α -pinene is oxidised to verbenone (Schwenk and Borgwardt, *Ber.*, 1932, **65**, 1601), involving the conversion $>\text{C}:\text{CH}\cdot\text{CH}_2\cdot\text{CH}< \longrightarrow >\text{C}:\text{CH}\cdot\text{CO}\cdot\text{CH}<$; the simple aliphatic alcohols give alkylglyoxals, and succinic ester gives fumaric ester (Astin, Newman, and Riley, *loc. cit.*). The oxidising action of selenium dioxide on ergosterol and dihydroergosterol has been studied by Callow and Rosenheim (J., 1933, 390; see also Truchet, *Compt. rend.*, 1933, **193**, 706; Henze, *Ber.*, 1934, **67**, 750).

The present paper describes the oxidising action of selenium dioxide on *d*-ethyl tartrate. The principal product was *ethyl d-ketohydroxysuccinate*, thus demonstrating still another type of oxidation and providing a simple means of preparing this compound.

EXPERIMENTAL.

Ethyl tartrate (103 g.; 3 mols.) and selenium dioxide (18.3 g.; 1 mol.) were heated (120—130°) under reflux until all the dioxide had disappeared (4 hours); 5.0 g. of selenium (38%) were precipitated. The residual liquid was decanted, the selenium washed with alcohol, and the liquid and washings fractionated under reduced pressure, giving first alcohol and water and then a yellow distillate. At 180°/30 mm. decomposition commenced, the liquid charred, and the distillate became contaminated with red selenium. Two fractions, (A) b. p. 173°/30 mm. and (B) 173—215°/30—200 mm., were collected. These were diluted with ether, filtered to remove selenium, and fractionated separately in a vacuum. The following fractions were collected: (1) 17 c.c. up to 173°/30 mm.; (2) 20 c.c., b. p. 173—177°/30 mm. (unchanged ethyl tartrate); (3) b. p. 177—195°/30—60 mm. (more ethyl tartrate and organo-selenium compounds). Fraction (1), diluted with ether, filtered from the small amount of selenium which separated, and redistilled in a vacuum, gave 16 c.c., b. p. 168—170°/28 mm., which crystallised after several days, forming 10.75 g. of *ethyl ketohydroxysuccinate*. Recrystallisation from ether gave white shining needles, m. p. 96—98° (Found: C, 46.9, 47.0; H, 6.1, 6.1; *M* by Rast's method 226, by elevation of b. p. of ether 223. C₈H₁₂O₆ requires C, 47.0; H, 5.9%; *M*, 204). $[\alpha]_D^{20} = +14^\circ$ in 20% aqueous solution. $[\alpha]_D^{18} = -15.6^\circ$ in 12% solution in absolute alcohol. The compound was readily soluble in methyl alcohol, ethyl alcohol, acetone, chloroform, ethyl acetate, water, benzene, toluene and nitrobenzene, moderately soluble in ether and in light petroleum, and very sparingly soluble in carbon tetrachloride. Two recrystallisations from anhydrous ether gave m. p. 98—99°. The m. p. was very sensitive to traces of moisture; after drying for several weeks over phosphoric oxide, m. p. 105—106° was obtained. The compound was slightly deliquescent.

The optical activity of the compound (*vide infra*) left no doubt that it was the ketohydroxysuccinate and not either the dihydroxy-maleate or -fumarate. This formulation was in accord with its chemical properties. It reduced ferric chloride, ammoniacal silver nitrate, and Fehling's solution. Phenylhydrazine in acetic acid, added to an aqueous solution of the compound gave a yellow precipitate which after recrystallisation from alcohol consisted of lemon-yellow plates and orange needles. The lemon-yellow plates, which were picked out by hand, had m. p. 121°, alone and mixed with the bisphenylhydrazone of ethyl diketosuccinate (I) (Found: C, 62.6; H, 5.7. Calc.: C, 62.9; H, 5.8%). This compound exists in three forms, the one obtained being the α -modification (Anschütz and Pauly, *Ber.*, 1895, 28, 64). The remaining mixture of orange and yellow crystals was boiled for a few minutes with glacial acetic acid and diluted with water. When the precipitate was recrystallised from alcohol, orange needles of the 4-phenylhydrazone of ethyl 4:5-diketo-1-phenyl-4:5-dihydropyrazole-3-carboxylate (II), m. p. and mixed m. p., 153.5°, were obtained (Found: N, 16.9. Calc.: N, 16.7%). Anschütz and Pauly (*loc. cit.*) prepared this compound by the action of glacial acetic acid on any of the three isomeric osazones of ethyl diketosuccinate. Anschütz and Parlato (*Ber.*, 1892, 25, 1979) obtained only (II) by the action of phenylhydrazine acetate on ethyl diketosuccinate. (I) could only be obtained by the action of alcoholic phenylhydrazine on ethyl diketosuccinate.

The ester (2 g.) in methyl alcohol was treated with caustic potash (1.5 g.) in the same solvent. An immediate white precipitate (2.5 g.) was obtained which was washed with methyl alcohol and ether (Found: K, 36.7. Calc. for potassium ketohydroxysuccinate: K, 34.8%). This salt was treated for 1 hour with hydrogen chloride (2 equivs.) in ethyl acetate, and the excess of acid removed in a vacuum; the viscous yellow syrup obtained deposited oxalic acid, m. p. 96—98°, on cooling in ice. Another attempt to prepare the free acid was made through the lead salt, which, suspended in ethyl acetate, was decomposed by hydrogen sulphide; oxalic acid was again produced. Examination of the products of alkaline (caustic potash) hydrolysis revealed only the presence of oxalic acid (m. p. 100.5° and mixed melt. Found: C, 19.1; H, 4.52. Calc.: C, 19.0; H, 4.8%), ethyl alcohol, carbon dioxide, and a little tartaric acid. No glycollic acid could be detected by the codeine test (Denigès, *Bull. Soc. chim.*, 1909, 5, 648).

When the ester was refluxed with dilute hydrochloric acid, a considerable amount of carbon dioxide was evolved. Tartaric acid [m. p. 124—132° with decomposition, after recrystallisation from acetone—light petroleum (b. p. 40—60°), and drying for 2 days in a vacuum desiccator. Found: C, 32.2; H, 4.2. Calc.: C, 32.0; H, 4.0%], ethyl alcohol, and a small quantity of some other substance which gave the iodoform reaction in the cold were also produced. The tartaric acid, which was dextrorotatory, was shown to be a mixture of the dextro- and the *meso*-form, as follows. About 0.2 g. of the acid was dissolved in water, neutralised with caustic potash, and acidified with dilute acetic acid. After 2 days the precipitated potassium hydrogen *d*-tartrate was removed; the filtrate, treated with calcium chloride solution, gave white crystalline calcium

mesotartrate. A solution of the acid gave no precipitate with saturated calcium sulphate solution, showing the absence of racemic acid.

Ethyl ketohydroxysuccinate was not attacked by boiling acetyl chloride, and a solution of the ester in benzene gave no hydrogen chloride on treatment with acetyl chloride.

The ester (3.02 g.) was refluxed with acetic anhydride (30 c.c.) for an hour, and the excess of anhydride removed in a vacuum on the steam-bath; 1.03 g. of crude ethyl diacetyl-*d*-tartrate, m. p. 50—56°, rising to 67—68° after two crystallisations from aqueous alcohol (Found : C, 49.5; H, 6.3. Calc. : C, 49.6; H, 6.2%), and 1.5 c.c. of a viscous brown liquid were obtained. Distillation of the latter in a vacuum gave a drop of acetic anhydride and about 0.5 c.c. of a pale yellow, viscous liquid, b. p. 185—206°/29 mm.; decomposition then occurred (also when the pressure was only 0.5 mm.). The viscous liquid soon crystallised, giving 0.25 g. of crude ethyl diacetyltartrate, m. p. 48—53° (67.5° after two crystallisations from aqueous alcohol). The mother-liquors from the recrystallisation failed to give any acetyl*mesotartrate*. The *d*-compound obtained had $[\alpha]_D^{17.5} - 8^\circ$ in 5% chloroform solution, which compared favourably with the value $[\alpha]_D - 8.8^\circ$ in 5% solution found by Freundler (*Ann. Chim. Phys.*, 1895, 4, 235). The theoretical yield of diacetyltartrate (both *d*- and *meso*-) by the reaction postulated (*vide infra*) would be 2.25 g. A total of 1.28 g. of the crude *d*-compound was isolated, *i.e.*, an amount slightly in excess of the theoretical quantity of the pure compound.

The ketohydroxy-ester did not decolorise bromine dissolved in carbon tetrachloride, carbon disulphide, or glacial acetic acid.

Attempts were made to improve the yield of ethyl ketohydroxysuccinate by varying the proportions of the reactants. Molecular proportions of ethyl tartrate and selenium dioxide of 6 : 1, 3 : 1, 2 : 1, and 1 : 1 gave respectively yields of 15.6, 16.0, 7.0, and nil % of the theoretical, calculated on the selenium dioxide used. No reduction of the dioxide occurred when either ethylene glycol or dioxan was used as a diluent. The low yield was due to the formation of other oxidation products and complex organo-selenium compounds. Carbon dioxide was invariably evolved during the initial refluxing. On refluxing ethyl tartrate (30 g.; 2 mols.) and selenium dioxide (8.1 g.; 1 mol.) at 130—140° for 3 hours, 2.5 g. of selenium (37%) were precipitated. The product was fractionated twice in a vacuum, and the following fractions collected : (1) b. p. 118—155°/32 mm., (2) 155—175°/36 mm., and (3) 175—195°/45 mm. (1) gave with aqueous phenylhydrazine acetate the bright yellow, finely crystalline bisphenylhydrazone of ethyl aldehydoglyoxylate, m. p. 222.5—223.5°, recrystallised from benzene-light petroleum (b. p. 40—60°) (Found : C, 66.3; H, 5.9; N, 18.4. Calc. : C, 65.9; H, 5.8; N, 18.1%). The mother-liquor from the original separation of this compound was evaporated to dryness, and the residue extracted with hot alcohol. A small final residue gave, on twice crystallising from benzene-light petroleum (b. p. 40—60°), white crystals, m. p. 172—180°. These were not identified. The alcoholic extract on evaporation gave a mixture of the bisphenylhydrazone of ethyl diketosuccinate and the pyrazolone formed from this compound (*vide supra*). This indicates the formation of either ethyl aldehydoglyoxylate or ethyl hydroxypyruvate (OH·CH₂·CO·CO₂Et).

The Reaction of Selenium Dioxide with Other Alkyl Tartrates.—Attempts were made to oxidise butyl and amyl tartrates with selenium dioxide. In each case oxidation occurred, but the liquid products soon began to decompose on distillation and no compounds were identified.

Methyl tartrate (56.5 g.; 2 mols.) and selenium dioxide (12.3 g.; 1 mol.) were heated together at 120° for 5 hours. When the product was distilled in a vacuum, methyl alcohol and water first came over; decomposition then occurred and continued throughout the distillation over the range 165°/60 mm. to 215°/200 mm. On redistillation the liquid began to boil at 60°/40 mm. and part of the distillate solidified. About 0.5 g., m. p. 96—98°, was obtained. The higher-boiling fractions were evil-smelling liquids from which no solid products could be obtained. The solid proved to be methyl fumarate, m. p. 101° (from methyl alcohol) and mixed melt (Found : C, 49.8; H, 5.55. Calc. : C, 50.0; H, 5.55%). The formation of this reduction product must obviously involve a complex reaction.

The Reaction of Selenium Dioxide with Ethyl Lactate.—Ethyl lactate (103 g.; 3½ mols.) and selenium dioxide (28 g.; 1 mol.) were heated under reflux at 120—130° for 4 hours. Much carbon dioxide was evolved. 14.5 G. of selenium (72.5%) were precipitated. After removal of the more volatile portion of the liquid product (alcohol and water) the residue was distilled in a vacuum over the range 50°/28 mm. to 215°/80 mm.; charring and decomposition then occurred. On redistillation of the liquid, the following fractions were collected : (1) 31—63°/23 mm., mostly ethyl lactate and water; (2) 61°/21 mm., colourless; (3) 62—160°/27 mm., yellow; and (4) 160—215°/35 mm., evil-smelling viscous liquid which deposited selenium. Ethyl pyruvate has the same b. p. as ethyl lactate (154—155° at ordinary pressure). (2) was therefore tested by

means of the sodium nitroprusside reaction (Simon, *Compt. rend.*, 1897, **125**, 534) and with phenylhydrazine. Both tests showed the presence of only a trace of pyruvate.

Fraction (3) gave with aqueous phenylhydrazine acetate the bisphenylhydrazone of ethyl aldehydoglyoxylate, m. p. 222—223° [from benzene—light petroleum (b. p. 40—60°)] and mixed melt (Found : C, 66.3; H, 5.9; N, 18.4. Calc. : C, 65.9; H, 5.8; N, 18.1%).

Taking into account the known reactions of selenium dioxide, it appears probable that the bisphenylhydrazone was derived from either $\text{CHO}\cdot\text{CO}\cdot\text{CO}_2\text{Et}$ or $\text{CHO}\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{Et}$. Because of the small yield of this substance, the reaction was not investigated further.

DISCUSSION.

Fenton and Wilks (J., 1912, **101**, 1574) described an ester which they believed to be ethyl ketohydroxysuccinate. Fenton (J., 1896, **69**, 546) had obtained dihydroxymaleic acid by the action of hydrogen peroxide on tartaric acid in the presence of reduced iron. This gave, with alcoholic hydrogen chloride, an ethyl ester, m. p. 72—73°, which was later found to consist of two compounds, since, on digestion with ether, part dissolved immediately and crystallised in long silky needles, m. p. 68° (*A* form). The remaining sparingly soluble portion, after repeated washing with ether, consisted of short rod-like prisms, m. p. 126—128° (*B* form). Both had the same composition corresponding to ethyl dihydroxymaleate. Their properties, however, differed considerably. Fenton believed the *A* form to be the dihydroxymaleate and the *B* form to be the ketohydroxysuccinate.

The differences in the properties of these two esters *A* and *B* and the isomeric ester *C* obtained from ethyl tartrate by means of selenium dioxide, are summarised below.

(1) Alcoholic ferric chloride gave a dark but transient green colour with *A*, no colour with *B*, and was reduced by *C*.

(2) Alkali hydroxides gave a lemon-yellow colour with *A* and no colour with *B* or *C*.

(3) Phenylhydrazine acetate reacted slowly with *A* and *B* (more quickly with *A*) in hot alcoholic solution. The product eventually obtained in each case was the pyrazolone derivative. *C* reacted immediately with aqueous phenylhydrazine acetate, giving the bisphenylhydrazone and the pyrazolone.

(4) *A* gave ethyl diacetoxymaleate with acetyl chloride, whereas *B* and *C* were unaffected; but *B* was practically insoluble in this reagent, and *C* was readily soluble.

(5) *A* was unaffected by acetic anhydride. *B* dissolved at once and, after $\frac{1}{2}$ hour's heating and removal of the excess of anhydride, gave crystals of the *A* form (m. p. 68°). *C* gave principally ethyl *d*-diacetyltartrate (m. p. 67.5°).

(6) After 12 hours over phosphoric oxide or sulphuric acid in the presence of air, *A* was entirely converted into a yellow liquid, believed to be ethyl diketosuccinate. *B* and *C* were unaffected by this treatment.

(7) *A*, dissolved in acetone, immediately decolorised dilute aqueous permanganate, whereas *B* and *C* reacted only slowly.

Fenton and Wilks regarded *A* and *B* as keto-enol isomerides, *A*, because of its behaviour with ferric chloride, acetyl chloride, permanganate, and phenylhydrazine, being the enolic form. They write, however, "the alternative hypothesis is, however, by no means excluded." The general properties, molecular weight, and optical activity of *C* can leave little doubt that it is the ketohydroxysuccinate. It is possible that *A* and *B* esters are *cis*- and *trans*-isomerides of ethyl dihydroxymaleate.

The existence of optical activity in a compound of this type is somewhat surprising, particularly in view of the relatively high temperature employed in its preparation. It can be attributed either to the absence of tautomerism, to the stabilising influence of the negative groups on the electronic structure of the asymmetric carbon atom, or to the complete absence of racemising conditions during the preparation (compare Kuhn and Albrecht, *Ber.*, 1927, **60**, 1297, on the optical activity of the sodium salt of 2-nitrobutane, and Leuchs, *Ber.*, 1913, **46**, 2435, on the bromination of 2-benzyl-1-hydrindone-*o*-carboxylic acid).

The behaviour of the compound on hydrolysis with both acid and alkali and with acetic anhydride presented anomalies which were to be expected with a compound of this type. The formation of oxalic acid on alkaline hydrolysis resembled the acid hydrolysis of

acetoacetic ester. The production of tartaric acid on hydrolysis with hydrochloric acid and the formation of *d*-diacetyltartrate on treatment with acetic anhydride are more difficult to understand. It is possible that an oxidation-reduction reaction involving two molecules of the ketohydroxysuccinate occurred. That both *d*- and *meso*-tartaric acid were detected amongst the products of acid hydrolysis and that the theoretical amount of *d*-diacetyltartrate was formed on treatment with acetic anhydride, are facts which strongly support this hypothesis.

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