343. *Addition of Thiol Compounds to the Double Bond. Part I. Preparation of Tertiary Mercapto-acids.*

By ZOLTAN FÖLDI and JANOS KOLLONITSCH.

Addition of hydrogen sulphide and of benzylthiol to *iso*propylidene compounds has been studied. Several β-mercapto-acids and derivatives containing the tertiary β-mercapto-group have been prepared.

THE main object of the present work was to prepare β-mercapto*iso*valeric acid and derivatives. Our first attempts, which started from ethyl β-bromo*iso*valerate or from β-bromo*iso*valeric acid, were unsuccessful. Replacement of the bromine atom by the thiol group or substitututed thiol group did not occur, as in each case hydrogen bromide was split off, giving rise to ethyl ββ-dimethylacrylate or ββ-dimethylacrylic acid. For this reason, our interest turned to addition of hydrogen sulphide and of thiols to unsaturated acids.

Addition of hydrogen sulphide, of thiophenols, and of mercapto-acids to αβ-unsaturated acids and ketones has been the subject of numerous investigations (Wallach, *Annalen*, 1894, **279**, 385; 1905, **343**, 32; Posner, *Ber.*, 1901, **34**, 1395; 1902, **35**, 799; 1904, **37**, 502; 1905, **38**, 646; 1907, **40**, 4788; Axberg and Holmberg, *Ber.*, 1933, **66**, 1194; Holmberg, *Brit. Abstr.*, 1944, *A*, II, 2943; Nicolet, *J. Amer. Chem. Soc.*, 1935, **57**, 1098; Carter *et al.*, *J. Biol. Chem.*, 1941, **139**, 247).

In exploratory experiments we prepared methyl 2-mercapto*iso*butyl ketone by the action of liquid hydrogen sulphide on mesityl oxide, in order to collect some information on the efficiency of various catalysts. Triethylamine proved to be an excellent catalyst, affording yields up to 80% of the theory, while diethylamine led to yields of only about 10%. Under similar conditions ethyl ββ-dimethylacrylate showed no appreciable tendency to add either hydrogen sulphide or ethylthiol. Free ββ-dimethylacrylic acid proved to be still more resistant to addition, though a large excess of triethylamine was used. As the vicinity of only one carboxyl group to the double bond proved to be quite inadequate to induce addition, we investigated the addition to ethyl *iso*propylidenemalonate. By using considerably larger amounts of triethylamine than used with mesityl oxide, we obtained *ethyl β-mercapto-α-carbethoxy*isovalerate in yields up to 60% of theory. Attempts, however, to hydrolyse this ester to the corresponding acid were unsuccessful. Alkaline hydrolyses in aqueous or alcoholic solution effects a rather complex disintegration of the molecule, such as splitting off of considerable amounts of hydrogen sulphide, affording *iso*propylidenemalonic acid, and cleavage to malonic acid. Acid hydrolysis was also unsatisfactory.

The synthesis of *β-mercapto*isovaleric *acid* was finally achieved by reaction of hydrogen sulphide with *iso*propylidenemalonic acid. Under mild conditions, β-mercapto-α-carboxy-*iso*valeric acid was formed in satisfactory yield; on decarboxylation by heating at about 150°, this gave the desired β-mercapto*iso*valeric acid. That the thiol group is a tertiary one is shown by the green coloration in the Rheinboldt test (*Ber.*, 1927, **60**, 184). The addition is therefore " normal " with respect to Markownikoff's rule.

We have also obtained under similar conditions from *iso*propylidenemalonic acid and benzylthiol *β-benzylthio-α-carboxy*isovaleric acid, and from ethyl α-nitro-ββ-dimethylacrylate (Bouveault and Wahl, *Compt. rend.*, 1900, **131**, 687, 748) and benzylthiol *ethyl α-nitro-β-benzylthio*isovalerate. (The constitution of the latter is in doubt, for the compound is insoluble in aqueous sodium hydroxide.)

These reactions show a much greater reactivity of the double bonds in these compounds than in ββ-dimethylacrylic acid; this is in accordance with observations of Scheiber and Meisel (*Ber.*, 1915, **48**, 248, 264), who investigated the reactions of ethyl acetoacetate with ethyl ββ-dimethylacrylate and with ethyl *iso*propylidenemalonate and found the latter, likewise, more reactive.

EXPERIMENTAL.

*Methyl β-Mercapto*isobutyl *Ketone.*—Into a mixture of mesityl oxide (35·5 g.), triethylamine (3 g.), and dry ether, cooled by an acetone–carbon dioxide freezing mixture, dry hydrogen sulphide is introduced until an increase by volume of about 10—15 c.c. takes place. The mixture is then kept in an autoclave at room temperature overnight and finally heated at 50° for 2 hours. The mixture yields, on distillation under 15 mm., after a little forerun, 38 g. of the mercapto-ketone (b. p. 56—60°) as a colourless liquid with a pungent mercaptan odour, and giving the Rheinboldt test characteristic of a tertiary thiol group. For characterisation, the *mercury mercaptide* has been prepared. To the mercapto-ketone (1·32 g.) saturated aqueous mercuric chloride solution (22 c.c.) is added. A voluminous, white precipitate occurs which, after standing overnight, is collected, washed with water, and dried in a desiccator over sulphuric acid; yield, 2·25 g., m. p. 73—75° (not sharp) [Found : Hg, 42·2. $(C_6H_{11}OS)_2Hg$ requires Hg, 43·2%].

Mesityl oxide (20·5 g.) and diethylamine (1 c.c.), treated as above with hydrogen sulphide, yielded only 3 g. of the mercapto-ketone, after a large forerun of mesityl oxide.

*Ethyl β-Mercapto-α-carbethoxy*isovalerate.—A mixture of ethyl *iso*propylidenemalonate (50 g.), triethylamine (30 g.), and absolute ethanol (30 c.c.) was saturated with hydrogen sulphide as described above and then kept in a steel bomb at room temperature for 48 hours and warmed for 2 hours in a water-bath at 70°. The reaction mixture, a colourless liquid mixed with crystals, was diluted with water (30 c.c.), acidified with 5N-hydrochloric acid (80 c.c.), and extracted with ether; the ethereal layer was dried (Na_2SO_4), freed from ether, and the residue (52 g.) fractionated. After a slight forerun, 35 g. of *ethyl β-mercapto-α-carbethoxy*isovalerate were obtained as a colourless liquid, b. p. 90—93°/1 mm. (Found : S, 13·3. $C_{10}H_{18}O_4S$ requires S, 13·6%). The substance has a characteristic mercaptan-like odour. Its solution in ether gives with sodium nitrite and sulphuric acid a green coloration (tertiary mercapto-group). It gives with aqueous mercuric chloride a white precipitate, reduces Fehling's solution, and gives an intense carmine-violet coloration with sodium nitroprusside.

Alkaline hydrolysis. The ester (2·34 g.) is heated with 2·5N-sodium hydroxide (10 c.c.) for 1½ hours on the steam cone, then cooled and acidified with concentrated hydrochloric acid (3 c.c.). Hydrogen sulphide is evolved and an oil separates, which is taken up in ether. The residue (0·96 g.) from the ethereal layer partly crystallises on standing, and after being washed with ethyl chloride affords 0·2 g. of white crystals, m. p. *ca.* 105° (indef.) (equiv., *ca.* 76). It is soluble in water, reduces Fehling's solution, and gives a precipitate with aqueous mercuric chloride. The substance is believed to be the β-lactone of β-mercapto-α-carboxy*iso*valeric acid. The residue from the ethyl chloride mother-liquor, dissolved in water, yields on addition of ammonia and calcium chloride and on standing, a white precipitate of *calcium β-mercapto-α-carboxy*isovalerate (0·07 g.) (Found : Ca, 15·5; H_2O, by drying at 110°, 17·2. $C_6H_8O_4SCa,2\frac{1}{2}H_2O$ requires Ca, 15·4; H_2O, 17·3%).

The aqueous layer from which the separated oil has been removed by ether is further extracted with ether. The ethereal extract yields, on addition of ammoniacal calcium chloride and on standing, white sandy crystals of *calcium* iso*propylidenemalonate* (0·32 g.) (Found : Ca, 15·5; H_2O, by drying at 110°, 30·1. $C_6H_6O_4Ca,4\frac{1}{2}H_2O$ requires Ca, 15·2; H_2O, 30·8%).

The aqueous solution which has been extracted with ether is evaporated to dryness under diminished pressure, and the solid residue thoroughly extracted with ether. On evaporation of the ether, white leaflets (0·44 g.) are obtained which yield, on addition of ammoniacal calcium chloride, white sandy crystals of calcium malonate (0·65 g.) (Found : Ca, 21·8; H_2O, 22·8. Calc. for $C_3H_2O_4Ca,2\frac{1}{2}H_2O$: Ca, 21·4; H_2O, 24·1%).

*β-Mercapto-α-carboxy*isovaleric *Acid.*—*iso*Propylidenemalonic acid (11·2 g.), dissolved in alcohol (15 c.c.), was mixed with triethylamine (25 c.c.) under cooling with ice, and saturated with hydrogen sulphide while cooled in solid carbon dioxide–acetone. Then the mixture was kept in a steel bomb overnight at room temperature and finally warmed for 2 hours at about 50°. The contents were diluted with ether and acidified with hydrochloric acid. The ethereal layer was dried (Na_2SO_4) and gave on evaporation of the solvent a white crystalline residue. This was extracted with hot chloroform; the mercapto-acid was precipitated from the chloroform solution with light petroleum (b. p. 55—60°). About 10 g. of the crude *mercapto-acid* were obtained, m. p. 115—125° (decomp.). It was purified through two more precipitations with light petroleum from chloroform solution. The pure acid forms long colourless needles, m. p. 136—137° (decomp.) (Found : S, 18·3. $C_6H_{10}O_4S$ requires S, 18·0%), and gives a green coloration in the Rheinboldt test, and a cobalt-blue coloration with aqueous ferric chloride solution.

*β-Mercapto*iso*valeric Acid.*—The foregoing acid (7·9 g.) was decarboxylated by heating at 140—150° for ½ hour. The loss of weight was 2·08 g. (Calc.: 1·98 g.). The remaining oil was distilled at 1 mm. pressure; the fraction, b. p. 74—80°, is a colourless liquid with the odour of both a mercaptan and *iso*valeric acid; it solidified on standing to a white crystalline mass, m. p. *ca.* 20—23°. On refractionation, the fraction of b. p. 112—115°/10 mm. solidified in the receiver and had m. p. 34—35°, (Found: SH, by iodometric titration, 24·6; equiv., 133. $C_5H_{10}O_2S$ requires SH, 24·6%; equiv., 134). The *mercapto-acid* is sparingly soluble in water, and gives with ferric chloride a cobalt-blue coloration.

*β-Benzylthio-α-carboxy*iso*valeric Acid.*—*iso*Propylidenemalonic acid (7·2 g.) was dissolved in 85% alcohol (30 c.c.) and mixed under ice-cooling with diethylamine (10 c.c.), benzylthiol (8 c.c.), and triethylamine (5 c.c.); a clear solution was obtained. The flask was hermetically closed, then warmed for 5 mins. in a steam-bath and kept overnight at room temperature. The solvents and the excess of diethylamine and triethylamine were evaporated in a vacuum and the residue was mixed with water (60 c.c.) and 5N-hydrochloric acid (30 c.c.); 12 g. of crude *β-benzylthio-α-carboxy*iso*valeric acid* separated, m. p. 122—126°. The crude acid was dissolved in ether (25 c.c.) and precipited with light petroleum (70 c.c.), giving 10 g. of the pure acid, m. p. 133—134° (decomp.) (Found: equiv., 273. $C_{13}H_{16}O_4S$ requires equiv., 268).

*Ethyl α-Nitro-β-benzylthio*iso*valerate.*—Ethyl α-nitro-ββ-dimethylacrylate (1·73 g.) was mixed with anhydrous ethanol (3 c.c.), and triethylamine (0·1 c.c.) and benzylthiol (1·34 g.) were added. A clear reddish solution was obtained; the temperature of the mixture rose to 60° and it became thicker. The flask was closed and kept overnight. The reaction mixture was then dissolved in ether (15 c.c.), the ethereal layer washed with N-hydrochloric acid (2 × 10 c.c.) and then with water (2 × 5 c.c.), dried (Na_2SO_4), and freed from ether, and the residue kept under 0·3 mm. at 120°. The resulting oil (2·6 g.) was distilled: b. p. 160—162°/0·3 mm.; the *ester* is insoluble in N-sodium hydroxide (Found: S, 10·0. $C_{14}H_{19}O_4NS$ requires S, 10·7%).

The authors' thanks are due to the staff of the Analytical Department of Chinoin Works for the analyses.

RESEARCH LABORATORIES OF CHINOIN WORKS,
UJPEST, HUNGARY.

[*Received, November 4th*, 1947.]