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Studies on Alkylsulfinylcarboxylic Acids

I. The Preparation and Titrimetric Determination of Some New Sulfinyl Compounds

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In order to make a kinetic study, various compounds of the general type: R—SO—R′—COOH were needed. Some of these were found to consume more than two equivalents of bromine when titrated with bromide-bromate. The same compounds also reacted too slowly with hydrogen bromide in glacial acetic acid for allowing an accurate determination with that method.

It has been shown that compounds of the type $R-S-C(CH_3)_2COOH$ [1] and $R-S-CH_2CH(CH_3)COOH$ [2] with R = CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, C_6H_5-, $C_6H_5CH_2$-, and $C_6H_5CH_2CH_2$- all consume 4 equivalents of bromine when titrated with bromide-bromate. The corresponding sulfinyl acids will of course consume half the amount, *i.e.*, two equivalents. This property has been used for the quantitative determination of such compounds. Another generally adopted method has been the reaction with hydrogen bromide in glacial acetic acid; the then liberated bromine being determined iodometrically.[3]

In connection with a kinetic study (which will be described in a later paper) a series of new alkylsulfinylcarboxylic acids was prepared. These are:

$(CH_3)_3C \cdot SO \cdot C(CH_3)_2COOH$
$(CH_3)_2CH \cdot SO \cdot CH_2CH_2COOH$
$(CH_3)_3C \cdot SO \cdot CH_2CH_2COOH$
$CH_3CH_2CH(CH_3) \cdot SO \cdot CH_2CH_2COOH$
$HOCO \cdot (CH_2)_4 \cdot SO \cdot CH_2CH_2COOH$
$CH_3CH_2CH_2 \cdot SO \cdot C(CH_3)_2CH_2COOH$
$HOCO \cdot CH_2CH_2 \cdot SO \cdot C(CH_3)_2CH_2COOH$
$HOCO \cdot (CH_2)_4 \cdot SO \cdot (CH_2)_4 \cdot COOH$

The equivalent weights of all these compounds have been determined in three different ways, *viz.* by titration with sodium hydroxide and by the two methods mentioned above.

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By using bromide-bromate titration it was found that α-(*tert.*-butylsulfinyl)-isobutyric acid and β-(*tert.*-butylsulfinyl)-propionic acid together with their corresponding sulfide-acids all consumed two equivalents of bromine more than calculated for the oxidation to sulfones. Besides the two derivatives of isovaleric acid, β-(propylsulfinyl)-isovaleric acid and β-(β-carboxyethylsulfinyl)-isovaleric acid also consumed more bromine than calculated. The results are given in Table 1.

In the case of the *tert.*-butyl compounds these results would be due to the following reaction:

$$(CH_3)_3C-S-R-COOH \xrightarrow{Br_2} (CH_3)_3C-SO-R-COOH \xrightarrow{Br_2} (CH_3)_3C-SO_2-R-COOH \xrightarrow{Br_2} (CH_3)_3COH + HOSO_2-R-COOH$$

This was verified by reproducing this reaction on a preparatory scale. In such an experiment β-sulfopropionic acid could be isolated as Ba-salt when starting with β-(*tert.*-butylsulfinyl)-propionic acid. Analyses and details are given in the experimental part of this work.

In the case of the isovaleric acid derivatives the results indicate an analogous but more slowly proceeding C—S bond fission due to oxidation, but this has not yet been clearly confirmed.

When hydrogen bromide in glacial acetic acid as a reducing agent was used for the titrimetric determination of the sulfinyl compounds, it was found that the *tert.*-butyl- and isovaleric acid compounds mentioned above reacted so slowly that this method could not be used for their quantitative determination. The results are shown in Table 1.

All sulfinyl compounds have been prepared through oxidation of their corresponding sulfides in acetone solution with perhydrol in an excess of 5—10 %.[4] The temperature has been kept at about ± 0° during the time of the reaction which has been 2—3 days. After removal of the acetone the crude product appeared as an oil in many cases and was therefore placed in a desiccator to crystallize, which process often proceeded slowly and took a very long time. When crystallized, the substances were thoroughly washed with dry ether in order to remove any traces of sulfide compound which might have remained unreacted. They have then been recrystallized when possible. Many

Table 1. Equivalent weights found for the various sulfinyl compounds.

Compound	Equivalent weights					Number of equivalents of bromine consumed
	NaOH		HBr	$KBrO_3$		
	found	calc.	found	found	calc.	
$(CH_3)_3C{\cdot}SO{\cdot}C(CH_3)_2COOH$	191.2	192.3		47.0	96.1	4.09
$(CH_3)_2CH{\cdot}SO{\cdot}CH_2CH_2COOH$	164.2	164.2	82.2	82.9	82.1	1.98
$(CH_3)_3C{\cdot}SO{\cdot}CH_2CH_2COOH$	177.3	178.3		43.3	89.1	4.12
$CH_3CH_2CH(CH_3){\cdot}SO{\cdot}CH_2CH_2COOH$	178.5	178.3	88.8	87.6	89.1	2.04
$HOCO(CH_2)_4{\cdot}SO{\cdot}CH_2CH_2COOH$	112.2	111.1	115.6	115.8	111.1	1.92
$CH_3CH_2CH_2{\cdot}SO{\cdot}C(CH_3)_2CH_2COOH$	192.7	192.3		86.2	96.1	2.23
$HOCOCH_2CH_2{\cdot}SO{\cdot}C(CH_3)_2CH_2COOH$	112.1	111.1		74.1	111.1	3.00
$HOCO(CH_2)_4{\cdot}SO{\cdot}(CH_2)_4COOH$	125.9	125.2	126.5	117.1	125.2	2.14

of the compounds have been quite sensitive to temperature rise, and this fact combined with the difficulty with which some of them crystallize have made recrystallization impossible in many cases.

EXPERIMENTAL

Preparation of the mercapto-acids. β-Mercaptopropionic acid was prepared from β-chloropropionic acid and sodium hydrogen sulfide in water solution.[5] α-Mercaptoisobutyric acid from α-bromoisobutyric acid and potassium xanthogenate with subsequent fission of the α-xanthogenate isobutyric acid in ethanol and concentrated ammonia.[6] β-Mercapto-isovaleric acid was obtained by the method of Földi and Kollonitsch [7] which implies that hydrogen sulfide is added to isopropylidene malonic acid and that decarboxylation of the β-mercapto-α-carboxyisovaleric acid thus formed then follows.

Preparation of the sulfide- and sulfinyl acids

*α-(*tert.*-Butylthio)-isobutyric acid (I).* 18 g (0.15 mole) α-mercaptoisobutyric acid, 22.2 g (0.3 mole) *tert.*-butanol and 60 ml 3 M hydrochloric acid were refluxed for 4 h. An oil was obtained which was taken up in ether, the ether-solution dried, the ether distilled off and the residue distilled at reduced pressure, yielding an oil, b.p. 99.5°/2 mm, which crystallized immediately upon cooling. 12.8 g (48 %) with m.p. 56.2–58.2° were obtained. (Found: C 54.3; H 9.17; S 18.1. Calc. for $C_8H_{16}O_2S$: C 54.5; H 9.15; S 18.2).

*α-(*tert.*-Butylsulfinyl)-isobutyric acid (II).* M.p. 102–103°. (Found: C 50.1; H 8.48; S 16.65; equiv. wt. 191.2. Calc. for $C_8H_{16}O_3S$: C 50.0; H 8.39; S 16.7; equiv. wt. 192.3).

β-(Isopropylthio)-propionic acid (III). 53.1 g (0.5 mole) β-mercaptopropionic acid, 40.0 g (1.0 mole) sodium hydroxide in 300 ml water, 61.5 g (0.5 mole) isopropylbromide and ethanol were mixed to homogeneous solution. The mixture was stirred at room temperature overnight, then refluxed for 1 h and finally cooled, acidified and extracted with ether. The ether-solution was dried, the ether distilled off and the residue vacuum-distilled. 55.5 g (75 %) with b.p. 106°/1.5 mm, $n_D^{25} = 1.4752$ were obtained. (Found: C 48.4; H 8.23; S 21.4. Calc. for $C_6H_{12}O_2S$: C 48.6; H 8.16; S 21.6).

β-(Isopropylsulfinyl)-propionic acid (IV). The acid was recrystallized from ethyl acetate + light petroleum. M.p. 50.5–60.0°. (Found: C 43.8; H 7.38; S 19.3; equiv. wt. 164.2. Calc. for $C_6H_{12}O_3S$: C 43.9; H 7.37; S 19.5; equiv. wt. 164.2).

*β-(*tert.*-Butylthio)-propionic acid (V).* 10.6 g (0.1 mole) β-mercaptopropionic acid, 16.4 g (0.22 mole) *tert.*-butanol and 40 ml 2.5 M hydrochloric acid were refluxed for 3 h. An oil was obtained which was taken up in ether, the ether-solution dried, the ether distilled off and the residue vacuum-distilled. The main fraction, b.p. 109°/2 mm, solidified upon cooling. 14.2 g (87.7 %) were obtained.

*β-(*tert.*-Butylsulfinyl)-propionic acid (VI).* M.p. 108.5–110.5°. (Found: C 46.9; H 7.87; S 17.9; equiv. wt. 177.3. Calc. for $C_7H_{14}O_3S$: C 47.2; H 7.92; S 18.0; equiv. wt. 178.3).

*β-(*sec.*-Butylthio)-propionic acid (VII).* β-Mercaptopropionic acid was treated with *sec.*-butylbromide and alkali in the same way as described for the preparation of III. 53.1 g (0.39 mole) mercapto-acid yielded 56.1 g (69 %) β-(*sec.*-butylthio)-propionic acid with b.p. 114–5°/2 mm. (Found: C 51.3; H 8.64; S 19.9. Calc. for $C_7H_{14}O_2S$: C 51.8; H 8.70; S 19.8).

*β-(*sec.*-Butylsulfinyl)-propionic acid (VIII).* M.p. 49–52°. (Found: C 46.8; H 8.15; S 17.9; equiv. wt. 178.5. Calc. for $C_7H_{14}O_3S$: C 47.2; H 7.92; S 18.0; equiv. wt. 178.3).

β-(ω-Carboxybutylthio)-propionic acid (IX). 18.1 g (0.1 mole) ω-bromovaleric acid (prepared according to Hunsdiecker [8]) were neutralized with sodium carbonate. To 10.6 g (0.1 mole) β-mercaptopropionic acid first a water solution of 8.0 g (0.2 mole) sodium hydroxide was added and then the neutralized bromo acid under stirring. The solution was then refluxed for 4 h, cooled, acidified and extracted with ether, because the sulfide acid thus formed precipitated only partially. The ether was removed, leaving a crystal mass which after drying in a desiccator had m.p. 75–77°. Several recrystallizations from benzene + light petroleum and ethyl acetate + light petroleum finally gave 7.4 g (36 %)

β-(ω-carboxybutylthio)-propionic acid with m.p. 80.3–80.8°. (Found: C 46.5; H 6.77; S 15.5. Calc. for $C_8H_{14}O_4S$: C 46.6; H 6.84; S 15.5).

β-(ω-Carboxybutylsulfinyl)-propionic acid (X). The acid was recrystallized from ethyl acetate + light petroleum. M.p. 75°. (Found: C 43.0; H 6.32; S 14.2; equiv. wt. 112.2. Calc. for $C_8H_{14}O_5S$: C 43.2; H 6.35; S 14.4; equiv. wt. 111.1).

β-(Propylthio)-isovaleric acid (XI). β-Mercaptoisovaleric acid was treated with propylbromide and alkali in the same way as described for the preparation of III. 11.2 g (0.084 mole) mercapto-acid yielded 9.7 g (66 %) β-(propylthio)-isovaleric acid with b.p. 119–20°/2 mm and $n_D^{25} = 1.4760$. (Found: C 54.5; H 9.29; S 18.15. Calc. for $C_8H_{16}O_2S$: C 54.5; H 9.15; S 18.2).

β-(Propylsulfinyl)-isovaleric acid (XII). M.p. 60–62°. (Found: C 49.9; H 8.26; S 16.5; equiv. wt. 192.7. Calc. for $C_8H_{16}O_3S$: C 50.0; H 8.39; S 16.7; equiv. wt. 192.3).

β-(β-Carboxyethylthio)-isovaleric acid (XIII). This compound was prepared from β-mercaptoisovaleric acid and β-bromopropionic acid in analogy with the synthesis of IX. After removal of the ether a thick oil was obtained which soon crystallized. Two recrystallizations from chloroform + light petroleum and later two from toluene yielded a product with m.p. 65.1–67.4°. Starting from 11.2 g (0.084 mole) β-mercaptoisovaleric acid 9.8 g (57 %) β-(β-carboxyethylthio)-isovaleric acid with that m.p. were obtained. (Found: C 46.0; H 6.83; S 15.3; equiv. wt. 103.4. Calc. for $C_8H_{14}O_4S$: C 46.6; H 6.84; S 15.5; equiv. wt. 103.1).

β-(β-Carboxyethylsulfinyl)-isovaleric acid (XIV). M.p. 62–64°. (Found: C 42.6; H 6.39; S 14.45; equiv. wt. 112.1. Calc. for $C_8H_{14}O_5S$: C 43.2; H 6.35; S 14.4; equiv. wt. 111.1)

δ-Thiodi-valeric acid (XV). This compound was prepared in two different ways: (A) From ethyl ω-bromovalerate and sodium sulfide in absolute ethanol.[9] 54 g bromo ester yielded (after recrystallization from ethyl acetate + light petroleum) 7.1 g (22 %) δ-thiodivaleric acid with m.p. 95°. (B) From ω-bromovaleric acid and sodium sulfide in water solution. From 23.4 g bromo acid 8.0 g (53 %) sulfide acid with m.p. 95° were obtained.

δ-Sulfinyldi-valeric acid (XVI). M.p. 85–86°. (Found: C 47.9; H 7.33; S 12.8; equiv. wt. 125.9. Calc. for $C_{10}H_{18}O_5S$: C 48.0; H 7.25; S 12.8; equiv. wt. 125.2).

Preparation of the β-sulfopropionic acid Ba-salt

β-(*tert.*-Butylsulfinyl)-propionic acid was treated with bromine-water until this was no longer decolourized. After that the whole mixture was placed in a water-bath for several hours. A viscous residue was obtained, which crystallized when put into a desiccator. This crystal mass was very hygroscopic, and therefore its barium salt was made, which was dried in a desiccator and analyzed for carbon, hydrogen and barium. (Found: C 11.7; H 2.29; Ba 43.5. Calc. for $C_3H_4O_5S$ Ba; 1.5 H_2O: C 11.4; H 2.23; Ba 43.4).

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