Optically Active Thiophene Compounds. II. α-Thenyl α-Thienylacetic Acid and α-Thenylphenylacetic Acid

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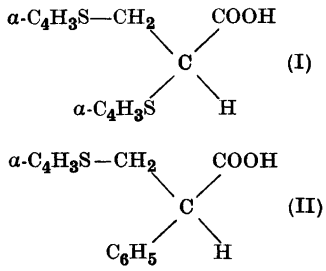
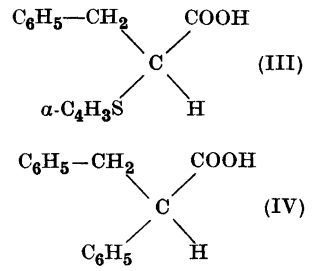
In connection with work in progress on optically active thiophene derivatives [1] we have prepared α-thenyl α-thienylacetic acid (I) and α-thenylphenylacetic acid (II). The end in view is to resolve the acids into the optical antipodes and compare them with the antipodes of benzyl α-thienylacetic acid (III) and benzylphenylacetic acid (IV).



(I)

(II)



(III)

(IV)

For the optical resolution of the acids, *l*-ephedrine seems to be a satisfying operating agent. These experiments will be published later. Rupe and Kerkovins had previously resolved the benzylphenylacetic acid (IV) by means of strychnine [2]. Our results indicate that this resolution was not complete.

Thenylthienylacetic acid has been prepared from ethyl thienylcyanoacetate and thenyl chloride, using anhydrous potassium carbonate as the condensing agent and dry acetone as solvent [3]. The ethyl thienylcyanoacetate thus obtained was decarboxylated and hydrolyzed to give thenylthienylacetic acid.

Thenylphenylacetic acid has been prepared from ethyl phenylmalonate and thenyl chloride analogously to the preparation of benzylphenylacetic acid [4], but the preparation from ethyl phenylcyanoacetate and thenyl chloride will probably give a better yield.

Ethyl thenylthienylcyanoacetate: In a round-bottomed, three-necked flask, fitted with a mercury-sealed stirrer and reflux condenser, were placed 12 g (0.061 moles) of ethyl thienylcyanoacetate, 10 g (0.075 moles) of thenyl chloride, 25 g (0.180 moles) of anhydrous potassium carbonate, and 200 ml of acetone. The mixture was stirred and refluxed for 20 hours, the acetone removed by distillation, and the residue treated with 100 ml of water. The upper oily layer was separated, the water layer extracted three times with ether, the ether combined with the oily layer, the mixture dried with anhydrous sodium sulphate and distilled. 14 g (0.048 moles) of ethyl thenylthienylcyanoacetate were obtained, boiling at 195–205° C/9 mm Hg. Yield 79 %.

Thenylthienylacetic acid: 14 g (0.048 moles) of ethyl thenylthienylcyanoacetate and 6.5 g (0.116 moles) of potassium hydroxide, dissolved in 100 ml of alcohol, were heated on a water bath for 10 minutes. The potassium carbonate obtained was filtered off and washed with alcohol. The filtrate and 6.5 g (0.116 moles) of potassium hydroxide, dissolved in dilute alcohol, were placed in a round-bottomed flask, fitted with a reflux condenser, and boiled in an oil bath until no more ammonia escaped (12 hours). The alcohol was

removed by distillation, the residue acidified with dilute hydrochloric acid, and the precipitated acid dissolved in ether. After removing the ether 11.2 g (0.047 moles) of thenylthienylacetic acid were obtained. Yield 98 %. The crude acid was recrystallized from dilute formic acid and finally from petrol (b. p. 60—70° C). M. p. 90.5—92.5° C.

	Equiv. wt.	C	H	S
$C_{11}H_{10}O_2S_2$ Calc.	238.3	55.44	4.23	26.91
Found	238.8	55.19	4.12	26.78

Ethyl thenylphenylmalonate: In a round-bottomed, two-necked flask, one neck being fitted with a reflux condenser, 50 ml of absolute alcohol were placed, and then, through the other neck, 4.6 g (0.20 moles) of sodium, cut in pieces. When the sodium had reacted (at the end of the reaction, the flask had to be warmed in an oil bath), 47.0 g (0.20 moles) of ethyl phenylmalonate was added through a dropping funnel. Then 26.5 g (0.20 moles) of thenyl chloride were added, and the mixture heated in an oil bath, until the reaction had ceased. The alcohol was removed by distillation, and water was added to dissolve the sodium chloride, the oily layer separated and the water layer extracted three times with ether. The ether and oily layers were combined, dried with anhydrous calcium chloride and distilled. 36.0 g (0.11 moles) of thenylphenylmalonate were obtained as a light yellow oil, boiling at 185—195° C/9 mm Hg. Yield 55 %.

Thenylphenylacetic acid: In a round-bottomed flask, fitted with a reflux condenser, were placed 36.0 g (0.11 moles) of ethyl thenylphenylmalonate and 10.0 g (0.44 moles) of sodium hydroxide, dissolved in dilute alcohol. The mixture was boiled for one hour in an oil bath. The alcohol was removed by distillation, the residue acidified with dilute hydrochloric acid, the precipitated oily acid dissolved in ether and the ether removed. 22 g (0.095 moles) of thenylphenylacetic acid were obtained. Yield 86 %. The crude acid was recrystallized from petrol (b. p. 60—70° C). M. p. 71.5—72.0° C.

	Equiv. wt.	C	H	S
$C_{13}H_{12}O_2S$ Calc.	232.1	67.21	5.21	13.49
Found	231.5	66.89	5.07	13.58

The authors are indebted to the Royal Swedish Academy of Science for financial support from the Nobel Fund of Chemistry (*Kemiska prisgruppens särskilda fond*).

1. Fredga, A., and Palm, O. *Arkiv Kemi, Mineral. Geol.* **A 26** (1949) no. 26.
2. Rupe, H., and Kerkovins, W. *Ber.* **45** (1912) 1398.
3. Pettersson, K. *Acta Chem. Scand.* **4** (1950) 395.
4. Wislicenus, W., and Goldstein, K. *Ber.* **28** (1895) 815.

Received October 7, 1950.

The High Rotatory Power of Cystine

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In a recent publication[1] Fieser has drawn attention to the high rotatory power of cystine already pointed out by van't Hoff. While the other acyclic amino acids, including cysteine, are characterized by low specific rotations (about 10°), cystine shows the remarkable value $[\alpha]_D = -214°$ (acid solution). The rotation is greatly dependent on the pH of the medium and in alkaline solution much lower values are reported. According to Fieser, the rotation of cystine appears as extraordinary today as it did to van't Hoff in 1898. As a possible explanation he suggests the formation of hydrogen bonds between the carboxyles and the amino groups, resulting in an endocyclic ring structure.