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Synthesis of Racemic m-Methylbenzylsulfoxyacetic Acid and Its Resolution into Optical Antipodes

Synteza racemicznego kwasu m-metylobenzylosufinylooctowego i jego rozdział na antypody optyczne

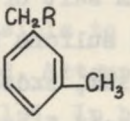
Синтез рацемической м-метилбензилсульфинилуксусной кислоты и ее разделение на оптические антиподы

According to some authors [1-7] alkyl substituents have two effects - the hyperconjugation effect, which in unsaturated systems resembles the mesomeric effect (+M), and the inductive effect, which in unsaturated compounds seems to have positive values (+I) and in saturated compounds negative ones (-I). It is possible that these effects can influence the molar rotation of unsaturated compounds and aromatic - aliphatic compounds containing chirality centres on heteroatoms. In our opinion the solution of this problem requires first of all experimental studies. For this reason in our previous work we have investigated optical relationships in the group of isomeric tolylsulfoxydimethylacetic acids [8], for which we have selected phenylsulfoxydimethylacetic acids as the reference systems. In these studies we have found that all the above compounds have normal rotatory dispersion in the visible part of the spectrum. The enantiomers rotating the plane of polarized light in the same

direction had the same spatial structure. As a rule, the ortho and para acids had molar rotations higher and the meta acids lower than the unsubstituted system i.e. carboxyisopropylsulfoxybenzene. The observed optical order could be due to the hyperconjugation effect of methyl groups situated in the quinonoidal positions with respect to the sulfinyl chirality centre on the free π electrons of the benzene ring. The methyl groups could also have a weak negative inductive effect (-I) which could cause a decrease of molar rotations of the compounds of the meta series to values lower than those of the unsubstituted system. Although this working hypothesis is in agreement with the suggestions made by Coulson [6] and Kwart [7], it is contrary to the predictions based on the σ Hammett's constants [9]. Taking into account the fact that further information was desirable, we became interested in the optical order in the group of isomeric (position isomerism) methylbenzylsulfoxyacetic acids for which we have chosen enantiomeric benzylsulfoxyacetic acids as the reference system. It could be expected that the shift of the sulfoxide chirality centre from the aromatic ring along the side chain would decrease the hyperconjugation effect and would expose the inductive effect. It cannot be excluded that a larger experimental material could make it possible to draw substantiated conclusions having a more general character.

In the present communication we are reporting the results of our studies on the synthesis of racemic m-methylbenzylsulfoxyacetic acid and its resolution into optical isomers.

The starting material of our syntheses was m-methylbenzylsulfoxyacetic acid 2 which was not previously described in the chemical literature. We obtained it by condensation of ω-bromo-m-xylene with sodium thioglycolate, which was carried out under mild conditions. Compound 2 was characterized as its amide 3 and anilide 4. Its structure was confirmed by its IR spectra (the characteristic bands are given in the Experimental Part).



1: R = Br
2: R = $S.CH_2.COOH$
3: R = $S.CH_2CO.NH_2$
4: R = $S.CH_2.CO.NH.C_6H_5$
5: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.COOH$
6: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.CO.NH_2$
7: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.CO.O.CH_2.CO.C_6H_4Br$
8: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.CO.O.CH_2.CO.C_6H_4.C_6H_5$
9: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2COOH.CND$ *
10: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.COOH$
11: R = $\overset{(-)}{\underset{(+)}{SO}}.CH_2COOH.CND$ *
12: R = $\overset{(-)}{\underset{(+)}{SO}}.CH_2.COOH$
13: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.CO.NH_2$
14: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.CO.O.CH_2.CO.C_6H_4Br$
15: R = $\overset{(+)}{\underset{(-)}{SO}}.CH_2.CO.O.CH_2.CO.C_6H_4.C_6H_5$
16: R = $SO_2.CH_2.COOH$

We obtained racemic m-methylbenzylsulfoxyacetic acid 5 by oxidation of acid 2 with 30% H_2O_2 at room temperature in glacial acetic acid. It readily gave crystallizing amide 6 and p-bromophenacyl and p-phenylphenacyl esters (7 and 8 respectively). Its methyl ester could not be obtained in the crystalline state. The structure of acid 5 was confirmed by its IR spectra (the characteristic bands are given in the Experimental Part). It

*CND = cinchonidine.

should be mentioned that sodium salt of 2 could be readily converted into the corresponding sulfone by oxidation under drastic conditions (100°C, aqueous medium, excess of the oxidizing agent).

We have resolved racemic acid 5 by crystallization of its salts with optically active alkaloid. The neutral cinchonidine salt, which crystallizes from ethyl acetate, was the most suitable for the isolation of the dextrorotatory enantiomer 10. After four crystallizations it was optically homogeneous. It forms regular needles m. p. 126°C, $[\alpha]_D^{20} = -18.1^\circ$ in 96% ethanol. The search for an optically active base suitable for the separation of the laevorotatory m-methylbenzylsulfoxyacetic acid 12 did not give positive results. This could be done only by concentration of mother liquors remaining after the isolation of the dextrorotatory enantiomer. After standing at room temperature for several hours, the mother liquors deposited a considerable amount of cinchonidine salt which was strongly laevorotatory. It was purified by fractional crystallization from ethyl acetate. After two crystallizations, it was optically homogeneous and had m. p. 166°C, $[\alpha]_D^{20} = -156.0^\circ$ in 96% ethanol. Optically active acids 10 and 12 isolated from the diastereomeric cinchonidine salts were crystallized from ethyl acetate. They melted at 151 - 152°C and had a relatively low optical activity $[\alpha]_D^{20} = \pm 79.8^\circ$ in 96% ethanol. Mixing of the antipodes in equimolar proportions followed by crystallization caused regeneration of the racemic acid. The m. p. of the racemate is much higher than that of the antipodes ($\Delta t = 26°C$). The IR spectrum of the racemic acid does not significantly differ from those of the enantiomers which are identical. The relatively easy resolution of the racemic acid and the differences as well as similarities between the physical properties of the antipodes indicate that the racemic acid is a pseudoasymmetric system of mixed crystals.

In order to obtain a larger comparative material for the planned polarimetric studies we have prepared the amide 13 as well as p-bromophenacyl 14 and p-phenylphenacyl 15 esters of

the dextrorotatory enantiomer 10. Mild conditions used in these preparations make it possible to assume that the dextrorotatory acid 10 was not racemised. Attempted synthesis of methyl and p-nitrobenzyl esters failed. In both cases the products were oils which could not be purified to the state necessary for polarimetric measurements.

We have completed our investigations by determining the rotatory dispersion in the region 200-300 nm as well as the circulatory dichroism and UV spectrum of the dextrorotatory enantiomer 10.

The optical rotatory dispersion (ORD) curve shown in Fig.1 has a peak at 237 nm corresponding to molar rotation $[\phi] = 13645^{\circ}$ and at $\lambda_z = 228$ nm it cuts the axis of zero rotations. Anal-

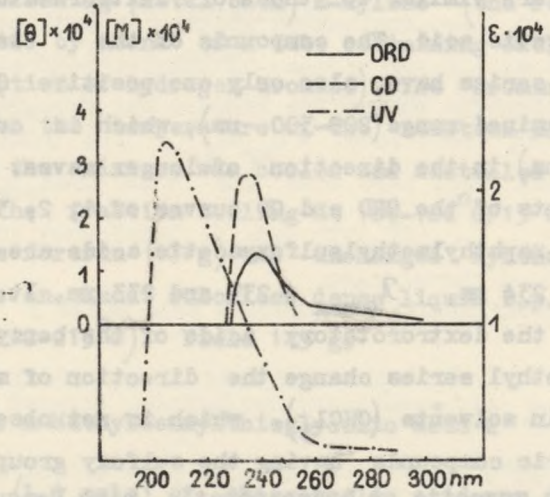


Fig. 1. Optical rotatory dispersion (ORD), circular dichroism (CD) and UV spectrum (UV) of dextrorotatory m-methylbenzylsulfoxyacetic acid in 96% ethanol

ORD ($c = 0.007$ g/100 ccm, $d = 0.1$ dm); $\lambda_{pk} = 237$ nm, $\lambda_z = 228$ nm; $[M]^{26}_{237} = 13\,645.0^{\circ}$ ($\alpha = 0.045^{\circ}$).

CD ($c = 0.00053$ mole/dm^3, $d = 1$ cm); $\lambda_{\theta\ max} = 234$ nm; $[\theta]_{234} = 28019.6$ ($\Delta A = 0.0028$).

UV ($c = 0.000038831$ mole/dm^3, $d = 1$ cm); $\lambda_{max} = 204$; $\varepsilon_{204} = 23713.0$ ($A = 0.9208$).

ogously the circular dichroism (CD) curve has a pronounced positive maximum at λ = 234 nm with molar ellipticity [θ] = 28019. In the examined region of the UV spectrum a strong absorption appears only at λ_{max} = 204 nm (ε_{204} = 23,713) but it cannot be excluded that this band screens a weak optically active band at λ_{max} = 228 nm. It is significant that the characteristic points of the ORD (λ_z) and CD ($\lambda_{\theta max}$) curves show only a slight scatter. Analysis of the results of optical measurements leads to the conclusion that dextrorotatory m-methylbenzylsulfoxyacetic acid has only one positive Cotton effect in the region 200-300 nm, which is localized at λ = 228 nm. It should be mentioned that the chiraloptical properties of dextrorotatory 1, 2, 3, 4-tetrahydro 5- and 6- naphthylmethylsulfoxyacetic acids [10, 11] are similar to those of dextrorotatory m-methylbenzylsulfoxyacetic acid. The compounds of the tetrahydronaphthylmethyl series have also only one positive Cotton effect in the examined range (200-300 nm), which is only slightly shifted (5 nm) in the direction of longer waves. The characteristic points of the ORD and CD curves of 1, 2, 3, 4-tetrahydro-5- and 6-naphthylmethylsulfoxyacetic acids are as follows: λ_z = 233 and 234 nm, $\lambda_{\theta max}$ = 233 and 233 nm. It should be stressed that the dextrorotatory acids of the benzyl and tetrahydronaphthylmethyl series change the direction of molar rotation in certain solvents ($CHCl_3$), which is not observed in the case of isomeric compounds having the sulfoxy group bonded directly to the aromatic or hydroaromatic ring Measurements of molar rotations of m-methylbenzylsulfoxyacetic acids and of some of their derivatives in various solvents and in a wide spectral range will be carried out in the near future. Further studies on the effect of substituents having the character of straight chain and branched alkyls on the rotation of sulfinylic chirality centres will be continued by one of us (M.J.).

EXPERIMENTAL PROCEDURE

The melting points are not corrected. The polarimetric measurements were carried out in the previously described [12] apparatus in the solvents quoted in the text. The IR spectra were obtained in UNICAM SP-200 spectrophotometer. The ORD, CD and UV spectra were obtained by means of JASCO (ORD/CD/UV/5) apparatus. The spectra were obtained for suspensions of the examined compounds in paraffin oil (IR) and for their solutions in ethanol (ORD, CD and UV).

1. m-Methylbenzyl bromide 1

240 g of bromine was added dropwise during about 3 hrs. to 150 g of refluxing (metal bath) m-xylene (the reflux condenser was connected by means of a tube containing $CaCl_2$ to a device for absorption of hydrogen bromide). The bromination was terminated when the temperature of the reaction mixture reached 180°C. Then the mixture was cooled and distilled under reduced pressure. The fraction boiling at 104-106°C/13 mm Hg was collected. The forerun (17 g) was unchanged xylene. ω-Bromo-m-xylene was an almost colorless dense liquid b.p. 212°C (lit. [13] b. p. 212-215°C). Yield 145 g.

2. m-Methylbenzylthioglycolic acid 2

101 g (1.1 mole) of thioglycolic acid was dissolved in 60 ccm of water. The solution was stirred mechanically and treated first with 88 g (2.2 mole) of NaOH in 132 ccm of water and then with 185 g (1 mole) of ω-bromo-m-xylene dissolved in 150 ccm of 96% ethanol. These reagents were added dropwise. During the addition the solution was cooled externally with ice water. Then the ice bath was removed and the mixture was stirred at room temperature for 2 hrs. A fine crystalline precipitate separated. In order to dissolve it, 1.5 dm^3 of water was added.

The solution was extracted with ether (3 x 200 ccm). The aqueous layer was freed from dissolved ether and acidified with 10% HCl to pH = 1. Dense oil separated. It was extracted with ether (2 x 200 ccm). The ether extract was washed with water and dried over $MgSO_4$. After removal of ether the residue was distilled under reduced pressure. The fraction boiling at 160-162°C/ /3.5 mm Hg/was collected. The distillate soon solidified. It was crystallized from petroleum ether 100 ccm of the solvent for 1 g of the substance. Long needles m. p. 74°C. Yield 160 g. m-Methylbenzylthioglycolic acid is realidy soluble in chloroform, acetone and methanol, fairly soluble in petroleum ether and insoluble in water.

Analysis:

For the formula: $C_{10}H_{12}O_2S$ (196.27) -

calculated: 61.19 % C, 6.17 % H;

found: 61.16 % C, 5.89 % H.

IR: (cm^{-1}): 739, 780, 895, 1000, 1090, 1160 δC_{Ar}-H (subst. 1,3); 1430, 1510, 1590, 1610 $\nu C_{Ar}=C_{Ar}$; 710 νC-S; 940 δOH (COOH); 1220, 1300, 1430 δOH and νC-O COOH; 1690 νC= =O (COOH).

3. m-Methylbenzylthioglycolic acid amide 3

10 g (0.06 mole) of powdered acid 2 was added with stirring in small portions to 12 g (0.1 mole) of thionyl chloride. The mixture was refluxed under $CaCl_2$ tube for 30 min. The excess of thionyl chloride was distilled off under reduced pressure (12 mm Hg, water bath). The oily residue (11 g) was suspended in 40 ccm (0.8 mole) of conc. ammonia solution (d=0.88) and shaken mechanically at room temperature for 2 hrs. A fine crystalline precipitate was separated, filtered off and dried in vacuo over H_2SO_4. The crude product (6.4 g) was crystallized from 50% methanol (100 ccm). Needles m. p. 11.5°C. Yield 2.2 g. The amide is readily soluble in benzene, chloroform, acetone, dioxane and 96% ethanol and is insoluble in water.

Analysis:

For the formula: $C_{10}H_{13}NOS$ (195.26) -

calculated: 7.17 % N;

found: 6.94 % N.

4. m-Methylbenzyltioglycolic acid anilide 4

10 g (0.05 mole) of crude chloride of acid 2 prepared as in section 3 was introduced into a solution of 18 g (0.2 mole) of aniline in 50 ccm of benzene. The mixture was shaken mechanically at room temperature for 2 hrs., then it was washed with dilute hydrochloric acid (50 ccm of 10% HCl) and water (2 x 100 ccm) and dried over anhydrous $MgSO_4$. The solid residue (1.6 g) remaining after the evaporation of benzene (in the air) was crystallized from petroleum ether (200 ccm). Plates m. p. 79°C. Yield 1.6 g. The anilide is readily soluble in benzene, chloroform, acetone and 96% ethanol and fairly soluble in petroleum ether.

Analysis:

For the formula: $C_{16}H_{17}NOS$ (271.39) -

calculated: 5.16% N;

found: 5.18% N.

5. Racemic m-methylbenzylsulfoxyacetic acid 5

A solution of 47 g (0.24 mole) of acid 2 in 80 ccm of glacial acetic acid ahaken mechanically and cooled externally with water at 10-12°C, was treated every two hours with 4 portions of 7 ccm of 29% hydrogen peroxide. Then the solution was allowed to stand for 48 hours at room temperature. A fine crystalline precipitate was filtered off (28 g). The filtrate, evaporated to half its volume in vacuum desiccator containing solid KOH, soon yielded the second portion of the sulfoxide. It was filtered off (10 g) and added to the first portion. The crude pro-

duct (38 g) was crystallized from acetone (360 ccm). Colorless rods m. p. 126°C. Yield 34 g. The racemic acid is readily soluble in chloroform, sparingly soluble in acetone and methanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{10}H_{12}O_3S$ (212.26) -

calculated: 56.58% C, 5.70% H;

found: 56.79% C, 5.64% H.

IR: (cm^{-1}) : 730, 770, 900, 1000, 1090, 1160 δC_{Ar}-H (subst. 1,3); 1470, 1490, 1590, 1610 $\nu C_{Ar}=C_{Ar}$; 700 νC-S; 1000 νS=O; 930, δOH (COOH); 1220, 1300, 1420 δOH and ν C-O (COOH); 1705 νC=O (COOH).

6. Amide of racemic m-methylbenzylsulfoxyacetic acid 6

An ethereal solution of diazomethane prepared [14] from 1.1 g of nitrosomethylurea was added dropwise with vigorous stirring to a solution of 4.5 g of acid 5 in 30 ccm of anhydrous methanol which was cooled in ice water. The mixture was allowed to stand for 20 mins. at room temperature and then washed with a 2% Na_2CO_3 solution (20 ccm) and water (2 x 40 ccm). The organic layer was separated and evaporated on water bath. The remaining light yellow oil (4.5 g) was suspended in 50 ccm of conc. ammonia (d = 0.88) and was shaken mechanically for 2.5 hrs. at room temperature. A fine crystalline precipitate separated. It was filtered and dried in vacuo over H_2SO_4. The crude product (4 g) was crystallized from methanol (20 ccm). Needles m. p. 152° C. Yield 3 g. The amide is readily soluble in chloroform, fairly soluble in acetone and 96% ethanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{10}H_{13}NO_2S$ (211.28) -

calculated: 6.63% N;

found: 6.56% N.

IR: (cm^{-1}): 720, 770, 910, 1000, 1090, 1170 δC_{Ar}-H (subst. 1,3); 1470, 1520 $\nu C_{Ar}=C_{Ar}$; 700 νC-S; 1020 νS=O; 1420 (CN); 1620 δN-H; 3150, 3390 νN-H; 1660 νC=O ($CONH_2$).

7. p-Bromophenacyl ester of racemic m-methylbenzylsulfoxyacetic acid 7

2.33 g (0.011 mole) of powdered racemic acid 5 was added to a solution of 0.4 g (0.01 mole) of NaOH in 10 ccm of water. The sulfoxide dissolved immediately. The solution was treated with 2 g (0.007 mole) of p-bromophenacyl bromide in 35 ccm of hot 96% ethanol and was refluxed for 1 hour. Then it was filtered while still hot and was allowed to stand at room temperature. A fine crystalline precipitate soon separated. It was filtered off and dissolved in chloroform (30 ccm). The solution was washed with 5% Na_2CO_3 (30 ccm) water (2 x 50 ccm) and after drying over anhydrous $MgSO_4$, it was treated with petroleum ether (90 ccm). Fine crystals soon separated. They were filtered off (1.5 g) and recrystallized from methanol (11 ccm). Plates m. p. 129°C. Yield 1 g. The ester is readily soluble in chloroform, fairly soluble in benzene and 96% ethanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{18}H_{17}BrO_4S$ (409.28) -

calculated : 52.82% C, 4.18% H;

found : 52.56% C, 4.06% H.

8. p-Phenylphenacyl ester of racemic m-methylbenzylsulfoxyacetic acid 8

2.33 g (0.011 mole) of powdered acid 5 was added to a solution of 0.6 g (0.01 mole) of NaOH in 100 ccm of water. The sulfoxide dissolved immediately. The solution was treated with 2 g (0.007 mole) of p-phenylphenacyl bromide suspended in 30 ccm of 96% ethanol. The mixture was refluxed for 1 hour. Then it was cooled, the product 3 g was filtered off

and dissolved in chloroform (30 ccm). The solution was washed successively with 5% Na_2CO_3 (30 ccm) and water (2 x 50 ccm) and after drying over anhydrous $MgSO_4$ it was treated with petroleum ether (100 ccm). Fine crystals soon separated. They were filtered (2.5 g) and recrystallized from methanol (14 ccm) Fine irregular crystals m. p. 128°C. Yield 1 g. The ester is readily soluble in chloroform, fairly soluble in acetone and 96% ethanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{24}H_{22}O_4S$ (406.48) -

calculated: 70.90% C, 5.45% H;

found: 70.70% C, 5.42% H.

9. Cinchonidine salt of dextrorotatory m-methylbenzylsulfoxyacetic acid 9

A mixture of 21.2 g (0.1 mole) of powdered racemic acid 5 and 29.4 g (0.1 mole) of cinchronidine was dissolved in 820 ccm of boiling ethyl acetate. The solution was filtered and allowed to stand for crystallization at room temperature. After 24 hrs., the first portion of crystals was filtered off. Needles m. p., 138°C $[\alpha]_D^{20} = -30.0°$ ($c = 0.25$, $d = 4$, $\alpha = -0.30°$) in 96% ethanol. After two additional crystallizations from ethyl acetate, the cinchonidine salt had physical properties which remained unchanged by further crystallization. Needles m. p. 126°C, $[\alpha]_D^{20} = -18.1°$ ($c = 0.25$, $d = 4$, $\alpha = -0.181°$) in 96% ethanol. Yield 7 g. The salt of dextrorotatory acid is readily soluble in chloroform and 96% ethanol, fairly soluble in ethyl acetate and insoluble in petroleum ether.

Analysis:

For the formula: $C_{29}H_{34}N_2O_4S$ (506.65) -

calculated: 5.53% N;

found: 5.56% N.

Table 1. The course of fractional crystallization of cinchonidine salt of dextrorotatory m-methylbenzylsulfoxyacetic acid (the crystallization time 24 hrs.)

Fraction No.	Volume of ethyl acetate (ccm)	Weight of the salt (g)	Specific rotation in 96% ethanol $[\alpha]_D^{20}$	M. p. of the salt °C
1.	820	18	-30.0°	138
1.1.	150	12	-23.0°	123
1.1.1.	140	10	-20.4°	125
1.1.1.1.	100	7	-18.1°	126
1.1.1.1.1.	80	5	-18.1°	126

10. Dextrorotatory m-methylbenzylsulfoxyacetic acid 10

30 g (0.06 mole) of powdered salt 9 (m. p. 126°C, $[\alpha]_D^{20}$ = = -18.1°) was suspended in 300 ccm of water and after stirring was acidified with 14 g (0.07 mole) of 18% hydrochloric acid. The suspension was stirred for 1 hour at room temperature. The dextrorotatory enantiomer separated. It was suspended in 50 ccm of water and made alkaline with 20% NaOH (20 ccm). The solution of the sodium salt was extracted with chloroform (5 x 50 ccm). The aqueous solution was freed from dissolved chloroform by distillation under reduced pressure (12 mm Hg, water bath at 40°C,) and was acidified to Congo with 15% hydrochloric acid. A fine crystalline precipitate separated immediately. It was filtered off and after washing with water, dried in a vacuum desiccator (H_2SO_4). The crude sulfoxyacid (10 g) was crystallized from ethyl acetate (480 ccm). Plates m. p. 151°C $[\alpha]_D^{20}$ = +79.8° (c = 0.125, d = 4, α = +0.399°) in 96% ethanol. Yield 5 g. The dextrorotatory enantiomer is readily soluble in chloroform, fairly soluble in acetone and 96% ethanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{10}H_{12}O_3S$ (212.26) -

calculated: 56.58% C, 5.70% H;

found: 56.60% C, 5.71% H.

IR: (cm^{-1}) : 730, 765, 900, 1000, 1090, 1160 $\delta C_{Ar}-H$ (subst. 1,3); 1440, 1490, 1590, 1610 $\nu_{Ar}=C_{Ar}$; 700 $\nu C-S$; 1000 $\nu S=O$; 930 δOH (COOH); 1270, 1300, 1440 δCH and $\nu C-O$; 1710 $\nu C=O$.

11. Cinchonidine salt of laevorotatory m-methylbenzylsulfoxyacetic acid 11

The mother liquors from the crystallization of the first fraction of the cinchonidine salt of the dextrorotatory enantiomer were allowed to stand at room temperature. A fine crystalline precipitate separated. After 24 hours it was filtered off. Fine needles (13 g) m. p. 162°C, $[\alpha]_D^{20} = -150.0^\circ$ ($c = 0.25$, $d = 4$, $\alpha = -1.50^\circ$) in 96% ethanol. After two crystallizations from ethyl acetate, the physical properties of this salt remained unchanged by further crystallization. Needles m. p. 166°C, $[\alpha]_D^{20} = -156.0^\circ$ ($c = 0.25$, $d = 4$, $\alpha = -1.56^\circ$) in 96% ethanol. Yield 4 g. The cinchonidine salt of the laevorotatory enantiomer is readily soluble in benzene, chloroform and 96% ethanol and fairly soluble in ethyl acetate.

Analysis:

For the formula: $C_{29}H_{34}N_2O_4S$ (506.65) -

calculated: 5.53% N;

found: 5.78% N.

12. Laevorotatory m-methylbenzylsulfoxyacetic acid 12

15 g (0.03 mole) of powdered salt 11 (m. p. 166°C, $[\alpha]_D^{20} = -156.0^\circ$) was suspended in 100 ccm of water and after stirring was acidified with 10 g (0.05 mole) of 18% hydrochloric acid. The suspension was stirred at room temperature for another 1 hour. The laevorotatory enantiomer separated. It was filtered off,

Table 2. The course of fractional crystallization of cinchonidine salt of laevorotatory m-methylbenzylsulfoxyacetic acid (the crystallization time 24 hrs.)

Fraction No.	Volume of ethyl acetate (ccm)	Weight of salt (g)	Specific rotation in 96% ethanol $[\alpha]_D^{20}$	M.p. of salt °C
0 (mother liquor from the table in section 9)	800	13	-150.0°	162
1.	880	6	-154.0°	165
1.1.	600	4	-156.0°	166
1.1.1.	450	3	-156.0°	166

suspended in 50 ccm of water and made alkaline with 20% NaOH (10 ccm). The alkaline solution was extracted with chloroform (5 x 40 ccm), then it was freed from dissolved chloroform by distillation under reduced pressure (12 mm Hg, water bath at 40°C) and was acidified to Congo with 15% hydrochloric acid. A fine crystalline precipitate separated immediately. It was filtered off and after washing with water, dried in a vacuum desiccator (H_2SO_4). The crude sulfoxyacid (6 g) was recrystallized from ethyl acetate 230 ccm. Square plates m. p. 152°C, $[\alpha]_D^{20}$ = = -79.4° (c = 0.25, d = 4, α = -0.794°) in 96% ethanol. Yield 1.3 g. The laevorotatory enantiomer is readily soluble in chloroform, fairly soluble in acetone and 96% ethanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{10}H_{12}O_3S$ (212.26) -

calculated: 56.58% C, 5.70% H;

found: 56.62% C, 5.53% H.

13. Amide of dextrorotatory m-methylbenzylsulfoxyacetic acid 13

2.12 g (0.01 mole) of dextrorotatory m-methylbenzylsulfoxyacetic acid 10 was converted into its methyl ester as in section 6. 2.2 g of the ester (slightly yellow nonsolidifying oil), suspended in 30 ccm of conc. (d = 0.88) ammonia and shaken mechanically for 2 hours at room temperature. A fine crystalline precipitate separated. It was filtered off and, after washing with water, it was dried in a vacuum desiccator (H_2SO_4). The crude amide (1.7 g) was crystallized from a mixture of chloroform (180 ccm) and petroleum ether 600 ccm. Small irregular crystals m. p. 166°C, $[\alpha]_D^{20} = +80.9^\circ$ (c = 0.125, d = 4, α = $= +0.405^\circ$) in 96% ethanol. The amide is readily soluble in chloroform, fairly soluble in acetone and methanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{10}H_{13}NO_2S$ (211.29) -

calculated: 6.63% N;

found: 6.61% N.

IR: (cm^{-1}): 730, 770, 890, 1060, 1085, 1170 $\delta C_{Ar}-H$ (subst. 1,3); 1460, 1575 $\nu C_{Ar} = C_{Ar}$; 700 $\nu C-S$; 1020 $\nu S=O$; 1420 (CN); 1630 $\delta N-H$; 3150, 3390 $\nu N-H$; 1670 $\nu C=O$ ($CONH_2$).

14. p-Bromophenacyl ester of dextrorotatory m-methylbenzylsulfoxyacetic acid 14

1.2 g (0.006 mole) of powdered dextrorotatory acid 10 was added to a solution of 0.2 g (0.005 mole) of NaOH in 5 ccm of water. The sulfoxide dissolved immediately. The solution was treated with 1.3 g (0.005 mole) of p-bromophenacyl bromide in 30 ccm of hot 96% ethanol and was refluxed for 1 hour. Then it was allowed to stand at room temperature. A fine crystalline precipitate separated. It was filtered off and dissolved in chloroform (30 ccm). The solution was washed with 5% Na_2CO_3

(30 ccm) and water (2 x 60 ccm) and, after drying over anhydrous $MgSO_4$, it was treated with petroleum ether (90 ccm). Fine crystals soon filled the liquid. They were filtered off (2g) and recrystallized from methanol (19 ccm). Plates m. p. 129°C, $[\alpha]_D^{20}$ = +61.5° (c = 0.083, d = 4, α = +0.205°) in 96% ethanol. Yield 1.4 g. The ester is readily soluble in chloroform, fairly soluble in acetone and methanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{18}H_{17}BrO_4S$ (409.28) -

calculated: 52.82% C, 4.18% H;

found: 52.65% C, 4.06% H.

15. p-Phenylphenacyl ester of dextrorotatory m-methylbenzylsulfoxyacetic acid 15

1.3 g (0.006 mole) of powdered dextrorotatory acid 10 was added to a solution of 0.2 g (0.005 mole) of NaOH in 5 ccm of water. The sulfoxide dissolved immediately. The solution was treated with 1.3 g of p-phenylphenacyl bromide in 30 ccm of 96% ethanol and was refluxed for 1 hour. Then it was allowed to stand at room temperature. A fine crystalline precipitate separated. It was filtered off and dissolved in chloroform (30 ccm). The solution was washed with a 5% Na_2CO_3 solution (30 ccm) and with water (2 x 50 ccm) and, after drying over anhydrous $MgSO_4$, it was treated with petroleum ether (90 ccm). A fine crystalline precipitate separated. It was filtered off (1.2 g) and recrystallized from 96% ethanol (22 ccm). Fine needles m. p. 128°C, $[\alpha]_D^{20}$ = +76.6° (c = 0.040, d = 4, α = +0.122°) in 96% ethanol. Yield 1 g. The ester is readily soluble in chloroform, fairly soluble in acetone and methanol and insoluble in petroleum ether.

Analysis:

For the formula: $C_{24}H_{22}O_4S$ (406.48) -

calculated: 70.90% C, 5.45% H;

found: 70.70% C, 5.42% H.

16. m-Methylbenzylsulfonylacetic acid 16

4.2 g. of powdered acid 2 was suspended in 10 ccm of water and was neutralized to a pH of 10 with 25% NaOH solution. The mixture was heated on water bath and treated every 2 hrs. with 5 portions of 2 ccm of 29% hydrogen peroxide. The reaction mixture was allowed to stand at room temperature for 24 hrs. and then was acidified to Congo with 10% hydrochloric acid. The sulfone precipitated in the form of fine crystals. They were filtered off (3.6 g) and, after drying in a vacuum desiccator (H_2SO_4), they were recrystallized from a mixture of chloroform (30 ccm) and petroleum ether (80 ccm). Colorless plates m. p. 113°C. Yield 1.8 g. The sulfone is readily soluble in chloroform, acetone and 96% ethanol, fairly soluble in benzene and insoluble in petroleum ether.

Analysis:

For the formula: $C_{10}H_{12}O_4S$ (228.27) -

calculated: 52.62% C, 5.29% H;

found: 52.68% C, 5.12% H.

IR: (cm^{-1}): 725, 760, 890, 1000, 1100, 1160 δC_{Ar}-H (subst. 1.3); 1465, 1490, 1590, 1610 $\nu C_{Ar} = C_{Ar}$; 690 νC-S; 1130 $\nu_{as} SO_2$; 1320 $\nu_s SO_2$; 920 δOH (COOH); 1225, 1290, 1440 δOH and νC-O (COOH); 1710 C=O COOH.

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STRESZCZENIE

Opisano metodę syntezy oraz określono podstawowe własności fizyczne optycznie czynnych kwasów m-metylobenzylosulfinylooctowych i ich niektórych pochodnych o charakterze amidowym i estrowym. Budowa strukturalna poszczególnych połączeń potwierdzona została na drodze badania widm oscylacyjnych. Określono dyspersję rotacyjną, dichroizm kołowy oraz widmo elektronowe w rejonie 200-300 nm prawoskrętnego enancjomeru. Tok syntez oraz stałe fizyczne nowo otrzymanych połączeń podano w tekście angielskim.

РЕЗЮМЕ

В данной работе представлено метод синтеза, а также определено основные физические особенности оптически активных m-метилбензилсульфинилуксусных кислот и их некоторые производные амидового и эстрового характера. Структуральное строение отдельных соединений подтверждено путем исследований спектров колебаний. Определено вращательную дисперсию, круговой дихроизм, а также электронный спектр в районе 200-300 нанометров правовращающегося энантиомера. Ход синтеза и физические постоянные новополученных соединений представлено в тексте на английском языке.