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Marian JANCZEWSKI, Jerzy KSIĘŻOPOLSKI

The Effect of Molecular Structure on Optical Properties of Sulfoxide Systems. o-Bromobenzylsulfinylacetic Acids and Some of Their Derivatives. V *

Wpływ budowy cząsteczkowej na własności optyczne układów sulfotlenkowych. Kwasy o-bromobenzylosulfinylooctowe i niektóre ich pochodne. V

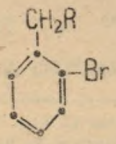
Влияние молекулярного строения на оптические свойства сульфоокислых систем. о-бромобензилосульфинилоуксусные кислоты и некоторые их производные. V

The problem of the effect of position isomerism of certain substituents and functional groups in arene nuclei on optical properties of aromatic--aliphatic systems containing carbon and heteroatomic chirality centres has been studied in our laboratory, involving the group of compounds in which the asymmetric atoms are bonded directly to the aromatic fragments of the molecules [1—7]. The results prompted us to further studies on systems with chirality centres separated from the aromatic fragments by methylene and vinyl groups or heteroatoms.

In the previous papers the synthesis and some physical properties of enantiomeric p-bromophenylsulfinylacetic [8] and p-bromobenzylsulfinylacetic [9] acids were described.

In the present communication we are reporting the synthesis and the determination of principal optical properties of enantiomeric o-bromobenzylsulfinylacetic acids and their derivatives.

* The work was financed by the Polish Academy of Sciences, MR.I/12.1. Part IV. Janczewski M., Janowski W., Księżopolski J., Lewkowska J., Kowalik H.: Ann. Univ. M. Curie-Skłodowska, Lublin, sectio AA 33, 153 (1978).



1: R=Br
2: R=S · CH_2 · COOH
3: R=S · CH_2CO · NH_2
4: R=$\overset{(\pm)}{SO}$ · CH_2 · COOH
5: R=$\overset{(\pm)}{SO}$ · CH_2 · CO · NH_2
6: R=$\overset{(\pm)}{SO}$ · CH_2 · CO · OCH_2 · C_6H_4 · NO_2.
7: R=$\overset{(\pm)}{SO}$ · CH_2 · CO · OCH_2 · CO · · C_6H_4 · Br
8: R=$\overset{(\pm)}{SO}$ · CH_2 · CO · OCH_2 · CO · · C_6H_4 · C_6H_5
9: R=$\overset{(-)}{SO}$ · CH_2 · COOH · Strych. *
10: R=$\overset{(-)}{SO}$ · CH_2 · COOH
11: R=$\overset{(+)}{SO}$ · CH_2 · COOH · Cinchnd. **
12: R=$\overset{(+)}{SO}$ · CH_2 · COOH
13: R=$\overset{(+)}{SO}$ · CH_2 · CO · NH_2
14: R=$\overset{(+)}{SO}$ · CH_2 · CO · OCH_2 · C_6H_4 · NO_2
15: R=$\overset{(+)}{SO}$ · CH_2 · CO · OCH_2 · CO · · C_6H_4 · Br
16: R=$\overset{(+)}{SO}$ · CH_2 · CO · OCH_2 · CO · · C_6H_4 · C_6H_5
17: R=SO_2 · CH_2 · COOH

The starting material was the already known o-bromobenzylthioglycolic acid 2, which was obtained in a good yield by coupling o-bromobenzyl bromide with thioglycolic acid in alkaline alcoholic medium. The structure of mercaptoacid was confirmed by its infrared spectrum (the characteristic bands are given in the Experimental Part). Racemic o-bromobenzylsulfinylacetic acid (4) was obtained by oxidation of the compound 2 with 30% hydrogen peroxide in glacial acetic acid at room temperature. When the oxidizing agent was used in excess, a good yield of the sulfone 17 was obtained (the IR spectra confirming the structure of the two oxidation products are shown in the Experimental Part). Racemic acid 4 was characterized as its amide (5) and p-nitrobenzyl (6), p-bromophenyl (7) and p-phenylphenacyl (8) esters. In our further studies, racemic acid 4 was resolved by crystallization of its diastereomeric salts with strychnine and cinchonidine. Strychnine combined with racemic acid 4 at an equimolar ratio formed in acetone with laevorotatory antimer a more sparingly soluble salt and separated enantiomers very slowly. Optically homogenous salt of the laevorotatory acid 9 had m.p. 135—136°C and $[\alpha]_D^{20} = -82.0°$ (ethanol). Cinchonidine was combined with optically inactive acid 4 also at an equimolar ratio. During cyrstallization from ethyl acetate the cinchonidine salt evolved a dextrorotatory enantiomer in the first fractions. Optically pure salt 11 showed m.p. 133°C and $[\alpha]_D^{20} = -19.6°$ (ethanol).

* Strych. — strychnine.
** Cinchnd. — cinchonidine.

Optically active o-bromobenzylsulfinylacetic acids 10 and 12 separated from alkaloid salts and purified from chloroform showed a relatively high specific rotation. After mixing the antimers in equimolecular relation and crystallization racemic acid 4 was obtained; its melting point was much higher ($\Delta t = 42°$) than that of antimers 10 and 12. The IR spectrum of racemic acid 4 was different in the "fingerprint region" from the spectra of enantiomers 10 and 12, which were identical. A relatively difficult resolution of the optically inactive acid 4 as well as the physical differences mentioned above indicate that racemic acid 4 is a true racemate.

Preliminary studies showed that optically active o-bromobenzylsulfinylacetic acids 10 and 12 possess a considerable resistance to racemization in alkaline media, but lose quite rapidly the ability to rotate the plane of polarized light in organic solvents in the presence of concentrated hydrochloric acid. Racemization processes were studied using a mixture (2:1 v/v) of dioxane and dilute (7:1 v/v $HCl:H_2O$, $d = 1.15$) hydrochloric acid as solvent. In these conditions the racemization of optically active acids 10 and 12 occurred, according to the kinetic equation, for the first order reactions ($K = (1/t) \ln \alpha_0/\alpha$). The racemization constants (K), the activation entropies ($\Delta S^{\#}$) and the activation enthalpies ($\Delta H^{\#}$) calculated for four temperatures after averaging the kinetic measurements by the least squares method, are shown in Table 1. The activation parameters of the racemization processes have been determined by the classical kinetic methods on the basis of the Eyring equation [10].

Table 1. Thermodynamic characterization of racemization of the optically active o-bromobenzylsulfinylacetic acids

Racemization temperature °C	Racemization constants $K \cdot 10^5 sec^{-1}$	Activation entropy ($\Delta S^{\#}$) eu	Activation enthalpy ($\Delta H^{\#}$) Kcal/mole
16	3.52±0.79	—12.13±1.47	19.14±0.13
20	4.86±0.62	—12.75±0.84	19.14±0.07
24	8.56±0.81	—12.79±0.63	19.13±0.06
28	13.72±1.18	—12.81±0.57	19.12±0.05
32	19.88±1.55	—12.84±0.52	19.11±0.05

The activation energy (E_a) and the preexponential factor ($A = K_{max}$) have been determined from the empirical Arrhenius equation: ($K = A \cdot e^{-Ea/RT}$) $E_a = 19.717$ Kcal/mole, $A = 2.72 \times 10^{10}$ sec^{-1}. It should be stressed that p-bromobenzylsulfinylacetic acid behaved similarly in the racemization process; the only difference was that it showed twice as high racemization entropy values, which is consistent with its geometrical structure.

In order to obtain a larger comparative material for chiralooptical studies we have prepared the following derivatives of dextrorotatory acid 12: amide (13) p-nitrobenzyl ester (14), p-bromophenacyl ester (15) and p-phenylphenacyl ester (16). The syntheses of these compounds were first elaborated for the optically inactive material. The mild conditions in which the reactions were carried out were not likely to cause racemization at the asymmetric sulfur atom. The molar rotations of acid 12 and its derivatives 13, 14, 15 and 16 were determined in Perkin-Elmer spectropolarimeter 241-MC in the region $300<\lambda<623$ nm at wave lengths shown in the table, using methanol (M), ethanol (E), acetone (A), dioxane (D) and chloroform (Ch) as solvents.

The results are shown in Table 2. As it appears from the comparison of the numerical values given in this table, the nature of solvent has a considerable effect on the value of molar rotation. In the visible part of the spectrum the effect of the solvents can be arranged in the following order

Table 2. Rotatory dispersion of the dextrorotatory

Compound	Solvent	Molar rotation $[M]_\lambda^{20}$			
		$\lambda=623.4$	$\lambda=600.0$	$\lambda=589.3$	$\lambda=579.1$
Dextrorotatory o-bromobenzylsulfinylacetic acid	M	238.34 (223.83)	243.88 (246.91)	260.51 (258.76)	271,59 (270.91)
	E	254.96 (256.06)	277.14 (281.85)	293.76 (295.04)	304.85 (308.55)
	A	188.45 (185.48)	205.08 (204.88)	216.16 (214.85)	232.79 (225.09)
	D	160.74 (147.36)	166.28 (162.47)	171.82 (170.22)	177.37 (178.18)
Amide of dextrorotatory o-bromobenzylsulfinylacetic acid	M	204.35	215.40	226.44	237.49
	E	248.54	270.63	281.68	287.20
	A	176.74	198.83	215.40	226.44
	D	82.84	99.41	104.93	110.46
	Ch	—22.09	—24.85	—27.61	—28.99
p-Nitrobenzyl ester of dextrorotatory o-bromobenzylsulfinylacetic acid	M	98.94	123.67	131.92	140.17
	E	98.94	107.18	115.43	123.67
	A	16.49	27.13	32.98	41.26
	Ch	—140.17	—148.41	—189.41	—206.13
p-Bromofenacyl ester of dextrorotatory o-bromobenzylsulfinylacetic acid	M	246.57	256.05	265.54	275.02
	E	246.57	256.05	265.54	275.02
	A	161.22	218.12	227.60	237.08
	D	180.18	189.67	199.15	208.63
p-Phenylphenacyl ester of detxrorotatory o-bromobenzylsulfinylacetic acid	M	216.82	245.11	254.54	273.39
	E	216.83	245.11	245.54	273.39
	A	141.41	164.98	188.55	207.40
	D	188.55	216.83	235.68	245.11
	Ch				

Concentration: c=0.1 g/100 ccm.

Solvents: A — acetone, Ch — chloroform, D — dioxane, E — ethanol, M — methanol.

according to decreasing numerical values of molar rotation: a) for free acid 12: E>M>A>D; b) for acid amide 13: E>M>A>D>Ch; c) for p-nitrobenzyl ester 14: M>E>A>Ch; d) for p-bromophenacyl ester 15: M>E>A>D; e) for p-phenylphenacyl ester 16: M>E>D>Ch. The decreases of the numerical value of molar rotation accompanying the change of solvents in the order given by the above sequences are moderate, except for the rapid decrease observed for amide 13 in dioxane and chloroform, for p-nitrobenzyl ester 14 in acetone and chloroform and for p-phenylphenacyl ester 16 in chloroform.

Analysis of the numerical data summarized in Table 2 shows that the curves representing function $1/\alpha(\lambda^2)$ in the region $436<\lambda<623$ nm for dextrorotatory acid 12 and its derivatives 13, 14, 15 and 16 are almost straight lines, which leads to the conclusion that the optical rotary dispersion of the compounds examined in the visible part of the spectrum has the character of normal dispersion. It should be stressed that in the

o-bromobenzylsulfinylacetic acid and some of its derivatives

Molar rotation $[M]_\lambda^{20}$							
λ=560.0	λ=546.1	λ=480.0	λ=440.0	λ=400.0	λ=380.0	λ=360.0	λ=340.0
293.76	315.94	465.59	609.71	848.05	1025.42	1252.67	1629.58
(296.26)	(317.19)	(489.08)	(602.97)	(837.39)	(1016.13)	(1266.18)	(1633.03)
332.56	360.28	520.02	676.22	931.19	1119.64	1369.07	1762.61
(336.68)	(359.83)	(515.46)	(671.49)	(923.21)	(1113.91)	(1379.76)	(1769.37)
243.88	266.05	382.45	509.93	704.93	875.76	1097.47	1418.96
(246.50)	(264.21)	(385.14)	(509.12)	(713.52)	(870.99)	(1093.03)	(1420.89)
199.54	210.62	293.76	393.54	554.28	665.13	836.96	1075.30
(194.64)	(208.45)	(301.24)	(395.46)	(549.54)	(667.69)	(834.12)	(1080.94)
254.06	276.15	397.66	530.22	729.05	883.70	1104.62	1408.40
325.86	353.48	508.12	651,73	889.22	1082.53	1336.60	1723.22
243.01	265.11	386.62	508.12	706.96	861.61	1077.01	1386.31
121.50	132.55	193.31	243.01	342.43	414.23	519.17	673.82
—30.37	—33.13	—44.18	—55.23	—77.32	—98.37	—115.98	—149.12
148.41	173.15	239.11	329.81		461.73	535.94	
131.92	148.41	197.88	280.34		395.77	478.22	
49.47	57.71	115.43	140.17		239.11	263.84	
—214.37	—222.62	—313.32	—404.01		—577.17	—667.86	
312.95	327.18	483.66	625.91	863.00	1043.19	1313.47	1650.14
303.47	312.95	445.72	597.40	815.58	976.80	1232.86	1574.27
256.05	275.02	398.31	550.04	758.68	919.40	1156.44	1517.37
227.60	237.08	331.92	436.24	587.98	720.75	910.42	1185.44
287.53	315.82	452.52	589.22	810.76	994.60	1244.43	
282.82	301.68	443.09	584.50	820.19	1018.17	1360.99	
263.97	282.82	395.95	537.36	736.62	736.62	1160.01	
263.97	282.82	377.10	490.23	678.78	810.76	999.31	
9.42	18.85	23.56	32.98	47.13	56.56	94.27	

region $436<\lambda<623$ nm the numerical values of molar rotation in all solvents used for the measurements show a considerable decrease in the sequence: dextrorotatory acid 12>amide 13>p-nitrobenzyl ester 14.

The data presented above make possible the determination of relative configurations of optically active o-bromobenzylsulfinylacetic acids on the basis of the Freudenberg shift rule and the comparison of the direction of molar rotation changes, occurring under the influence of solvents in the reference systems and the compounds studied. The configuration standard in the first case were dextrorotatory p-bromobenzylsulfinylacetic and 2-naphthylmethylsulfinylacetic acids [9] with relative configuration D(+), in the second case, however, both compounds mentioned as well as dextrorotatory benzylsulfinylacetic acid which previously had been arbitrarily assigned configuration D(+) [11].

Table 3. Molar rotations $[M]_D^{20}$ of the dextrorotatory and 2-naphtylmethylsulfinylacetic (C)

Compound	Methanol			Ethanol		
	Acid	Amide	p-Nitrobenzyl ester	Acid	Amide	p-Nitrobenzyl ester
A	260.5	226.4	131.9	293.8	281.7	115.4
B	238.3	201.6	109.3	282.7	259.6	107.2
C	204.8	148.4	62.3	223.5	204.0	52.7

Comparison of the Freudenberg optical shifts presented in Table 3 and molar rotation changes caused by changes in the character of solvent, which are summarized in Table 4, indicates that spatial configurations of dextrorotatory benzylsulfinylacetic, p-bromobenzylsulfinylacetic and 2-naphthylmethylsulfinylacetic and o-bromobenzylsulfinylacetic acids are identical. Configuration correlations assumed for benzylsulfinylacetic acids seem to be justified by very close similarities of their CD spectra. The CD spectrum of laevorotatory p-bromobenzylsulfinylacetic acid shows in acetonitrile two weak negative maxima at $\lambda=278$ nm

Table 4. Effect of the solvent on the optical rotation $[M]_D^{20}$ of the dextrorotatory benzylsulfinylacetic (A), p-bromobenzylsulfinylacetic (B), o-bromobenzylsulfinylacetic (C) and 2-naphthylmethylsulfinylacetic (D) acids

Solvent	A	B	C	D
Ethanol	174.5	282.7	293.8	223.5
Methanol	134.8	238.3	260.5	204.8
Acetone	99.1	171.0	216.2	136.6
Dioxane	35.1	83.1	171.8	8.7

([Θ]=−672.2) and λ=272 nm ([Θ]=−856.6) and one strong negative maximum at λ=235 nm ([Θ]=−43278.6) and one positive maximum at λ=218 nm ([Θ]=+26598.7). Similarly, the dichroic spectrum of laevorotatory benzylsulfinylacetic acid in acetonitrile also shows two very weak negative maxima at λ=268 nm ([Θ]=−940.1) and λ=263 nm ([Θ]=−1055.2), one strong negative maximum at λ=227 nm ([Θ]=−35179.4) and one positive maximum at λ=212 nm ([Θ]=+11191.9). The CD spectrum of dextrorotatory o-bromobenzylsulfinylacetic acid also measured in acetonitrile shows three negative maxima, two of which are weak at λ=276 nm ([Θ]=−633.2) and λ=268 nm ([Θ]=−205.1), one strong at λ=208 nm ([Θ]=−21405.4) and one very strong positive maximum at λ=237 nm ([Θ]=+36121.6). Thus the CD spectra with large molar ellipticties in the short wave-length region (208<λ<237 nm) show

o-bromobenzylsulfinylacetic (A), p-bromobenzylsulfinylacetic (B), acids and some of their derivatives

Acetone			Dioxane			Chloroform		
Acid	Amide	p-Nitrobenzyl ester	Acid	Amide	p-Nitrobenzyl ester	Acid	Amide	p-Nitrobenzyl ester
216.2	215.4	32.9	171.8	104.9	—	—	−27.6	−189.6
171.8	—	41.2	83.1	60.8	−131.9	—	−22.1	−127.8
136.6	—	10.9	8.4	−30.9	−186.9	—	—	−306.7

identical character for acids (non-substituted acid and its o- and p-bromoderivatives) of the same configurations. Differences in CD spectra involve very weak bands in the region 236<λ<278 nm and are most likely associated with position isomerism of halogen atom in the aromatic ring.

On the basis of the numerical data (320<λ<623 nm) summarized in Table 2, functions [M] (λ) have been calculated for dextrorotatory acid 12 in four solvents. These functions have the character of the following three-term equations:

a) in methanol:

$$[M]_{\lambda}^{20}=\frac{-2.0494543\times10^{8}}{\lambda^{2}-(203.9988)^{2}}+\frac{2.7938312\times10^{8}}{\lambda^{2}-(233.7749)^{2}}-\frac{6.8762260\times10^{6}}{\lambda^{2}-(278.4808)^{2}}$$

b) in ethanol:

$$[M]_{\lambda}^{20}=\frac{-1.3676615\times10^{8}}{\lambda^{2}-(208.1050)^{2}}+\frac{2.3129406\times10^{8}}{\lambda^{2}-(241.0012)^{2}}-\frac{1.4981031\times10^{7}}{\lambda^{2}-(272.0020)^{2}}$$

c) in acetone:

$$[M]_\lambda^{20} = \frac{-1.8518165 \times 10^8}{\lambda^2-(211.5230)^2} + \frac{2.5762308 \times 10^8}{\lambda^2-(241.0060)^2} - \frac{1.7283957 \times 10^7}{\lambda^2-(277.0340)^2}$$

d) in dioxane:

$$[M]_\lambda^{20} = \frac{-1.0109983 \times 10^8}{\lambda^2-(209.2804)^2} + \frac{1.512067 \times 10^8}{\lambda^2-(241.0186)^2} - \frac{5.2504035 \times 10^6}{\lambda^2-(279.57)^2}$$

The values of molar rotations calculated by means of the above equations are given in brackets in Table 2. The agreement between the values calculated and those determined experimentally is fairly good. Functions [M] (λ) describing in the rectangular system of coordinates (λ is the independent variable) the optical properties of dextrorotatory o-bromobenzylsulfinylacetic acid 12 change the sign within the interval $\lambda_1 < \lambda < \lambda_3$, and have in it one negative maximum and one positive minimum. Their asymptotes are λ axis and the straight lines perpendicular to it at points λ_1, λ_2 and λ_3.

In order to confirm the validity of the above equations [M](λ) we have determined the circular dichroism (CD) and the (UV) spectrum of dextrorotatory enantiomer 12 in methanol in the region $200 < \lambda < 300$ nm. The CD spectrum shows three negative maxima: one strong at $\lambda = 206$ nm ([Θ] = −36121,6) and two weak at $\lambda = 268$ nm ([Θ] = −214.1) and $\lambda = 276$ nm ([Θ] = −338.9) and one strong positive maximum at $\lambda = 230$ nm ([Θ] = + +52621,6). In the electronic spectrum there occur two strong adsorption bands located in the region $\lambda = 206$ nm ($\varepsilon_{206} = 21895.7$) and $\lambda = 230$ nm ($\varepsilon_{230} = 6780.8$) and one weak wide band in the range $\lambda = 273$ nm ($\varepsilon_{273} = 808.3$). It is of interest that the characteristic points in the spectra CD ($\lambda\Theta_{max}$) and UV ($\lambda\varepsilon_{max}$) do not show any significant differences on the wave length axis (λ). Analysis of the results of measurement leads to the conclusion that the optically active o-bromobenzylsulfinylacetic acids show in the spectral range examined (in methanol) four Cotton effects situated in the regions $\lambda_1 = 206$, $\lambda_2 = 230$, $\lambda_3 = 268$ nm and $\lambda_4 = 276$ nm. The weakest effect at $\lambda_3 = 268$ nm is not represented in the equations describing functions [M] (λ). The other three are situated in the regions in accordance with the predictions based on the analysis of function [M] (λ), and the signs of these effects coincide with those of the rotation constants occurring in the equations.

The optical effects caused by the introduction of bromine atom to the arene nucleus of the molecule of benzylsulfinylacetic acid (in ortho position) in the region of λ values, for which the optical rotatory dispersion is normal, are sometimes difficult to determine unambigously due to a considerable effect of the nature of the solvents. The clearest effects we obtained for free acids and their amides. The compounds mentioned

above in all solvents (except chloroform) used for measurements show much higher numerical values of molar rotations in relation to their corresponding non-substituted systems. The average proc. increase of mol. rotations % Δ [M] [2] for free acids is (methanol) about 95%, and for their amides (methanol) about 48%. The introduction of bromine atom to the molecule of benzylsulfinylacetic acid in the position ortho increases thus the rotation of the system very considerably. Analogous effects occur in the case of p-bromobenzylsulfinylacetic acids. The recorded observations do not allow us in this stage of studies to draw conclusions of a general character. However, it could be stated that methylene group does not fully isolate the sulfoxide system from the effects caused by introducing bromine atom to the aromatic ring. Our studies will be continued.

EXPERIMENTAL

The melting points are uncorrected. The polarimetric measurements were carried out in Perkin-Elmer 241-MC spectropolarimeter in the solvents given in the text. The IR and UV spectra were determined by means of SP-200 and SP-700 spectrophotometers. The CD spectra were obtained in Rouseel-Jouan III dichrograph. The compounds were examined in paraffin oil suspension (IR) and in the solvents given in the text.

1. o-Bromobenzyl bromide (1)

102 g of dried (H_2SO_4) bromine was added dropwise to 120 g of o-bromotoluene heated on oil bath (at 132°), irradiated (a 200 W bulb) and stirred vigorously. Then the reacting mixture was heated for next 0.5 h and then allowed to stand at room temperature for 12 hrs. The reaction mixture was distilled under reduced pressure and the fraction boiling at 122—127° (18 mm Hg) was collected. Colourless oil, b.p. 123—126° /18 mm Hg) (lit. [12] b.p. 129°/19 mm Hg).

2. o-Bromobenzylthioglycolic acid (2)

100 g (0.4 mole) of o-bromobenzyl bromide dissolved in 300 ccm of 96% ethanol was introduced to a solution of 46.5 g (0.5 mole) of thioglycolic acid in 400 ccm of 15% NaOH. The mixture was heated on water bath (at 60°) for 1 hr. and then it was allowed to stand at room temperature for 12 hrs. A fine crystalline precipitate separated. It was filtered off, washed with water (3×20 ccm) an dissolved in 1 l of hot water. After acidification (Congo) with dil. (1:1 v/v) hydrochloric acid the so-

lution was filled with fine crystals. They were filtered off (60 g), dried in a vacuum desiccator over $CaCl_2$ and crystallized from cyclohexane (300 ccm). Colourless plates, m.p. 43—44°. Yield 45 g. The compound is readily soluble in benzene, tetrachloromethane, chloroform, dioxane and methanol, and is sparingly soluble in cyclohexane.

Analysis:

For the formula: $C_9H_9O_2BrS$ (261.7) — calculated: 41.39% C, 3.47% H;
found: 41.26% C, 3.26% H.

IR(cm^{-1}): 720νC—S; 750, 1040, 1100, 1190δC_{Ar}—H (subst. 1, 2); 1440, 1529, 1560, 1583νC_{Ar}=C_{Ar}; 920δOH(COOH); 1210, 1270, 1410δOH and νC—O(COOH); 1690νC=O(COOH).

3. Amide of o-bromobenzythioglycolic acid (3)

5 g of acid 2 was converted into methyl ester as described in section 5. After distilling off the solvent under reduced pressure (12 mm Hg, water bath) the oily residue was suspended in 80 ccm of 14% NH_3 and mechanically shaken at room temperature for 2 hrs. A fine crystalline precipitate separated. The compound was filtered, washed with 5% Na_2CO_3 (3×25 cm) and with water. The crude acid amide (3.5 g) was dried in a vacuum desiccator over $CaCl_2$ and then crystallized from a mixture of cyclohexane (80 ccm) and acetone (20 ccm). Colourless plates, m.p. 83—84°. Yield 2 g. The amide is readily soluble in benzene and dioxane, but sparingly soluble in petroleum ether and cyclohexane.

Analysis:

For the formula: $C_9H_{10}BrNOS$ (261.15) — calculated: 5.38% N;
found: 5.70% N.

4. Racemic o-bromobenzylsulfinylacetic acid (4)

5 g of acid 2 was dissolved in 20 ccm of glacial acetic acid. The solution was cooled to 0°C, added 1.1 ccm of 30% H_2O_2 and mechanically shaken at room temp. for 12 hrs. Then it was added two portions of 0.6 ccm of 30% H_2O_2 each at 24 hrs. intervals, and the mixture was shaken for 48 hrs. at room temp. A fine crystalline presipitate separated from the solution. It was filtered (3.5 g), washed with water (3×25 ccm), dried and crystallized from a mixture of carbon tetrachloride (30 ccm) and acetone (40.5 ccm). Rods, m.p. 128—129°. Yield 2.5 g. The compound is readily soluble in cyclohexane and methanol, fairly soluble in benzene and acetone, and sparingly soluble in carbon tetrachloride and chloroform.

Analysis:

For the formula: $C_9H_9BrO_3S$ (277.14) — calculated: 39.00% C, 3.27% H;
found: 39.36% C, 3.17% H.

IR(cm^{-1}): 735νC—S; 770, 1040, 1100, 1190δC_{Ar}—H (subst. 1, 2); 1450, 1570, 1580νC_{Ar}=C_{Ar}; 1000νS—O; 910δOH; 1230, 1280, 1420δOH and νC—O(COOH); 1730 νC=O(COOH).

5. Amide of racemic o-bromobenzylsulfinylacetic acid (5)

To a suspension of 7 g of powdered acid 4 in ether (150 ccm) cooled from outside with water and ice was added dropwise, with vigorous stirring, the ether solution of diazomethane, prepared from 10 g of N,N-nitrosomethylurea [13], until a permanent coloration of the liquid appeared. The mixture was heated on water bath under a reflux condenser ($CaCl_2$) until the yellow colour of the liquid disappeared. The ether solution was cooled, first washed with 5% Na_2CO_3 (2×10 ccm) and then with water (3×10 ccm), and next it was dried with anhydrous $MgSO_4$. The solvent was distilled under reduced pressure (12 mm Hg, water bath), and the residue amounting 5 g was thick, non-solidifying almost colourless oil. 3 g of ester was suspended in 60 ccm of 20% NH_3 and mechanically shaken for 2 hrs. at room temp. An amorphous precipitate separated. The compound was filtered (2.5 g), washed with water, dried in a vacuum desiccator over $CaCl_2$ and crystallized from a mixture of acetone (60 ccm) and 96% ethanol (12 ccm). Colourless rods, m.p. 160—161°C. Yield 1.2 g. The amide is readily soluble in methanol and 96% ethanol, fairly soluble in chloroform and acetone, sparingly soluble in cyclohexane and carbon tetrachloride.

Analysis:

For the formula: $C_9H_{10}BrNO_2S$ (276.16) — calculated: 5.07% N;
found: 5.31% N.

6. p-Nitrobenzyl ester of racemic o-bromobenzylsulfinylacetic acid (6)

2 g of racemic acid 4 was suspended in 10 ccm of water and neutralized (phenolphthalein) with 3% NaOH solution. The solution was heated to 60°C, 2 g of p-nitrobenzyl bromide and 43 ccm of 96% ethanol was added. The mixture was refluxed for 2 hrs. on water bath. After filtering the solution was allowed to stand at room temp. A fine crystalline precipitate separated. It was filtered (1.1 g), washed with water, air-dried and crystallized from methanol (10 ccm). Colourless needles, m.p. 83—

84°C. Yield 1 g. The ester is readily soluble in chloroform and acetone, fairly soluble in methanol and 96% ethanol.

Analysis:

From the formula: $C_{16}H_{14}BrNO_5S$ (412.26) — calculated: 3.39% N; found: 3.70% N.

7. p-Bromophenacyl ester of racemic o-bromobenzylsulfinylacetic acid (7)

3 g of powdered acid 4 was suspended in 15 ccm of water and neutralized (phenolphthalein) with 3% NaOH. The solution was heated to 60°C. 3 g of p-bromophenacyl bromide in 75 ccm of 96% ethanol was added and the mixture was refluxed for 2 hrs. on water bath. After filtering the solution was allowed to stand at room temp. A fine crystalline precipitate soon separated. It was filtered (3 g), washed with water, air-dried and crystallized from 96% ethanol (84 ccm). Colourless needles, m.p. 140—141°C. Yield 1.5 g. The ester is readily soluble in acetone, fairly soluble in methanol and 96% ethanol.

Analysis:

For the formula: $C_{17}H_{14}Br_2O_4S$ (474.17) calculated: 43.06% C, 2.97% H; found: 43.06% C, 2.88% H.

8. p-Phenylphenacyl ester of racemic o-bromobenzylsulfinylacetic acid (8)

3 g of acid 4 was converted into p-phenylphenacyl ester as in section 16. For the reaction 3 g of p-phenylphenacyl bromide was used. Esterification was performed in 67% ethanol (50 ccm). The crude product was first washed with 5% Na_2CO_3 (3×30 ccm) and then with water (3×30 ccm). It was dried in a vacuum desiccator (H_2SO_4) and crystallized from a mixture of methanol (220 ccm) and petroleum ether (20 ccm). Colourless needles, m.p. 140—141°C. Yield 1.7 g. The ester is readily soluble in chloroform, fairly soluble in acetone, methanol and 96% ethanol, sparingly soluble in petroleum ether.

Analysis:

For the formula: $C_{23}H_{19}BrO_4S$ (471.37) calculated: 58.60% C, 4.06% H; found: 58.38% C, 3.92% H.

9. Strychnine salt of laevorotatory o-bromobenzylsulfinylacetic acid (9)

27.70 g (0.1 mole) of powdered racemic acid 4 was mixed with 33.44 g (0.1 mole) of strychnine and dissolved in 1.3 dcm^3 of boiling acetone. The

hot solution was filtered and allowed to stand at room temp. for crystallization. After 24 hrs. the first salt fraction was filtered off. Colourless needles, m.p. 126—127° with decompn. and $[\alpha]_D^{20} = -20.0°$ ($c=0.2$, $d=0.5$, $\alpha=-0.02°$) in 96% ethanol. After crystallization of the first salt fraction from acetone, repeated six times, a compound was obtained which did not change its physical properties by further purification. Needles, m.p. 136.5° and $[\alpha]_D^{20} = -82.0°$ ($c=0.2$, $d=0.5$, $\alpha=-0.082°$) in 96% ethanol. Yield 8 g. The salt is readily soluble in chloroform, methanol and 96% ethanol, fairly soluble in acetone, and sparingly soluble in carbon tetrachloride.

Analysis:

For the formula: $C_{30}H_{31}BrN_2O_5S$ (611.56) calculated: 4.59% N;
found: 4.60% N.

Table 5. Fractional crystallization of strychnine salt of laevorotatory o-bromobenzylsulfinylacetic acid (crystallization time 24 hrs.)

Fraction No.	Volume of acetone (ccm)	Weight of salt (g)	Specific rotation in 96% ethanol $[\alpha]_D^{20}$	M.p. of salt with decompn. °C
1.	1300	35	−20.0°	127
1.1.	1000	30	−29.0°	128
1.1.1.	850	26	−40.0°	130
1.1.1.1.	700	20	−58.0°	133
1.1.1.1.1.	450	14	−74.0°	135—6
1.1.1.1.1.1.	400	10	−81.0°	138
1.1.1.1.1.1.1.	300	8	−82.0°	138.5

10. Laevorotatory o-bromobenzylsulfinylacetic acid (10)

8 g of powdered strychnine salt 9 was added to 40 ccm of water and vigorously mixed for several min. The suspension was then alkalized with 49 ccm of 3% NaOH and stirred for 1 hr. at room temperature. The alkaloid base separated was filtered and washed with water. The filtrate was mixed with the washing and extracted with chloroform (3×50 ccm). The alkaline liquid was acidified (Congo) with 3% hydrochloric acid after removing the dissolved chloroform by distillation under reduced pressure (12 mm Hg, water bath). The acid solution was extracted with chloroform (14×100 ccm). The chloroform extract was washed with water (2×40 ccm) and dried with anhydrous $MgSO_4$. The solvent was removed by distillation under reduced pressure (12 mm Hg, water bath). The residue was thick oil which soon solidified. The compound (1 g) was cristallized from chloroform (8 ccm). Rods, m.p. 86—87°C and $[\alpha]_D^{20} =$

$-99.0°$ ($c=0.2$, $d=0.5$, $\alpha=-0.099°$) in 96% ethanol. Yield 0.5 g. It is readily soluble in dioxane, chloroform, acetone, methanol and 96% ethanol, sparingly soluble in petroleum ether.

Analysis:

For the formula: $C_9H_9BrO_3S$ (277.14) calculated: 39.00% C, 3.27% H;
found: 39.19% C, 3.14% H.

11. Cinchonidine salt of dextrorotatory o-bromobenzylsulfinylacetic acid (11)

27.71 g (0.1 mole) of powdered racemic acid 4 was mixed with 29.44 g (0.1 mole) of cinchonidine and dissolved in 420 ccm of boiling ethyl acetate. The solution was filtered and allowed to crystallize at room temp. The first fraction of the salt was filtered after 24 hrs. Colourless needles (28 g), m.p. 127—128°C, $[\alpha]_D^{20}=-41.0°$ ($c=0.5$, $d=0.5$, $\alpha=-0.102°$) in 96% ethanol. After four subsequent crystallizations of the first fraction of cinchonidine salt from ethyl acetate a compound was obtained, the physical properties of which were not changing during further purification. Needles, m.p. 133°, $[\alpha]_D^{20}=-19.6°$ ($c=0.5$, $d=0.5$, $\alpha=-0.049°$) in 96% ethanol. Yield 11 g. The salt of the dextrorotatory enantiomer is readily soluble in dioxane and chloroform, fairly soluble in methanol and 96% ethanol, sparingly soluble in carbon tetrachloride.

Analysis:

For the formula: $C_{28}H_{31}BrN_2O_4S$ (571.52) calculated: 4.90% N;
found: 5.11% N.

Table 6. Fractional crystallization of the cinchonidine salt of the dextrorotatory o-bromobenzylsulfinylacetic acid (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
1.	420	28.0	−41.0°	127—128
1.1.	595	19.0	−24.8°	130
1.1.1.	650	16.0	−20.0°	132
1.1.1.1.	550	13.5	−19.6°	133
1.1.1.1.1.	600	11.0	−19.6°	134

12. Dextrorotatory o-bromobenzylsulfinylacetic acid (12)

10.2 g of powdered cinchonidine salt 11 was suspended in 130 ccm of water and vigorously stirred for several min. The suspension was added to 1.5 g NaOH solution in 50 ccm of water and mixed for 1 hr. at

room temp. Liberated cinchonidine was filtered off and washed with water. The filtrate was mixed with the washing and extracted with chloroform (5×50 ccm). The alkaline liquid was acidified (Congo) with 3% hydrochloric acid after removing chloroform from it by distillation under reduced pressure (12 mm Hg, water bath). The acid solution was extracted (20×100 ccm) with chloroform. The combined chloroform extracts were washed with water and dried with anhydrous $MgSO_4$. The solvent was distilled under reduced pressure (12 mm Hg, water bath). The oily light yellow residue soon solidified. It was crystallized (3.5 g) from chloroform (30 ccm). Colourless rods, m.p. 86—87°C, $[\alpha]_D^{20} = +102.0°$ ($c=0.1$, $d=0.5$, $[\alpha]=+0.051°$) in 96% ethanol. Yield 1.8 g. The dextrorotatory enantiomer is readily soluble in chloroform, sparingly soluble in benzene.

Analysis:

For the formula: $C_9H_9BrO_3S$ (277.14) calculated: 39.00% C, 3.27% H;
found: 39.12% C, 3.22% H.

IR(cm^{-1}): 740νC—S; 770, 1040, 1100, 1180δC_{Ar}—H (subst. 1, 2); 1445, 1565, 1590$\nu C_{Ar}=C_{Ar}$; 1020νS=O; 910δOH(COOH); 1230, 1290, 1429δOH νC—O(COOH); 1730νC=O(COOH).

13. Amide of dextrorotatory o-bromobenzylsulfinylacetic acid (13)

3 g of dextrorotatory acid 12 was converted into amide under the conditions described in section 5. The crude product (2.7 g) was crystallized from 91% methanol (33 ccm). Needles, m.p. 149—150°C, $[\alpha]_D^{20} = +102°$ ($c=0.1$, $d=0.5$, $\alpha=+0.051°$) in 96% ethanol. The amide is readly soluble in dioxane, chloroform, methanol and 96% ethanol, sparingly soluble in cyclohexane and carbon tetrachloride.

Analysis:

For the formula: $C_9H_{10}BrNO_2S$ (279.16) calculated: 5.07% N;
found: 5.01% N.

14. p-Nitrobenzyl ester of dextrorotatory o-bromobenzylsulfinylacetic acid (14)

2 g of dextrorotatory acid 12 was converted into p-nitrobenzyl ester as in section 6 using 2 g of p-nitrobenzyl bromide and 50 ccm of 78% ethanol as solvent. The product obtained (1 g) was crystallized from methanol (15 ccm). Colourless needles, m.p. 71—72°C, $[\alpha]_D^{20} = +28.0°$ ($c=0.1$, $d=0.5$, $\alpha=+0.14°$) in 96% ethanol. Yield 0.6 g. The ester is readily soluble in chloroform, acetone, methanol and 96% ethanol, sparingly soluble in petroleum ether.

Analysis:
For the formula: $C_{16}H_{14}BrNO_5S$ (412.26) calculated: 3.39% N;
found: 3.39% N.

15. p-Bromophenacyl ester of dextrorotatory o-bromobenzylsulfinylacetic acid (15)

2.7 g dextrorotatory acid 12 and 2.7 g of p-bromophenacyl bromide was converted into ester under conditions described in section 7. The reaction time was 1.5 hr. The crude product was first washed with 5% $NaHCO_3$ solution and then with water. It was dried in a vacuum desiccator over $CaCl_2$ and crystallized from acetone (70 ccm). Plates, m.p. 159—160°C, $[\alpha]_D^{20} = +56.0°$ ($c=0.1$, $d=0.5$, $\alpha=+0.028°$) in 96% ethanol. Yield 1 g. This compound is fairly soluble in chloroform and dioxane, sparingly soluble in petroleum ether and acetone.

Analysis:
For the formula: $C_{17}H_{14}Br_2O_4S$ (474.18) calculated: 43.06% C, 2.97% H;
found: 43.44% C, 3.04% H.

16. p-Phenylphenacyl ester of dextrorotatory o-bromobenzylsulfinylacetic acid (16)

2.7 g of dextrorotatory acid 12 was suspended in 15 ccm of water and neutralized (phenolphthalein) with 3% NaOH. To the solution of sodium salt heated to 60°C, 2.5 g of p-phenylphenacyl bromide dissolved in 100 ccm of 96% ethanol was added and the mixture was heated for 1.5 hr. on water bath under reflux. From the solution allowed to stand at room temp. a fine crystalline precipitate separated. It was filtered, washed with 5% $NaHCO_3$ and water and dried in a vacuum desiccator over $CaCl_2$. The crude ester was crystallized from a mixture of acetone (20 ccm) and petroleum ether (20 ccm). Needles, m.p. 148—149°C, $[\alpha]_D^{20} = +52.0°$ ($c=0.1$, $d=0.5$, $\alpha=+0.026°$) in 96% ethanol. Yield 1.6 g. The ester is readily soluble in acetone and dioxane, sparingly soluble in petroleum ether and cyclohexane.

Analysis:
For the formula: $C_{23}H_{19}BrO_4S$ (471.37) calculated: 58.60% C, 4.06% H;
found: 58.59% C, 4.10% H.

17. o-Bromobenzylsulfonylacetic acid (17)

To 5 g of powdered acid 2, suspended in 35 ccm of glacial acetic acid, 4 ccm of 30% H_2O_2 was added and the mixture was mechanically shaken for 12 hrs. at room temp. Next, two 2 ccm portions of H_2O_2 were introduc-

ed at 12 hrs. intervals and shaking was continued for 24 hrs. As the reaction proceeded a fine crystalline precipitate separated. The compound was filtered (4 g), washed with water (2×25 ccm) and was crystallized from water (50 ccm). Colourless needles, m.p. 166—167°C. Yield 3 g. The sulfone is readily soluble in acetone and 96% ethanol, fairly soluble in benzene, sparingly soluble in carbon tetrachloride and chloroform.

Analysis:

For the formula: $C_9H_9BrO_4S$ (293.14) calculated: 36.87% C, 3.09% H;
found: 37.07% C, 2.99% H.

IR (cm^{-1}): 738νC—S; 760, 1040, 1090, 1190δC_{Ar}—H (subst. 1, 2); 1445, 1565, 1590$\nu C_{Ar}=C_{Ar}$; 1120νsSO_2; 1325$\nu asSO_2$; 920δOH(COOH); 1220, 1280, 1410δOH and νC—O(COOH); 1700νC=O(COOH).

18. Racemization of dextrorotatory o-bromobenzylsulfinylacetic acid (12)

Racemization of acid 12 was carried out in thermostated polarimetric tubes (ultrathermostat UTP Kraków, temperature sensitivity range ±0.01°) (d=0.5 dcm) fitted to Perkin-Elmer 241-MC polarimeter. The solvent was a mixture (2:1 v/v) of dioxane and dil. HCl (the acid was a mixt. 7:1 v/v conc. HCl:H_2O, d=1.15). The concentration of the optically active acid 12 was c=0.5. The rotation angle was determined every 5 min. immediately after dissolving acid 12 in the mixture of dioxane and dil. hydrochloric acid and filling the polarimetric tube with the solution. The measurements were carried out until the initial value of the rotation angle decreased by 90%. The solvent and the polarimetric tube were heated to the temperature at which racemization was carried out before the experiment. The racemization was studied at 16, 20, 24, 28 and 32°C. The polarimetric measurements were made using sodium light (λ=589 nm). The compound recovered from the control solutions in dioxane and dil. hydrochloric acid after the complete disappearance of optical activity (i.e. after complete racemization of acid 12) appeared to be, in every case, racemic acid 4. The calculations of the racemization parameters and experimental errors were carried out by means of a digital calculating machine ODRA-1013.

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STRESZCZENIE

Opisano syntezę i podstawowe własności kwasów o-bromobenzylosulfinylo- i sulfonylooctowych. Racemiczny kwas rozszczepiono w drodze krystalizacji frakcyjnej jego soli strychninowej (z acetonu) i cynchonidynowej (z octanu etylu) na enancjomery. Poszczególnym enancjomerom przypisano względne konfiguracje przestrzenne. Zdefiniowano w widzialnej części widma dyspersję rotacji optycznej prawoskrętnego antymeru i jego amidu oraz estrów: p-nitrobenzylowego, p-bromofenacylowego i p-fenylofenacylowego. Wyznaczono trójczłonowe równania opisujące rotację optyczną prawoskrętnego enancjomeru w widzialnej i nadfioletowej części widma. Określono stałe racemizacji (K) oraz parametry aktywacji (E_a, $\Delta H^{\#}$ i $\Delta S^{\#}$) dla procesu racemizacji optycznie czynnych kwasów o-bromobenzylosulfinylooctowych w oparciu o metody kinetyki klasycznej.

РЕЗЮМЕ

Представлено синтез и основные свойства о-бромобензилосульфинило- и сульфонилоуксусных кислот. Рацемическую кислоту расщеплено путем фракционной кристаллизации ее стрихиновой соли (с ацетона) и цинхонидиновой (с этилацетата) на энанциомеры. Отдельным энанциомерам приписано относительные пространственные конфигурации. Определено в видимой части спектра дисперсию оптического вращения правовращающегося антимера и его амида и р-нитробензилового, р-бромофенацилового и р-фенилофенацилового эстров. Установлено тричленистые уравнения представляющие оптическое вращение правовращающего энанциомера в видимой и ультрафиолетовой частях спектра. Определено постоянные рацемизации (К) и параметры активации (E_a, $\Delta H^{\#}$ и $\Delta S^{\#}$) для процесса рацемизации оптически активных о-бромобензилосульфинилоуксусных кислот, опираясь на метод классической кинетики.