Stereochemical Structure–Activity Relationship of N-(2,3-Epoxypropyl)-N-(α-methylbenzyl)benzenesulfonamide Derivatives

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The absolute configurations of two asymmetric centers in four stereoisomers of N-(2,3-epoxypropyl)-N-(α-methylbenzyl)benzenesulfonamide were determined and their biological activities were tested. Consequently, N-[(S)-2,3-epoxypropyl]-N-[(R)-α-methylbenzyl]benzenesulfonamide was found to be the most active isomer and the stereochemistry of the benzyl position was found to be more important than that of C2 in the epoxypropyl group for biological activity.

Some of the N-(2,3-epoxypropyl)-N-(α-methylbenzyl)benzenesulfonamide derivatives have a physiologically selective activity towards barnyardgrass and rice plants, and the spatial relationship between the epoxide moiety and other parts of molecule seems to be most important for exhibiting the high activity described in the previous paper.1)

Since N-(2,3-epoxypropyl)-N-(α-methylbenzyl)benzenesulfonamide derivatives consist of four epimeric stereoisomers due to two asymmetric carbons (C2 in the epoxypropyl group and the benzylic carbon), it is reasonable to examine the relationship between the stereochemical structure and the biological activity of the compounds. In this paper, we tried to clarify the stereochemistry of four stereoisomers and the stereochemical structure-activity relationship of N-(2,3-epoxypropyl)-N-(α-methylbenzyl)benzenesulfonamide (I).

Stereochemistry of the four stereoisomers, 1a ~ 1d
In a preliminary experiment, racemic 1 gave two peaks by an HPLC analysis and they could be separated by silica gel column chromatography into a less polar racemic diastereomer 1a,c, mp 76 ~ 77°C, and a polar one (1b,d), mp 69 ~ 70°C. N-[(R,S)-2,3-Epoxypropyl]-N-[(R)-α-methylbenzyl]benzenesulfonamide was prepared by the method described previously1) and chromatography over silica gel afforded the optically active diastereomer 1a (less polar, [α]D5 +46.4°) and 1b (polar, [α]D5 +37.7°). By a similar method, N-[(R,S)-2,3-epoxypropyl]-N-[(S)-α-methylbenzyl]benzenesulfonamide gave 1c, [α]D5 -46.3°, and 1d, [α]D5 -34.0°.

In the 200 MHz PMR spectra, 1a (1c) and 1b (1d) gave remarkably different signals. A 3H doublet (J = 7.1 Hz) due to the methyl group in 1a appeared at δ 1.48, which was 0.08 ppm downfield from that in 1b (δ 1.39). Signals due to protons attached to the oxirane ring showed characteristic shifts in 1a and b, as shown in Fig. 1. The signal (δ 2.48) due to the Ha proton in 1b appeared at 0.49 ppm downfield from that in 1a (δ 1.99). In addition, the signal (δ 2.58) due to the Hc proton in 1b appeared at

1) Phytotoxic Activity of Benzenesulfonamide Derivatives. Part III. For Part II, see ref. 1.
These corresponding shifts of the Ha and Hc protons suggest that the methyl group exhibits a shielding effect on the Ha proton in 1a as well as on the Hc proton in 1b. This means that the electro-magnetic circumstances surrounding the Ha proton in 1a are very similar to those around the Hc proton in 1b.

To clarify the absolute configuration of C₂ in the epoxypropyl moiety, the stereoisomers 1a~d were converted to the corresponding 2-hydroxypropyl derivatives (1'a~d), and their PMR spectra, melting points and [α]D were compared with those of authentic N-[(S)-2-hydroxypropyl]-N-[(R)-α-methylbenzyl]benzenesulfonamide (1'e) and N-[(S)-2-hydroxy-
propyl]-\(N\)-[(S)-\(x\)-methylbenzyl]benzenesulfonamide (1') prepared according to Scheme 1. Consequently, 1'a and d were found to be identical with 1'e and f, respectively. As the conversion of 1'a~d to 1'a~d proceeded with retention of the configuration at C2 in the epoxypropyl moiety,6) the absolute configurations in the four stereoisomers were determined to be (C2 in the epoxypropyl group, benzylic carbon): 1'a (R, R), 1'b (S, R), 1'c (S, S), 1'd (R, S).

Biological activities of the four stereoisomers

1) Petri dish test. The growth-retardation activities of 1'a~d against barnyardgrass and rice plants were tested. Figure 2 shows that 1'a exhibited the highest activity against both barnyardgrass and rice plants. The stereoisomer 1'a inhibited the growth of barnyardgrass more strongly than butachlor, \(N\)-butoxyethyl-2-chloro-2',6'-diethylacetanilide, and the growth of rice plants to a lesser extent. The other stereoisomers, 1'b~d, exhibited lower activity than 1'a. It was shown that the stereoisomers with an \(R\)-configuration at the benzylic carbon, i.e., 1'a and b, have higher activities than those with the \(S\)-configuration.

A mixture of 1'a~d (\(ID_{50}^b=0.15\) ppm, \(ID_{50}^{**}=0.3\) ppm) was about one-fifth as active as 1'a alone (\(ID_{50}^b=0.03\) ppm) against barnyardgrass and about two-thirds as active as 1'a alone (\(ID_{50}^b=0.2\) ppm) against rice plants. This may be attributed to a certain synergistic effect among the stereoisomers on their activities against rice plants.

2) Pot test. Pot tests in a paddy field condition were done as described previously.7) As shown in Table I, a similar order of activities to that in the petri dish test appeared.
Accordingly, the most active stereoisomer both in the petri dish and the pot tests was found to be \( N\)-[(\( R\))-2,3-epoxypropyl]-\( N\)-[(\( R\))-\( \alpha\)-methylbenzyl]benzenesulfonamide (1a). The stereochemistry of the benzyl position appeared to play a more important role in these biological activities, because 1b was more active than either 1c or d. The order of activities for these compounds indicates that the \( R\)-configuration at the benzyl position has priority for the action, which may also be enhanced by the \( R\)-configuration at the epoxide chirality. The results suggest that a certain receptor site can recognize this chirality at the benzyl position. That is, the configuration at the benzyl position would predict whether a stereoisomer could attach the certain receptor site or not.

The stereochemical structure–activity relationships of other \( N\)-(2,3-epoxypropyl)-\( N\)-(\( \alpha\)-methylbenzyl)benzenesulfonamide derivatives were also studied and similar results were obtained in every case. For example, the most active stereoisomer of \( N\)-(2,3-epoxypropyl)-\( N\)-(\( \alpha\)-methylbenzyl)-2,4,6-trimethylbenzenesulfonamide (2) was found to have an \( R\,R\) configuration which was identified by an X-ray crystallographical analysis.

Interactions between the two stereoisomers with an \( R\)-configuration at the benzyl position were studied by using the pot test, because the configuration at the benzyl position was presumed to predict the attachment of the molecule to a certain receptor site.

The results of the pot test showed that, in the case of compound 1, barnyardgrass recovered from growth-inhibition in the plots of low application rates due to its poor residual effect, so that the difference in activities between the stereoisomer 1a and the mixture of 1a and b was rather small. In the case of compound 2, however, the difference in activities between 2a and the mixture of 2a and b was remarkable as shown in Fig. 3. When the content of 2b exceeded 30\%, a significant reduction in activity occurred; and when the content of 2b was 50\%, the activity was less than 50\% that of 2a. This may be attributed to some antagonistic interaction between 2a and b.

In a preliminary experiment, the petri dish test was found to be inadequate for evaluating the interactions between the two stereoisomers, because it was impossible to evaluate the difference in growth-retardation ac-
tivities over a long period.

**EXPERIMENTAL**

IR spectra were recorded with a Shimadzu IR-400 spectrometer. PMR spectra were recorded with a JEOL JNM PMX-60 (60 MHz) spectrometer or a JEOL FX 200 (199.50 MHz) Fourier transform spectrometer. High pressure liquid chromatography was performed with a Toyo Soda HLC-803D apparatus equipped with a UV-8 model II spectrophotometer. The column used was TSKgel 120-OH and n-hexane (1%) ethanol was used as the eluting solvent at a flow rate of 1 ml/min. Absorption of the effluent was recorded at 254 nm and the peak area was integrated on a Shimadzu D-IP-4 polarimeter. All melting points and refractive indices were uncorrected.

**Separation of stereoisomer la~d.** Two grams of N-[(R, S)-2,3-epoxypropyl]-N-[(R)-a-methylbenzyl]benzenesulfonamide (a mixture of la and b) was chromatographed on a silica gel column (200 g, Kieselgel 60, Merck; 25 mm i.d. × 410 mm) and eluted with n-hexane-diehtyl ether (4:1, v/v). Each 10 ml of the eluent was collected and analyzed by HPLC. Fractions No. 38 to 47 gave 230 mg of la (isomer content: 97.8%) and No. 69 to 75 gave 200 mg of lb (isomer content: 95.1%), respectively.

By a similar method, lc and d were obtained in 98.5% isomer purity. The IR and PMR spectra of lc and d were identical with those of la and b, respectively. la: n\(\text{D}^5\) 1.5698, [\(\alpha\)]\(D^5\) +46.4° (c = 0.946, MeOH). IR \(\nu_{\max}^\text{cm}^{-1}\): 1445, 1324, 1155, 1083, 918, 880. Anal. Found: C, 64.28; H, 6.27; N, 4.52. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 64.33, H, 6.03; N, 4.41%. lc: n\(\text{D}^5\) 1.5695, [\(\alpha\)]\(D^5\) +46.3° (c = 0.123, MeOH). Anal. Found: C, 64.29; H, 6.06; N, 4.20. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 64.33; H, 6.03; N, 4.41%. ld: n\(\text{D}^5\) 1.5705, [\(\alpha\)]\(D^5\) +34.0° (c = 0.423, MeOH). Anal. Found: C, 64.32; H, 6.05; N, 4.34. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 64.33; H, 6.03; N, 4.41%.

**Reduction of la~d to la~d**. Three hundred mg of la in 5 ml of diethyl ether was added to 10 ml of a diethyl ether solution containing 100 mg of lithium aluminum hydride at 0°C, and the mixture was stirred for 15 min. Subsequent work-up and chromatography over silica gel afforded 250 mg of la, mp 74~75°C (recrystallized from n-hexane-ethyl acetate), [\(\alpha\)]\(D^5\) +37.8° (c = 1.138, MeOH). IR \(\nu_{\max}^\text{cm}^{-1}\): 3510, 3045, 1544, 1387, 1372, 1203, 1165, 1145, 1125, 962, 875. PMR \(\delta\) (200 MHz, CDCI\(_3\)): 0.85 (3H, d, J = 6.1 Hz), 1.29 (3H, d, J = 7.1 Hz), 2.54 (1H, OH), 2.93 (1H, dd), 3.11 (1H, m), 3.27 (1H, m), 5.27 (1H, q). Anal. Found: C, 63.75; H, 6.65; N, 4.44. Calcd. for C\(_11\)H\(_{12}\)NO\(_3\)S: C, 63.92; H, 6.63; N, 4.39%.

By a similar method, lb~d were obtained. lb: mp 87~88°C (recrystallized from n-hexane-ethanol), [\(\alpha\)]\(D^5\) +40.6° (c = 0.705, MeOH). Anal. Found: C, 63.95; H, 6.61; N, 4.39. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 63.92; H, 6.63; N, 4.39%. ld: mp 86~87°C (recrystallized from n-hexane-ethyl acetate), [\(\alpha\)]\(D^5\) +40.6° (c = 0.705, MeOH). Anal. Found: C, 63.95; H, 6.61; N, 4.39. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 63.92; H, 6.63; N, 4.39%.

(5)-2-Acetoxy-N-[(R)-a-methylbenzyl]propionamide. To a solution containing 4.27 g (32.3 mmol) of (S)-2-acetoxypropionic acid (bp 113~114°C (6 mmHg), [\(\alpha\)]\(D^5\) -47.5°, \(\delta\)) 4.7 g (38.8 mmol) of (R)-a-methylbenzylamine and 7.8 g (77.6 mmol) of triethylamine in 40 ml of dichloromethane, 9.9 g (38.8 mmol) of 2-choro-N-methylpyridinium iodide \(10\) was added and the mixture was heated under reflux for 1 hr. Subsequent work-up gave a crude product which was chromatographed over silica gel to give 7.5 g of (S)-2-acetoxy-N-[(R)-a-methylbenzyl]propionamide, [\(\alpha\)]\(D^5\) +79.6° (c = 0.758, MeOH). IR \(\nu_{\max}^\text{cm}^{-1}\): 3270, 1735, 1655, 1530, 1225. PMR \(\delta\) (60 MHz, CDCI\(_3\)): 1.44 (3H, d), 1.49 (3H, d), 2.11 (3H, s), 5.20 (2H, q). Anal. Found: C, 66.98; H, 7.15; N, 5.72. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 66.36; H, 7.28; N, 5.95%.

By a similar method, (S)-2-acetoxy-N-[(S)-a-methylbenzyl]propionamide was obtained, mp 139~140°C, [\(\alpha\)]\(D^5\) -137.4° (c = 0.860, MeOH). IR \(\nu_{\max}^\text{cm}^{-1}\): 3270, 1740, 1655, 1550, 1225. PMR \(\delta\) (60 MHz, CDCI\(_3\)): 1.48 (3H, d), 1.52 (3H, d), 2.11 (3H, s), 5.17 (2H, q). Anal. Found: C, 66.66; H, 7.39; N, 6.04. Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\)S: C, 66.36; H, 7.28; N, 5.95%.

N-[(S)-2-Hydroxypropyl]-N-[(R)-a-methylbenzyl]amine. To a solution of 1.5 g of lithium aluminum hydride in 100 ml of THF, 2.35 g (0.01 mol) of (S)-2-acetoxy-N-[(R)-a-methylbenzyl]propionamide was added at 0°C, and the mixture was heated under reflux for 6 hr. Subsequent work-up and chromatography over silica gel afforded 1.3 g (78%) of N-[(S)-2-hydroxypropyl]-N-[(R)-a-methylbenzyl]amine, mp 58~59°C (recrystallized from chloroform-methanol), [\(\alpha\)]\(D^5\) +59.6° (c = 0.258, MeOH). IR \(\nu_{\max}^\text{cm}^{-1}\): 3300 (broad), 1450, 1370, 1110, 1040, 758, 700. PMR \(\delta\) (60 MHz, CCl\(_4\)): 1.02 (3H, d), 1.31 (3H, d), 2.1~2.7 (2H, m), 2.70 (2H, s), 3.67 (1H, q), 3.7 (1H, m). Although this hydroxymine was found to contain some impurities by the elemental analysis, further purification was not done. By a similar method, N-[(S)-2-hydroxypropyl]-N-[(S)-a-methylbenzyl]amine was ob-
tained as an oily product with some impurities, 
\([\alpha]_{D}^{20} = -38.5^\circ\) (c = 0.544, MeOH). IR \(v_{\text{max}}\text{cm}^{-1} = 3300\) (broad), 1445, 1370, 1110, 1058, 697. PMR \(d (60\text{MHz, } \text{CCl}_4): 1.03 (3\text{H, d, } J = 7.1\text{ Hz), 1.31 (3H, d, } J = 2.2 \sim 2.6 (2\text{H, dd), 2.93 (2H, s, } 3.65 (1\text{H, q, } 3.7 (1\text{H, m).}}

\(\text{I'e and f were obtained by the reaction of the corresponding hydroxyamines and benzenesulfonyl chloride. I'e, mp 74 \sim 75^\circ\text{C (recrystallized from } \text{n-hexane-ethyl acetate), } [\alpha]_{D}^{5} + 41.8^\circ\) (c = 0.505, MeOH). Anal. Found: C, 64.03; H, 6.65; N, 4.34. Calcd. for \(\text{C}_{17}\text{H}_{21}\text{NO}_3\text{S}: C, 63.92; H, 6.63; N, 4.39\%.)

\(\text{I'f, mp 88 \sim 89^\circ\text{C (recrystallized from } \text{n-hexane-ethanol), } [\alpha]_{D}^{5} = -38.2^\circ\) (c = 0.950, MeOH). Anal. Found: C, 63.63; H, 6.63; N, 4.45. Calcd. for \(\text{C}_{17}\text{H}_{21}\text{NO}_3\text{S}: C, 63.92; H, 6.63; N, 4.39\%.

\(\text{N'-(7R)-2,3-Epoxypropyl]-N'-[(^)-a-methylbenzyl]-2,4,6-trimethylbenzenesulfonamide (2a) and N'-(5R)-2,3-epoxypropyl]-N'-(R)-a-methylbenzyl]-2,4,6-trimethylbenzenesulfonamide (2b) were obtained with a preparation method similar to that for 1a and b. 2a; mp 98 \sim 99^\circ\text{C, } [\alpha]_{D}^{20} + 58.1^\circ\) (c = 0.421, MeOH). IR \(v_{\text{max}}\text{cm}^{-1} = 2970, 2930, 1603, 1312, 1104, 938, 868. PMR \(\delta (200\text{ MHz, } \text{CDCl}_3): 1.69 (3\text{H, d, } J = 7.1\text{ Hz), 2.07 (1H, dd), 2.33 (3H, s), 2.53 (1H, dd, 2.63 (6H, s), 2.95 (1H, dd, 2.95 (1H, m), 3.40 (1H, dd, 4.89 (1H, q). Anal. Found: C, 66.85; H, 7.02; N, 3.91. Calcd. for \(\text{C}_{20}\text{H}_{25}\text{NO}_3\text{S: C, 66.82; H, 7.00; N, 3.89\%.)\n
\(2b; mp 119 \sim 120^\circ\text{C, } [\alpha]_{D}^{20} + 71.2^\circ\) (c = 0.411, MeOH). IR \(v_{\text{max}}\text{cm}^{-1} = 2970, 2930, 1603, 1310, 1142, 939, 858. PMR \(\delta (200\text{ MHz, } \text{CDCl}_3): 1.53 (3\text{H, d, } J = 7.1\text{ Hz), 2.32 (3H, s), 2.42 (1H, 2.53 (1H, 2.5 \sim 2.6 (1H, 2.66 (6H, s), 3.02 (1H, dd, 3.47 (1H, dd, 4.92 (1H, q). Anal. Found: C, 66.75; H, 6.96; N, 3.95. Calcd. for \(\text{C}_{20}\text{H}_{25}\text{NO}_3\text{S: C, 66.82; H, 7.00; N, 3.89\%.)\n
\(\text{Biological tests. Petri dish and pot tests were performed as described previously.}\)

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\(\text{REFERENCES}\)