Preparations of Cyclic Sulfoxide Derivatives and Their Evaluation as Transdermal Penetration Enhancers

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Novel cyclic sulfoxides, such as 2-octyl, 2-dodecyl and 2-hexadecyltetrahydrothiophene-1-oxide were prepared by the alkylation of tetrahydrothiophene-1-oxide. Additionally, 2-methyl, 2-ethyl and 2-propyl-5-dodecyltetrahydrothiophene-1-oxide were conducted by further alkylation. Their enhancing activity on the penetration of indomethacin through rabbit skin was evaluated in *in vitro* experiments, and the effect of the alkyl length on the enhancing activity was discussed. Among the 2-alkyl-tetrahydrothiophene-1-oxides, the compounds containing dodecyl and hexadecyl groups promoted a much greater penetration of the drug through the skin than the compound containing an octyl group. A stronger effect was observed in the experiment using 2-dodecyl-5-alkyltetrahydrothiophene-1-oxide, as compared with the that of 2-dodecyl-tetrahydrothiophene-1-oxide. The substitution of the alkyl groups to the next position of the sulfoxide group seemed to make the enhancing activities large.

Keywords cyclic sulfoxide; tetrahydrothiophene-1-oxide; alkylation; transdermal penetration; enhancer; indomethacin; lipophilicity

Transdermal drug delivery (T.D.D.) has attracted much attention as a novel way of drug administration because it has the potential to overcome the defects of oral or intravenous drug administration. Namely, T.D.D. can keep the drug concentration in the blood constant and prevent the need for frequent dosing. The stratum corneum that exists on the skin surface layer functions as a barrier to environmental insult of the substances.[1] The inclusion of a transdermal penetration enhancer into the T.D.D. system has been regarded as one of the means of enlarging the kinds of applicable drugs. There appear to be some reports concerning novel penetration enhancers in recent studies on T.D.D. Most of the penetration enhancers contain polar and non-polar groups in the molecule. Concerning the molecular structure, it is interesting that the penetration enhancers characteristically contain a cyclic group in the molecule. For example, cyclic amide such as Azone® (1-dodecyl-azacycloheptan-2-one),[2] pyrrolidone derivatives,[3–6] and cyclic urea[7,8] were prepared and their enhancing effects were investigated. Cyclic ketone, *i.e.*, cyclohexanone derivative, was synthesized and the effect of the alkyl group on the enhancing activity was discussed.[9] On the other hand, ordinary sulfoxide derivatives, such as dimethyl sulfoxide and decyl methyl sulfoxide, are well-known penetration enhancers,[10] however, cyclic sulfoxide derivatives have not been studied concerning the absorption promoter.

In the present article, novel transdermal penetration enhancers that possessed a cyclic sulfoxide group as the polar group and a long alkyl group as the non-polar group were prepared. These compounds were derived from tetrahydrothiophene-1-oxide. Their enhancing activities were investigated by *in vitro* skin permeation experiment and the enhancing mechanism of the compounds were discussed.

Experimental

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a Varian EM-390 90 MHz spectrometer, using $CDCl_3$. The chemical shifts were obtained on the basis of tetramethylsilane. Infrared (IR) spectra were recorded on a JASCO A-202 diffraction grating IR spectrophotometer. Mass spectra (MS) were measured by employing a Hitachi M-80A mass spectrometer.

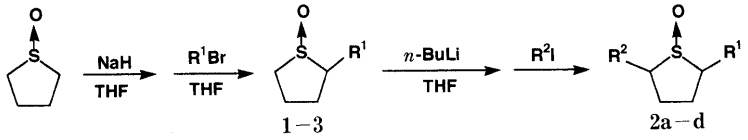
Typical Procedure for Preparation of 2-Alkyltetrahydrothiophene-1-oxides (1, 2a and 3) 20 ml of dehydrated tetrahydorofuran (THF) solution containing 4.71 g of tetrahydrothiophene-1-oxide (45 mmol) was added to a three-necked flask containing 1.08 g of sodium hydride (45 mmol), and the solution was refluxed for 2 h. After cooling to room temperature, 50 ml of THF solution containing 11.2 g of dodecyl bromide (45 mmol) was added to the solution and it was refluxed for 3 h. The precipitated salt was filtered off, and the filtrate was evaporated and purified by silica gel column chromatography to afford 4.4 g (37.6% yield) of **2a** as a white solid. IR (neat) ν: 2940, 2870, 1470, 1050 cm^{-1} (the same IR spectra were observed on all compounds, **1**, **2a**—**d** and **3**). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, J=7Hz, 3H), 1.23 (m, 22H), 2.11 (m, 2H), 2.50 (m, 2H), 2.89 (m, 3H). MS m/z: 273 ([M+1]$^+$), 255, 87, 69, 55. **1** and **3** were prepared by the same procedure as described above, using octyl bromide and hexadecyl bromide (37.1% and 63.4% yield, respectively). The spectra's data for **1**; ^{1}H-NMR ($CDCl_3$) δ: 0.86 (t, J=7 Hz, 3H), 1.22 (m, 14H), 2.12 (m, 2H), 2.48 (m, 2H), 2.83 (3H). MS m/z: 217 ([M+1]$^+$), 199, 87, 69. 37.1% yield. The spectra's data for **3**; ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, J=7 Hz, 3H), 1.25 (m, 30H), 2.09 (m, 2H), 2.47 (m, 2H), 2.87 (m, 3H). MS m/z: 328 (M$^+$), 331, 330, 185, 129, 97, 87, 57, 55.

Typical Procedure for Preparation of 2,5-Alkyltetrahydothiophene-1-oxides (2b, c and d) To 25 ml of THF solution containing 2.50 g of **2a** (9.2 mmol), 5.7 ml of 15% hexane solution of *n*-butyllithium (9.2 mmol) was added at 0 °C and the solution was stirred for 30 min. Then, 1.47 ml of ethyl iodide (9.2 mmol) was added to the solution and it was stirred for 12 h at room temperature. Saturated ammonium chloride aqueous solution was added to the reaction mixture and the organic layer was extracted with ethyl acetate. After the solvents were distilled off, the residue was purified by silica gel column chromatography to afford 1.02 g (25.6% yield) of **2c** as a transparent liquid. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, J=7 Hz, 3H), 1.11 (t, J=7 Hz, 3H), 1.28 (m, 22H), 1.65 (m, 2H), 2.22 (m, 2H), 2.44 (m, 2H), 2.98 (m, 2H). MS m/z: 300 (M$^+$), 283, 213, 125, 91, 55. **2b** and **2d** were synthesized by the same procedure as described above, using methyl iodide and propyl iodide (36.7% and 32.8% yield, respectively). The spectra's data for **2b**; ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, J=7 Hz, 3H), 1.26 (m, 22H), 1.32 (t, 3H), 1.82 (m, 2H), 2.11 (m, 2H), 2.85 (m, 2H). MS m/z: 286 (M$^+$), 269, 213, 125, 73, 41. The spectra's data for **2d**; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, J=7 Hz, 2×3H), 1.30 (m, 22H), 1.56 (m, 4H), 2.22 (m, 2H), 2.50 (M, 2H), 2.98 (m, 2H).

Measurement of Lipophilicity Physicochemical properties of the compounds were determined as lipophilicity, *i.e.*, lipophilic index ($\log k'$) measured by high performance liquid chromatography (HPLC) method.[11] The value of $\log k'$ is defined Eq. 1;

$$\log k' = \log[(t_r - t_0)/t_0] \quad (1)$$

where t_r and t_0 are the retention times of the sample and solvent (acetonitrile) peaks, respectively. The compounds (10 μg) were dissolved in 1 ml of acetonitrile and injected into HPLC (pump; CCPE, detector; RI-8010, column; TSK gel ODS-80TM, Tosoh Corporation). The mobile phase was a mixture of acetonitrile and water (9 : 1, (w/w)), where the



	1	2	3
R^1	C_8H_{17}	$C_{12}H_{25}$	$C_{16}H_{33}$

	a	b	c	d
R^1	$C_{12}H_{25}$	$C_{12}H_{25}$	$C_{12}H_{25}$	$C_{12}H_{25}$
R^2	H	CH_3	C_2H_5	C_3H_7

Chart 1. Preparations of 2-Alkyltetrahydrothiophene-1-oxides and 2-Dodecyl-5-alkyltetrahydrothiophene-1-oxides

flow rate was 1.0 ml/min.

***In Vitro* Skin Permeation Experiment** The abdomen of rabbit (Japanese White, male, 2.8—3.0 kg) was carefully shaved and blood was gradually withdrawn from the carotinoid artery. The abdominal skin was excised and mounted between two half cells of a two-chamber diffusion cell with a water jacket, of which the cross section was 0.95 cm^2. An ethanolic aqueous solution (50%, 2 ml) containing indomethacin (IMC, 2% (w/v), suspended) and a penetration enhancer (2% (w/v) completely dissolved except **2d**) was poured into the donor compartment. The receiver compartment was filled with 2 ml of isotonic phosphate buffer (pH 7.4). The diffusion cell was maintained at 37 °C by circulating constant-temperature water through the glass jackets surrounding each half cell. The solutions in both compartments were magnetically stirred. Portions (50 μl) of the solution were withdrawn from the receiver compartment at 2 h intervals up to 12 h. HPLC was used to measure the amount of IMC permeated. The mobile phase was the mixture of acetonitrile and 45 mM KH_2PO_4 aqueous solution adjusted to pH 3.00 with phosphoric acid (6:4 (w/w)). The sample solution was diluted with the mobile phase and injected into the HPLC system. The amount of IMC was determined by calculating the integrated area monitored at 240 nm (UV-8 model 2, Tosoh Corporation). Other conditions were the same as described above for the measurement of the lipophilic index.

Determination of Solubility of IMC The same suspension as that in the donor compartment was stirred at 37 °C for 1 d. After the filtration of insoluble IMC, the concentration of soluble IMC was measured by the same HPLC system as described above.

Results and Discussion

A methyl or methylene group at α-position of sulfoxide is easily deprotonated by bases such as sodium hydride and *n*-butyllithium to afford sulfinylcarboanion. Alkylating agents, such as alkyl halide, alkyl sulfonate, *etc.*, react with the carbanion to generate a new sulfoxide derivative.[12] The suitable selection of an appropriate base, alkylating agent and reaction condition may enable the introduction of a different alkyl group at the α-position of sulfoxide group. In this report, the novel cyclic sulfoxide derivatives containing two kinds of alkyl groups were prepared by two-step alkylation. The synthetic diagrams were shown in Chart 1. The first alkylation was carried out by the reaction of **2a** with sodium hydride followed by treating with corresponding alkyl halides, namely, octyl, dodecyl and hexadecyl bromides, and the second alkylation was conducted using *n*-butyllithium with the other alkyl halides, methyl ethyl and propyl iodides.

Figure 1 shows the permeation profiles of IMC through the skin using **1**, **2a** and **3** as transdermal penetration enhancers, which reflected the effect of the alkyl length of 2-alkyltetrahydrothiophene-1-oxide on the IMC penetrations. The values of the permeation coefficients (*P*), which are calculated from the slope at a steady state as in Fig. 1, are summarized in Table I. The solubilities of IMC in the donor solution and the lipophilic indices of the enhancers

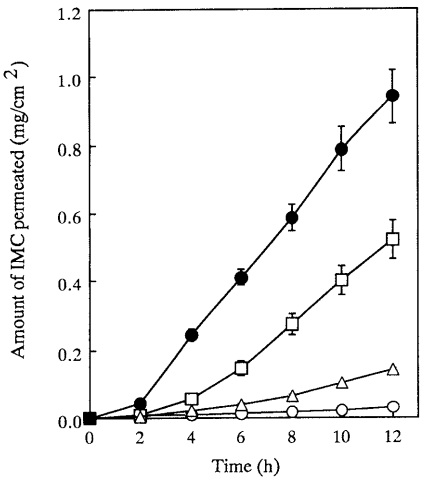


Fig. 1. Permeation Profiles of IMC through Rabbit Abdominal Skin Using 2-Alkyltetrathiophene-1-oxides as Penetration Enhancers

○, control; △, **1**; □, **2a**; ●, **3**.

TABLE I. Effect of Addition of Cyclic Sulfoxide Derivatives on Permeability and Solubility of IMC, and the Lipophilic Index of These Compounds

Sample No.	Permeation coefficient P ($\times 10^{-6}$ cm/s)	Solubility of IMC (mg/ml)[a]	Lipophilic index
1	0.88	5.36	−0.10
2a	2.78	6.27	0.34
2b	3.44	6.52	0.33
2c	7.09	6.31	0.34
2d	4.90	5.82	0.37
3	4.18	5.92	0.70
Control	0.24	4.42	—

a) In 50% ethanolic aqueous solution containing 2% (w/v) of penetration enhancer.

are also listed in Table I. All the compounds showed the high enhancing activities and the *P* values were 4—30 fold as much as that of a control (without an enhancer). Concerning the enhancing activities of **1**, **2a** and **3**, the enhancing effect increased with an increase of the carbon number of the long alkyl group at the 2-position. The lipophilic index also showed a similar tendency. In our previous paper, three kinds of compounds containing phosphoryl groups were prepared and the relationship between the enhancing activities and lipophilicities were investigated.[13] According to those results, a good linear relationship was observed between the lipophilicity and the enhancing efficacy of the penetration enhancer. In the cases of only **1**, **2a** and **3a**, the same manner was found out.

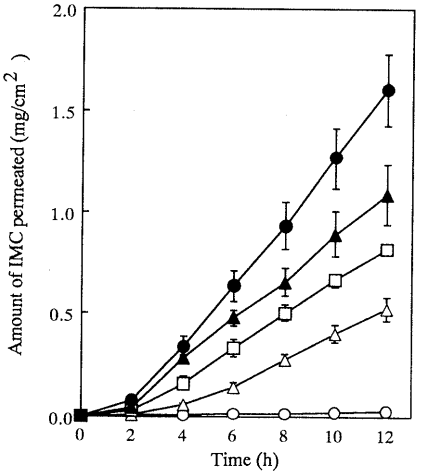


Fig. 2. Permeation Profiles of IMC through Rabbit Abdominal Skin Using 2-Dodecyl-5-alkyltetrathiophene-1-oxides as Penetration Enhancers
○, control; △, **2a**; □, **2b**; ●, **2c**; ▲, **2d**.

Additionally, the effects of the additions of **2a**, **2b**, **2c** and **2d** on the IMC penetration were evaluated. The permeation profiles were presented in Fig. 2. As shown in Fig. 2, the *P* values with **2b**, **2c** and **2d** were larger than that with **2a**. Therefore, the substitution of the alkyl groups to the 5-position of **2a** seemed to make the enhancing activities large. The *P* values were enlarged with an increase of the carbon number among **2a**, **2b** and **2c**, however, the lipophilicities remained constant, which contrasted with the results of **1**, **2a** and **3**.

Barry reported that dimethyl sulfoxide (DMSO) interacted with a lipid polar head group, followed by loosing a hydrocarbon chain.[14] In the same literature, it was suggested that the action of Azone was its insertion between the lipids, followed by the prevention of chain crystallization. These cyclic sulfoxide derivatives consist of a DMSO-like polar group and an Azone-like chemical structure. Judging from the structures of these compounds, it is considered that the enhancement of these derivatives might be due to the function to the lipids in the stratum corneum. The result, which the enhancing activity can not simply explain by the relation with the lipophilicity, suggests that the enhancing activities might be owing to the complex combination of the plural actions derived from DMSO-like and Azone-like parts.

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