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N-(4-BROMOBENZOYL)-*S,S*-DIMETHYLIMINOSULFURANE, A POTENT DERMAL PENETRATION ENHANCER

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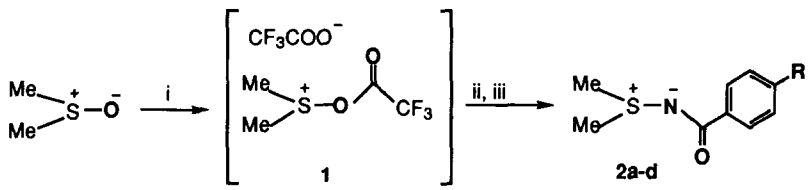
Abstract: *N*-Aroyl-, *N*-Arylsulfonyl-, and *N*-Aryl-*S,S*-dimethyliminosulfuranes have been synthesized and evaluated as potential dermal penetration enhancers. The title compound and Azone® exhibit similar activities for permeation of hydrocortisone through hairless mouse skin.

Despite their high chemical stability[1] and low toxicity,[2] aromatic iminosulfuranes (such as **2** in Scheme) have not been explored as potential pharmacological agents. Since the iminosulfurane functionality of these compounds is isoelectronic with the sulfoxide of DMSO, a classical dermal penetration enhancer,[3] it was reasoned that the iminosulfuranes might also enhance transport of drugs through skin. Accordingly, compounds **2** were synthesized as part of this work. Similarly substituted *N*-arylsulfonyl- and *N*-aryl-*S,S*-dimethyliminosulfuranes were prepared in an analogous way starting with arylsulfonamides and anilines, respectively (not shown). The synthetic route is a modification of a method described previously by Swern.[1] Excellent yields (up to 90%) are obtained, provided the conditions given in Scheme are strictly followed. For example, the intermediate product **1** is relatively stable at -50 °C but undergoes a rapid decomposition at -30 °C by Pummerer-type reaction to give methylthiomethyl trifluoroacetate.



2a: R = H; **2b**: R = Cl; **2c**: R = Br; **2d**: R = NO_2

(i) -60 °C, a slow addition of $(CF_3CO)_2O$ (1 equiv) in CH_2Cl_2 to DMSO (2 equiv) in CH_2Cl_2; (ii) -50 °C, a slow addition of 4-R-$C_4H_4CONH_2$ (1 equiv) in CH_2Cl_2/DMSO, then 3 h at -50 °C; (iii) quenching with 10% aq. NaOH (3 equiv) at -50 °C, extraction with CH_2Cl_2, crystallization from ether or ether/pentanes. **2a**, mp 108-110 °C [1]; **2b**, mp 110-112 °C; **2c**, mp 105-107 °C; **2d**, mp 224-227 °C [1].

The effects of DMSO and iminosulfuranes **2** on hydrocortisone (HC) skin permeation and retention are presented in the Table. DMSO (0.4 M in propylene glycol, PG) shows no significant activity and **2a** (0.4 M in PG) and **2d** (a suspension in PG) do not enhance within experimental error the permeation of HC through skin when compared with the control. The effect of chloro-substituted compound **2b** (0.4 M in PG) is similar to that of DMSO. To our surprise, however, the bromo analog **2c** (solubility of 0.18 M in PG) is a powerful enhancer and its activity is similar to that of Azone® (0.4 M in PG) under similar test conditions.[4] Azone® is one of the

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best dermal penetration enhancers known to date.[4,5] The skin content of HC is also enhanced in the presence of **2c**. On the other hand, similarly substituted *N*-aryliminosulfuranes derived from 4-substituted anilines show little effect on both transport of HC through skin and skin content of HC. Interestingly, arylsulfonyliminosulfuranes derived from sulfonamides are inhibitors of dermal penetration of HC (not shown).

One of the suggested mechanisms of the enhancement effect is lipid-protein-enhancer interactions, resulting in a change in lipid and protein conformation, thus creating channels for drug passage.[6] This may be the case for **2c**. Its high polarizability due to the presence of bromine atom (as opposed to high inherent polarity of nitro and sulfonyl derivatives) may increase stacking interactions of **2c** with aromatic substituents of proteins. Additionally, the carbonyl group of **2c** may be involved in hydrogen-bonding interactions, resulting in an even more stable protein - **2c** complex.

It should be noted that hairless mouse skin used in this study is a highly permeable model and further data will need to be obtained using human cadaver skin. However, the mouse model provides the means for initial selection of active compounds, and we have never found that an active compound in mouse was inactive in human.[7]

Table. Percutaneous permeation parameters of hydrocortisone[a]

Enhancer	T_{lag} h	Q_{24} μg/cm^2	ER_{Q24}	J μg/cm^{2}h	ER_J	SC μg/g	ER_{SC}
none	3.1 ± 0.6	43.1 ± 5.2	1.00	2.0 ± 0.2	1.00	1060 ± 79	1.00
DMSO	2.6 ± 0.5	45.5 ± 12.1	1.06	2.8 ± 0.3	1.37	382 ± 97	0.36
2a	0.8 ± 0.3	32.1 ± 10.0	0.74	1.8 ± 0.2	0.88	1149 ± 100	1.08
2b	4.0 ± 1.6	61.9 ± 11.0	1.44	3.1 ± 0.2	1.51	1434 ± 747	1.35
2c	1.5 ± 0.7	996 ± 192	23.1	42.9 ± 7.5	21.0	1584 ± 285	1.49
2d	6.4 ± 1.0	33.2 ± 6.5	0.77	1.8 ± 0.3	0.88	1736 ± 629	1.64

[a]The method has been described previously [4] and the given parameters are mean values of five independent experiments. Briefly, the experiments were conducted by using male hairless mouse skins mounted on Franz diffusion cells. The receptors were filled with isotonic phosphate buffer, pH 7.2, and maintained at 37 °C. Hydrocortisone was applied as a suspension in propylene glycol (PG, solubility 0.03 M at 32 °C). The concentration of DMSO, **2a** or **2b** in PG was 0.4 M. Compounds **2c** and **2d** were applied as suspensions in PG (the respective solubilities are 0.18 M and 0.02 M at 32 °C). T_{lag}, lag time; Q_{24}, receptor concentration after 24 h; J, flux; SC, skin content of hydrocortisone; ER, enhancement ratio calculated as parameter following enhancer treatment divided by the corresponding parameter from control.

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