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LIPOPHILICITY INDEXES OF SOME 3-ALKYLTHIO AND 3-ALKYLSULFINYL 4(1*H*)-QUINOLONES

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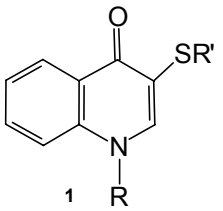
SUMMARY

RPTLC retention characteristics have been determined for two series of 1-alkyl-4(1*H*)-quinolinones with 3-alkylthio and 3-alkylsulfinyl groups. Experimentally obtained measures of lipophilicity, expressed as R_{M0} values, were compared with values of log *P* calculated by a computational method.

INTRODUCTION

The 4-quinolinone moiety is a fundamental pharmacophore in potent antibacterial drugs [1]; interesting biological activity has also been observed for other 4-quinolinones with sulfur functional groups, for example 4-quinolinone-3-sulfonamides have antihypertensive activity [2] and 3-alkylsulfinyl-4-quinolinones act as vasodilatators [3,4]. The lipophilicity of drugs has an important effect on their biological activity [5] and the correlation between biological properties and lipophilicity has been examined for antibacterial 4-quinolinones [6] and also to evaluate the proconvulsant activity of 4-quinolinone drugs [7]. This paper describes RPTLC evaluation of



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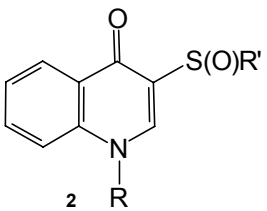

2

a, R = H, R' = CH_3
b, R = R' = CH_3
c, R = CH_3, R' = C_2H_5
d, R = CH_3, R' = *n*-C_3H_7
e, R = CH_3, R' = *n*-C_4H_9
f, R = *n*-C_4H_9, R' = CH_3

the lipophilicity indexes (R_{M0}) of some 4(1*H*)-quinolinones with 3-alkylthio and 3-alkylsulfinyl groups, **1** and **2**, and comparison of experimental data with values of log *P* obtained by means of a computer program.

EXPERIMENTAL

Chemicals and Reagents

Quinolinyl sulfides and sulfoxides **1** and **2** were prepared as described elsewhere [8,9]. Acetone, ethanol (both POCh, Poland), and tris(hydroxymethyl)aminomethane hydrochloride buffer solution pH 7.4 (Fluka) were of analytical grade.

Thin-Layer Chromatography

TLC was performed on 20 cm × 20 cm silica gel RP-18 F_{254}s plates (Merck, #115389). Before use the plates were activated by heating at 100°C for 1 h. Mixtures of acetone and Tris buffer solution (acetone concentrations 70, 60, 50, 40, 35, 30, and 25%, *v*/*v*) were used as mobile phases. Plates were spotted with ethanol solutions of the sulfides **1** or sulfoxides **2** (3 μL, 2 mg mL^{-1}), developed to a distance of 16 cm, dried, and inspected under UV light ($\lambda = 254$ nm). Each determination was performed in quadruplicate and R_M values were calculated for each compound in each system by use of the formula $R_M = \log(1/R_F - 1)$. For each quinoline derivative **1** and **2** R_M values obtained at each different acetone concentration were separately extrapolated to zero acetone concentration in the mobile phase by use of the formula [10] $R_M = R_{M0} + bC$, where b is a constant, C is the concentration of acetone in the mobile phase, and R_{M0} is the lipophilicity index.

RESULTS AND DISCUSSION

The results obtained are listed in Table I. The values of log P were calculated in accordance with the Hansch and Leo method [11]. The relationship between R_M values obtained from chromatography and the partition coefficients is described by the equation $R_M = a\log P + b$ [12], where a and b are constants for a particular system and P is the partition coefficient. In this work the relationship between experimentally obtained R_M values and theoretically calculated log P coefficients was linear for the logarithmic versions:

$\log R_{M0} = 0.2221 \log P - 0.5550$ ($r = 0.9986$, $s = 0.0095$)

for sulfides **1b–1f**, and

$\log R_{M0} = 0.2666 \log P - 0.3485$ ($r = 0.9996$, $s = 0.0062$)

for sulfoxides **2b–2f**.

Table I

Lipophilicity index and terms of the linear correlation ($R_M = R_{M0} + bC$) between R_M values and the concentration of acetone (C, % v/v) in the mobile phase

Cmpd	log P	R_{M0}	$-b$	r	s	log R_{M0}
1a	2.35	0.746	0.017	0.992	0.038	–0.127
1b	2.29	0.897	0.019	0.978	0.077	–0.047
1c	2.83	1.180	0.022	0.988	0.064	0.072
1d	3.37	1.576	0.026	0.991	0.069	0.198
1e	3.91	2.104	0.033	0.990	0.089	0.323
1f	3.91	1.998	0.032	0.984	0.074	0.301
2a	0.26	0.467	0.015	0.990	0.031	–0.331
2b	0.20	0.509	0.013	0.987	0.037	–0.293
2c	0.74	0.697	0.015	0.985	0.046	–0.157
2d	1.28	0.995	0.019	0.997	0.026	–0.002
2e	1.82	1.351	0.023	0.997	0.032	0.131
2f	1.82	1.384	0.023	0.993	0.046	0.141

Compounds **1a** and **2a**, which do not have *N*-substituted alkyl groups, did not comply with these equations, probably because of their acidity.

To determine the effect of the type of substituent on the lipophilicity linear correlations were calculated between the log R_{M0} value and the number of alkyl carbon atoms (n_C) per molecule:

$\log R_{M0} = 0.1199\ n_C - 0.2863$ ($r = 0.9986$, $s = 0.0095$, $n_C = 2$, 3, 4 or 5) for sulfides **1b–1f**, and

$\log R_{M0} = 0.2439\ n_C - 0.5831$ ($r = 0.9996$, $s = 0.0062$, $n_C = 2$, 3, 4 or 5) for sulfoxides **2b–2f**

When the dependence $\Delta R_{M0} = R_{M0}(n_C) - R_{M0}(n-1)_C = f(n_C)$ was analysed a good linear correlation was observed for all the sulfoxides investigated and for sulfides with N–H or N–methyl groups:

$\Delta R_{M0} = 0.1244\ n_C - 0.0958$ ($r = 0.9995$, $s = 0.0060$, $n_C = 2$, 3, 4, or 5) for sulfides **1a–1e**

$\Delta R_{M0} = 0.1070\ n_C - 0.1520$ ($r = 0.9873$, $s = 0.0259$, $n_C = 2$, 3, 4, or 5) for sulfoxides **2a–2f**

By use of the equation above the value obtained for compound **1f** should be 0.526 whereas we obtained 0.422. This discrepancy can be

explained by supposing that the adjacent *N*-butyl group sterically hinders solvation of a nitrogen atom, resulting in an increase of apparent lipophilicity. It can be suggested that for the lipophilicity of the compounds investigated the surroundings of the nitrogen atom are more important than those of the sulfur atom. This problem is not observed for the sulfoxides **2**, probably because of the large effect of the sulfinyl oxygen atom on R_M value.

The effect of the sulfinyl substituent can be represented by the value: $\Delta' R_{M0} = R_{M0}(\text{sulfide}) - R_{M0}(\text{sulfoxide})$, which for compounds **1a–1e** and **2a–2e** increased linearly with increasing number of alkyl carbon atoms (Table II). This is in accordance with the equation:

$$\Delta' R_{M0} = 0.1001\ n_C + 0.1825\ (r = 0.9996,\ s = 0.0047)$$

This equation is not valid for the relationship between **1e**/**2e** and **1f**/**2f**. For *S*-butyl and *N*-butyl compounds ΔR_{M0} is 0.070 greater and 0.069 smaller, respectively, than the theoretically calculated value, 0.683.

Table II

Effects of substituents on the chromatographic lipophilicity index R_M

$\Delta R_{M0} = R_{M0}(n_C) - R_{M0}(n-1)_C$				$\Delta' R_{M0} = R_{M0}(\text{sulfide}) - R_{M0}(\text{sulfoxide})$	
Cmpds	ΔR_{M0}	Cmpds	ΔR_{M0}	Cmpds	$\Delta' R_{M0}$
1b–1a	0.151	**2b–2a**	0.042	**1a–2a**	0.279
1c–1b	0.283	**2c–2b**	0.188	**1b–2b**	0.388
1d–1c	0.396	**2d–2c**	0.298	**1c–2c**	0.483
1e–1d	0.528	**2e–2d**	0.356	**1d–2d**	0.581
1f–1d	0.422	**2f–2e**	0.389	**1e–2e**	0.753
1e–1f	0.106	**2f–2e**	0.033	**1f–2f**	0.614

CONCLUSION

For the compounds investigated different dependencies between chromatographically obtained R_{M0} values and calculated log *P* values for quinolones and their *N*-alkyl derivatives were observed, even though buffer solution was used. The most interesting were those obtained for the methyl compounds **1e** and **1f** and the butyl compounds **2e** and **2f**. The problem of the contribution of *N*-alkyl and *S*-alkyl substituents to the lipophilicity of quinolone derivatives requires further investigation.

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