

DEPENDENCE OF $\log k$ OBTAINED BY HPLC ON $\log P'_{\text{exp}}$ IN THE SERIES PIPERIDINO AND MORPHOLINOETHYL ESTERS OF *o*-, *m*- AND *p*-ALKOXY SUBSTITUTED PHENYLCARBAMIC ACIDS

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Dependence of $\log k$ obtained by the HPLC method on $\log P'_{\text{exp}}$ obtained by the classical method was investigated in two series of basic ethyl phenylcarbamic acids. The linear dependence was found with *o*-substituted series and *p*-substituted morpholino derivatives. The relation with *p*-derivatives of the piperidino series is close to linearity, while that of *m*-derivatives of both series is not linear.

The method of high performance liquid chromatography for estimation of lipophilicity has been used since the half of seventieth; the suitable lipophilic parameter was suggested to be the logarithm of the capacity factor k . The expression $\log k$ corresponds to the variable R_M obtained from partition chromatography and its relation to the logarithm of partition coefficient $\log P$ is also linear as far as the Collander equation^{1,2} holds for both the chromatographic and reference systems. Estimation of lipophilicity of various compounds by the HPLC method and its comparison with values obtained by the classical method was reported by several authors³⁻¹⁰.

This paper presents the determination of lipophilicity of some morpholinoethyl esters and piperidinoethyl esters of substituted phenylcarbamic acid by the HPLC method and these results were compared with those obtained by classical method¹¹. The compounds under examination are potential local anaesthetics of which especially compound IV (heptacainium chloride) exhibits a high surface and infiltration anaesthesia^{12,13} at low toxicity.

EXPERIMENTAL

Apparatuses and Chemicals

Compounds under study were prepared according to refs^{12,13}, chemicals (Lachema, Czechoslovakia) were of p.a. grade and water was redistilled. Chromatograph Pye Unicam, model PU 4002 assembled of an

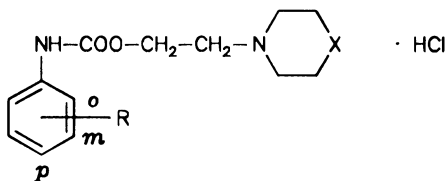
isocratic piston pump PU 4015, injection valve Rheodyne, model 7125, syringe loading sample injector with a 20 μ l loop, metal column 250 \times 4 mm packed with Separon SGX C18 grain size 10 μ m (Tessek, Czechoslovakia), flow rate 1.2 ml min⁻¹, a flow UV spectrophotometer PU 4025 adjustable in 1 nm intervals, detection at 278 nm, detector sensitivity 0.32 A.U.F.S.; integrator SP 4270 (Spectra-Physics U.S.A.); operating temperature 22 – 24 °C.

Procedure

Mobile phase: 6 various mobile phases differing in the methanol content in water were employed for both series of compounds; thus, 80, 83, 86, 89, 92, 95 vol.% methanol and 85, 88, 91, 94, 97, 100 vol.% methanol were those used for morpholino derivatives and piperidino derivatives, respectively. Each mobile phase contained 3.4 g of sodium acetate per 500 ml of the mobile phase for adjustment the pH value within 8.9 and 9.1 as measured with the Radelkis (Budapest) pH-meter, model OP-208/1. Before using the mobile phases were degasified by a stream of helium. Concentration of samples was 25 mg of the respective compound in 10.0 ml of water. A 0.1 M-NaNO₂ was used for determination of the retention time t_0 of the not retained compound. Statistical parameters were evaluated by the least squares method according to ref.¹⁵.

RESULTS AND DISCUSSION

The RP-HPLC system was employed for determination of lipophilicity of 18 compounds. The non-polar phase was packing of the column, i.e. silica gel chemically modified by octadecylsilane. The mobile phase was modified by addition of sodium acetate to prevent tailing.



	X	R		X	R
<i>I</i>	O	<i>o</i> -OC ₆ H ₁₃	<i>X</i>	CH ₂	<i>o</i> -OC ₆ H ₁₃
<i>II</i>	O	<i>m</i> -OC ₆ H ₁₃	<i>XI</i>	CH ₂	<i>m</i> -OC ₆ H ₁₃
<i>III</i>	O	<i>p</i> -OC ₆ H ₁₃	<i>XII</i>	CH ₂	<i>p</i> -OC ₆ H ₁₃
<i>IV</i>	O	<i>o</i> -OC ₇ H ₁₅	<i>XIII</i>	CH ₂	<i>o</i> -OC ₇ H ₁₅
<i>V</i>	O	<i>m</i> -OC ₇ H ₁₅	<i>XIV</i>	CH ₂	<i>m</i> -OC ₇ H ₁₅
<i>VI</i>	O	<i>p</i> -OC ₇ H ₁₅	<i>XV</i>	CH ₂	<i>p</i> -OC ₇ H ₁₅
<i>VII</i>	O	<i>o</i> -OC ₈ H ₁₇	<i>XVI</i>	CH ₂	<i>o</i> -OC ₈ H ₁₇
<i>VIII</i>	O	<i>m</i> -OC ₈ H ₁₇	<i>XVII</i>	CH ₂	<i>m</i> -OC ₈ H ₁₇
<i>IX</i>	O	<i>p</i> -OC ₈ H ₁₇	<i>XVIII</i>	CH ₂	<i>p</i> -OC ₈ H ₁₇

Under constant chromatographic conditions and precisely prepared mobile phase the plot $\log k$ per the volume composition of the mobile phase in per cent is a line¹⁴. Results of our study presented in Tables I and II also showed a linear course.

Comparison of the lipophilicity values represented by the parameter $\log k$ with those obtained by the classical method ($\log P'_{\text{exp}}$) is seen in Figs 1, 2. The $\log k$ values are taken from such a composition of the mobile phase where the best accordance between the experimental $\log k$ values and those calculated by linear regression was achieved.

TABLE I

Linear dependence parameters $\log k = k \varphi + q$ for morpholinoethyl esters of alkoxyphenylcarbamic acids^a

Compound	k	q	s	r_k
I	0.042	3.893	0.0078	0.9997
II	0.036	3.320	0.0505	0.9763
III	0.038	3.470	0.0150	0.9982
IV	0.046	4.361	0.0107	0.9994
V	0.045	4.166	0.0108	0.9994
VI	0.044	4.062	0.0119	0.9992
VII	0.052	5.009	0.0124	0.9994
VIII	0.051	4.840	0.0133	0.9992
IX	0.050	4.711	0.0144	0.9990

^a Vol.% of methanol in the mobile phase.

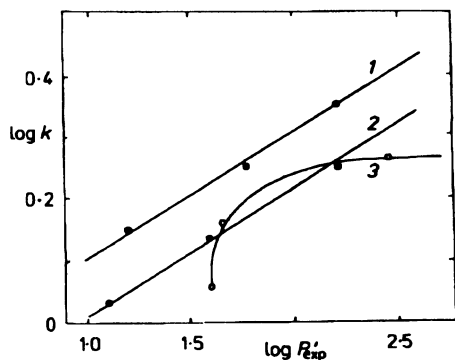


FIG. 1

Dependence of $\log k$ on $\log P'_{\text{exp}}$ for morpholinoethyl esters of alkoxyphenylcarbamic acids. Substitution: 1 *o*-, 2 *m*-, 3 *p*-

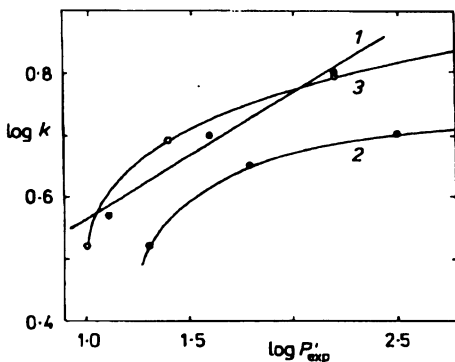


FIG. 2

Dependence of $\log k$ on $\log P'_{\text{exp}}$ for pipridinoethyl ester of alkoxyphenylcarbamic acids. Substitution: 1 *o*-, 2 *m*-, 3 *p*-

The best agreement in the morpholine and piperidine series of derivatives showed mobile phases with 89 vol.% and 88 vol.% of methanol, respectively.

Graphs illustrating the dependence of $\log k$ on $\log P'_{\text{exp}}$ (Figs 1, 2) reveal a linear relationship between results obtained by the RP-HPLC method and those by classical one with *o*-derivatives of both series and with *p*-derivatives of morpholinoethyl esters of phenylcarbamic acid. This dependence can be expressed by a line equation with *o*-morpholino derivatives $\log k = 0.068 + 0.184 \log P'_{\text{exp}}$ ($s = 0.0042$, $r_k = 0.9995$); with *o*-piperidino derivatives $\log k = 0.334 + 0.213 \log P'_{\text{exp}}$ ($s = 0.0111$, $r_k = 0.9977$); with *p*-morpholino derivatives $\log k = 0.176 + 0.192 \log P'_{\text{exp}}$ ($s = 0.0099$, $r_k = 0.9977$). Also results with *p*-substituted piperidinoethyl esters of phenylcarbamic acid approach the linearity, while dependence with the *m*-derivatives of both series was not found to be linear.

TABLE II

Linear dependence parameters $\log k = k \varphi + q$ for piperidinoethyl esters of alkoxyphenylcarbamic acids^a

Compound	k	q	s	r_k
<i>X</i>	0.052	5.173	0.0175	0.9984
<i>XI</i>	0.053	5.217	0.0210	0.9978
<i>XII</i>	0.053	5.171	0.0282	0.9963
<i>XIII</i>	0.057	5.745	0.0212	0.9982
<i>XIV</i>	0.061	6.042	0.0303	0.9967
<i>XV</i>	0.059	5.871	0.0245	0.9977
<i>XVI</i>	0.064	6.430	0.0220	0.9984
<i>XVII</i>	0.063	6.310	0.0253	0.9979
<i>XVIII</i>	0.066	6.597	0.0254	0.9979

^a Vol.% of methanol in the mobile phase.

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