Pflegel, H. (1982) Biopharmezeutische Aspekte parenteraler Arzneiformen. Pharmazie 37: 307–318
Stumpf, Ch., Chiari, I. (1965) Echte Gewöhnung an Hexobarbital. Naunyn Schmiedebergs Arch. Exp. Path. Pharmak. 251: 275–287
Stumpf, Ch., Viernstein, H. (1990) Central actions of central depressants given intravenously as suspensions. J. Pharm. Sci. 79: 1062–1064
Vesell, E. S. (1968) Factors altering the responsiveness of mice to hexobarbital. Pharmacology 1: 81–97
Vieth, J. B., Holm, E., Knopp, P. R. (1968) Electrophysiological studies on the action of Mogadon on centration nervous structures of the cat. A comparison with phenobarbital. Arch. Int. Pharmacodyn. 171: 323–338

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Partition and distribution coefficients of aryloxypropanolamine β-adrenoceptor antagonists

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Abstract—n-Octanol/water partition and distribution coefficients of fifteen β-blockers have been measured and the relationships between log P (neutral species), log P_i (fully ionized species) and log $D_{7.4}$ have been examined. A strict correlation exists among these three parameters, suggesting that the ionization exerts similar effects on the partition behaviour of these drugs.

The aryloxypropanolamines are the most widely represented chemical class within the group of the β-adrenergic blocking drugs. It is known that their cardiac activity is correlated with their lipophilic character and a number of studies have appeared in the literature dealing with this argument (Hellenbrecht et al 1974; Rauls & Baker 1979; Cruickshank 1980; Harada et al 1981; Gortner & Hellenbrecht 1988). The lipophilicity of these drugs has also been shown to have a role in some of their biochemical actions (Street & Walsh 1984), as well as in their binding to tissues (Dax & Partilla 1982; Ijzerman et al 1985, 1987; Bree et al 1986). Schoenwald & Huang (1983) studied the corneal penetration of β-blockers, while the relationships between the pharmacokinetics and the lipophilicity of these drugs in man have been thoroughly reviewed by Hinderling et al (1984). Several papers have been devoted to the study of the partition properties of β-blockers (Woods & Robinson 1981; Barbato et al 1990).

The partition coefficients published in the literature are collected in the database of the Pomona College MedChem Project (1986), which also provides a list of the most reliable data called STARLIST. From the same source a program is available called CLOGP, which allows one to calculate the partition coefficient of a given molecule. Considering the usefulness of a reliable method of calculation of the partition data, it is important to check the performance of the program with sets of carefully measured values. In two recent articles a good correlation between experimental and calculated partition coefficients of a number of β-blockers has been shown (Recanatini 1989; Mannhold et al 1990).

Because of their basic nature, the aryloxypropanolamines are partially ionized at physiological pH (7·4), and the ionization influences the partition behaviour of the compounds. In the following we will use the term partition coefficient (P) to mean the ratio of the concentrations of a single species between the two phases, and the term distribution coefficient (D) to mean the ratio of the concentrations of all the species (i.e. neutral, ionic, ion-pair, ion clusters) between the octanol and aqueous phases.

It is the aim of this paper to present a consistent set of log P and log $D_{7.4}$ data of a number of β-blocking drugs with the aryloxypropanolamine structure. We take into consideration the partition of the compounds both as neutral species and as ionic species; a comparison is made between these values and the distribution coefficients at physiological pH. A comparison between the experimental log P values and those calculated by means of the CLOGP program is also presented, in order to further explore the reliability of the calculated values.

Materials and methods

Chemicals. The following drugs were obtained from the indicated companies: diacetolol hydrochloride (May & Baker, Dagenham, UK); cetamolol hydrochloride (Wyeth-Ayerst, Princeton, USA); moprolol hydrochloride (Simes, Milano, Italy); bisoprolol fumarate (Merck, Darmstadt, Germany); bunitrolol and pargolol (Boehringer Ingelheim, Ingelheim, Germany); befunolol hydrochloride (Thilo, Sanerlach, Germany); metipranolol and carazolol (Boehringer Mannheim, Mannheim, Germany); mepindolol sulphate (Schering, Berlin, Germany); betaxolol (L.E.R.S., Paris, France); procinolol (Roussel Uclaf, Rounainville, France); flusoxosol hydrochloride (Hoffmann-La Roche, Basel Switzerland); penbutolol (Hoechst, Frankfurt, Germany); bornaprolol hydrochloride (Rhône-Poulenc, Gennevilliers, France).

All the substances used for the buffer solutions as well as n-octanol were of analytical grade and were purchased from Farmitalia-Carlo Erba, Milano, Italy.

Methods. All the partition measurements were carried out following the shake flask method (Leo et al 1971). Each reported value is the average of at least four runs, with a standard deviation $\leq 0{\cdot}03$; the amount of substance used in the partition studies was such to allow a tenfold interval of concentration whenever possible. It has to be noted that in no case was a dependence of the log $D_{7.4}$ values on the solute concentration found, which suggests that ion-pairing does not influence the partition behaviour.

The partition coefficients of the neutral compounds (log P) were measured using 0·1 M NaOH as aqueous phase (pH = 13), while those of the ionized molecules (log P_i) were measured using 0·1 M HCl (pH = 1·2); the potassium dihydrogen phosphate/sodium hydroxide buffer was used for the measurements at pH 7·4 (log $D_{7.4}$). The concentrations of the substances used were such that the resulting ionic strength of the solutions ranged between 0·1 and 0·3. Ionic strength below 0·1 had a negligible

effect on the distribution coefficients and a significant increase in log P appeared only at much higher values (Dearden & Bresnen 1988).

A Crison micro pH 2000 pH meter was used to measure the pH of the buffer solutions and a Varian DMS 90 UV-visible spectrophotometer was used for the quantitative determinations of the drugs in the standard solutions and in the partitioned solutions.

The CLOGP values were calculated by means of the CLOGP program Ver. 3.42.

Results and discussion

The experimentally determined data for the 15 β-blockers considered are presented in Table 1 as log P, log P_i and log $D_{7.4}$. In the case of the measurements performed using 0·1 M NaOH or 0·1 M HCl, a single species is assumed to be present, and we refer to these values as log P (of the neutral molecule) and log P_i (of the ionized molecule), respectively. However, the log P_i data of Table 1 actually show the partition of the ion-pairs formed by the ionized amine and the negatively charged counterion (in this case Cl^-). The variation in log P_i values throughout the series exactly parallels the variation in log P, which can be expressed by means of equation 1:

$$\log P_i = 1{\cdot}05(\pm 0{\cdot}08)\log P - 3{\cdot}00(\pm 0{\cdot}22) \quad (1)$$
$$n = 15 \quad r = 0{\cdot}991 \quad s = 0{\cdot}142 \quad F(1,13) = 745{\cdot}62$$

This equation shows that the structural changes which cause a variation in the partition coefficient of the neutral molecule cause an equal change in the partition coefficient of the ionized molecule. The average difference between log P and log P_i is 2·88 and this difference is constant throughout the set (s.d. = 0·14). This should mean that the amino nitrogen is electronically isolated from the aromatic moiety of the molecule. In fact the structural changes occur on that moiety and the interaction with the ionized amine either are absent or do not cause inhomogeneous effects on the partition.

The log $D_{7.4}$ is a composite parameter, which takes into account the presence of several species in the two phases. It is mainly influenced by the pK_a of the molecules, because the pK_a determines the fraction ionized at that pH. For this reason in a series of compounds with varying pK_a, log P and log $D_{7.4}$ should be correlated via the pK_a values. On the other hand, Ezumi & Kubota (1980) have demonstrated that in a series of similar compounds whose pK_a and Δlog P values are almost equal, log P and log D are in linear relation to each other, with a slope of 1. Considering the log P and the log $D_{7.4}$ values of Table 1, we obtained the following equation:

$$\log D_{7.4} = 1{\cdot}10(\pm 0{\cdot}16)\log P - 2{\cdot}42(\pm 0{\cdot}32) \quad (2)$$
$$n = 15 \quad r = 0{\cdot}985 \quad s = 0{\cdot}199 \quad F(1,13) = 412{\cdot}44$$

The pK_a values of most of the drugs of Table 1 are not known, but on the basis of equation 2 it is reasonable to state that they should be similar. This means that the ionization similarly affects the partition behaviour of all the compounds studied. Confirmation comes from the consideration of the differences between log P and log $D_{7.4}$, which are stable around the mean value (2·17 ± 0·21).

Given the relationship existing among log P, log D, pH and pK_a, one could calculate the ionization constant using the known data. This procedure, however, is not fully reliable in this author's opinion, as calculation errors inherent in a number of measurements may accumulate. However, even calculated pK_a values can be useful in giving at least an estimate of the ionization constants. The pK_a values were thus calculated, using the expression derived by Horváth et al (1977) for relating the chromatographic capacity factors of weak acids and bases with the hydrogen ion concentration, the ionization constant and two limiting capacity factors of the un-ionized and the fully ionized species. Recently, Barbato et al (1990) made use of this relationship for describing the ionization/partition profiles of weak bases in terms of octanol/water partition and distribution coefficients:

$$D = \frac{P + P_i([H^+]/K_a)}{1 + ([H^+]/K_a)}$$

The pK_a values obtained in this way are reported in Table 1, together with the experimental values available in the literature. All the calculated ionization constants lie in a narrow interval but show some discrepancy with respect to the few measured ones.

Table 1. Partition data and ionization constants of β-blockers.

Name	log P	log P_i	log $D_{7.4}$	CLOGP	(log P-CLOGP)	pK_a[a]
Diacetolol	0·94	−1·99	−1·21	0·55	−0·39	9·6
Cetamolol	1·36	−1·62	−1·03	0·27	−1·09	9·9
Moprolol	1·69	−1·21	−0·64	1·11	−0·58	9·9
Bisoprolol	1·87	−0·96	−0·23	1·21	−0·66	9·6
Bunitrolol	1·97	−0·93	−0·36	1·74	−0·23	9·9
	(2·05[b])		(−0·51[b])			(9·40[c])
			(−0·40[c])			
Befunolol	2·02	−0·90	−0·12	1·76	−0·26	9·6
			(−0·08[d])			
Metipranolol	2·28	−0·35	0·43	3·12	0·84	9·3
			(0·36[c])			(9·70[c])
Mepindolol	2·30	−0·58	0·05	2·30	0·00	9·8
Pargolol	2·32	−0·68	−0·19	1·16	−1·16	10·1
Betaxolol	2·81	−0·14	0·55	2·32	−0·49	9·8
						(9·21[e])
Procinolol	3·07	0·02	0·84	2·67	−0·40	9·7
Carazolol	3·59	0·72	1·50	3·03	−0·56	9·6
Flusoxosol	3·70	0·71	1·44	3·66	−0·04	9·7
Penbutolol	4·06	1·24	1·97	4·20	0·14	9·6
			(1·92[c])			(9·40[c])
Bornaprolol	4·17	1·68	2·53	4·10	−0·07	9·1

[a] Calculated values; see text. [b] Experimental values from Barbato et al (1990). [c] Experimental values from Mannhold et al (1990). [d] Experimental value from Harada et al (1981). [e] Experimental value from Bree et al (1986).

In Table 1, the calculated CLOGP values and the differences, CLOGP − log P, are also reported. The average Δ value is −0·33, which confirms the value of −0·37 reported earlier (Recanatini 1989); the standard deviation is somewhat higher (0·49) and this can be due to some positive deviations which appear in the present series. We noted a positive deviation for bupranolol in the previous paper, but had not enough data to consider it anything but an outlier. In the series of Mannhold et al (1990) the deviations between CLOGP and log P for the common compounds point in the same direction.

The correlation between experimental and calculated partition coefficients from Table 1 is expressed by equation 3:

$$\text{CLOGP} = 1{\cdot}17(\pm 0{\cdot}28)\ \log P - 0{\cdot}75(\pm 0{\cdot}76) \qquad (3)$$
$$n = 15 \quad r = 0{\cdot}928 \quad s = 0{\cdot}481 \quad F(1,13) = 80{\cdot}45$$

An overall good correlation exists between experimental and calculated log P values. Although the standard deviation is high, indicating some scattering of the points around the correlation line, the slope is close to 1 suggesting that the structural variations which cause changes in the partition coefficients throughout the series are well accounted for by the algorithm.

Finally, the experimentally measured partition data found in recent articles are reported in Table 1. The values from different laboratories are in good agreement, with differences within the experimental error. Considering that the measurements have all been performed by means of the shake flask method, the consistency of the data can be regarded as another indication of the reliability of this procedure.

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References

Barbato, F., Caliendo, G., La Rotonda, M. I., Morrica, P., Silipo, C., Vittoria, A. (1990) Relationships between octanol-water partition data, chromatographic indices and their dependence on pH in a set of beta-adrenoceptor blocking agents. Il Farmaco 40: 647–663

Bree, F., El Tayar, N., Van de Waterbeemd, H., Testa, B., Tillement, J.-P. (1986) The binding of agonists and antagonists to rat lung beta-adrenergic receptors as investigated by thermodynamics and structure-activity relationships. J. Receptor Res. 6: 381 409

Cruickshank, J. M. (1980) The clinical importance of cardioselectivity and lipophilicity in beta blockers. Am. Heart J. 100: 160–178

Dax, E. M., Partilla, J. S. (1982) Adrenergic ligand liposolubility in membranes. Direct assessment in a beta-adrenergic binding system. Mol. Pharmacol. 22: 5–7

Dearden, J. C., Bresnen, G. M. (1988) The measurement of partition coefficients. Quant. Struct.-Act. Relat. 7: 133–144

Ezumi, K., Kubota, T. (1980) Simultaneous determination of acid dissociation constants and true partition coefficients by analyses of the apparent partition coefficients. I. Chem. Pharm. Bull. 28: 85–91

Gortner, L., Hellenbrecht, D. (1988) Quantitative structure-activity studies of β-adrenoceptor blocking drugs to decrease ventricular arrhythmias in guinea pigs. Arzneim. Forsch. 38: 1796–1799

Harada, S., Ban, T., Fujita, T., Koshiro, A. (1981) Negative inotropic effects and the hydrophobicity of beta-adrenergic blocking agents. Arch. Int. Pharmacodyn. 252: 262–271

Hellenbrecht, D., Müller, K. F., Grobecker, H. (1974) Prediction of the non-specific cardiodepressant effects of β-adrenoceptor blocking agents in vitro and in vivo by means of the Hansch analysis. Eur. J. Pharmacol. 29: 223–235

Hinderling, P. H., Schmidlin, O., Seydel, J. K. (1984) Quantitative relationships between structure and pharmacokinetics of beta-adrenoceptor blocking agents in man. J. Pharmacokin. Biopharm. 12: 263–287

Horváth, C., Melander, W., Molnár, I. (1977) Liquid chromatography of ionogenic substances with nonpolar stationary phases. Anal. Chem. 49: 142–154

Ijzerman, A. P., Dorlas, R., Aué, G. H. J., Bultsma, T., Timmermann, H. (1985) Factors controlling β_1-adrenoceptor affinity and selectivity. Biochem. Pharmacol. 34: 2883–2890

Ijzerman, A. P., Nagesser, A., Garritsen, A. (1987) The membrane stabilizing activity of β-adrenoceptor ligands. Quantitative evaluation of the interaction of phenoxypropanolamines with the [^{3}H]batrachotoxinin A 20-α-benzoate binding site on voltage-sensitive sodium channels in rat brain. Ibid 36: 4239–4244

Leo, A., Hansch, C., Elkins, D. (1971) Partition coefficients and their uses. Chem. Rev. 71: 525–554

Mannhold, R., Dross, K. P., Rekker, R. F. (1990) Drug lipophilicity in QSAR practice: I. A comparison of experimental with calculative approaches. Quant. Struct.-Act. Relat. 9: 21–28

Pomona College MedChem Project (1986) Release 3.42, Claremont, CA, USA

Rauls, D. O., Baker, J. K. (1979) Relationships of nonspecific antiarrhythmic and negative inotropic activity with physicochemical parameters of propranolol analogues. J. Med. Chem. 22: 81–86

Recanatini, M. (1989) Comparison between measured and calculated partition coefficients of β-receptor antagonists. Prog. Chem. Biol. Res. 291: 75–78

Schoenwald, R. D., Huang, H.-S. (1983) Corneal penetration behavior of β-blocking agents I: physicochemical factors. J. Pharm. Sci. 72: 1266–1271

Street, J. A., Walsh, A. (1984) Inhibition of synaptosomal [^{3}H]noradrenaline uptake by β-adrenoceptor blocking drugs: influence of lipophilicity. Eur. J. Pharmacol. 102: 315–324

Woods, P. B., Robinson, M. L. (1981) An investigation of the comparative liposolubilities of β-adrenoceptor blocking agents. J. Pharm. Pharmacol. 33: 172–173