

CHROM. 11,820

Note

Structure- R_M investigation of 3-acyloxy-1,4-benzodiazepines

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(First received January 5th, 1979; revised manuscript received February 28th, 1979)

The study of quantitative structure-activity relationships (QSAR) of 1,4-benzodiazepines is based on different hydrophobic parameters. Partition coefficients (P) were the first to be considered¹⁻³. After Tomlinson⁴ had pointed out the advantages of thin-layer chromatographic (TLC) R_M values in QSAR studies, Huls-hoff and Perrin⁵ developed a method for the determination of the R_M values of very lipophilic compounds. This method was applied to 1,4-benzodiazepines and compared with a high-performance liquid chromatographic method⁶.

R_M values can also be used in QSAR studies of prodrugs. This is supported by a structure-pharmacokinetic study of 1,4-benzodiazepine prodrugs⁷, which indicated a correlation between the brain penetration of oxazepam and the R_M values of its esters. In this work, the R_M values of 33 closely related potential prodrugs have been determined. The compounds investigated were all 3-acyloxy-1,4-benzodiazepines differing either in the acyl moiety or in ring substitution.

EXPERIMENTAL

Materials

The acetoxy-1,4-benzodiazepines were prepared by rearrangement of the corresponding N^4 -oxides⁸. Other esters were synthesized by pyridine-catalysed acylation using alcohols and acyl chlorides⁹.

Light petroleum (b.p. 40-70°) was supplied by Carlo Erba (Milan, Italy) and Kieselgel HF₂₅₄ by Merck (Darmstadt, G.F.R.). Distilled water was used throughout.

TLC experiments

Glass plates (20 × 20 cm) were coated with an aqueous slurry of Kieselgel HF₂₅₄ to a thickness of 0.25 mm, using standard equipment. Water was allowed to evaporate at room temperature for at least 1 day, then the plates were treated with light petroleum containing 5% of liquid paraffin. The substrates (in 10 μ l of dimethyl sulphoxide) were spotted on a line 2 cm from the lower edge of the plate. The plates were equilibrated overnight in a saturated chamber¹⁰ and then developed in aqueous methanol. The spots were detected under ultraviolet light at 254 nm.

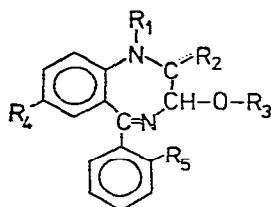


Fig. 1. Chemical structure of 1,4-benzodiazepines.

RESULTS AND DISCUSSION

R_M values of 33 3-acyloxy-1,4-benzodiazepines were determined. The effects of the following structural modifications were examined:

(1) different esters of oxazepam and lorazepam with varying alkyl chain length and branching, and ω -phenyl and/or α -halogen substituents in the acyl moiety;

(2) 3-acetoxy-1,4-benzodiazepines with different ring substituents in positions 1-, 2-, 7- and 5-(2'). The effect of methanol concentration on R_F values was examined for 17 oxazepam esters (Table I). For the determination of the corresponding R_M data a methanol concentration of 65% was used, which resulted in a suitable R_F range for the whole series.

TABLE I

 R_F AND R_M VALUES OF OXAZEPAM ESTERS IN DIFFERENT METHANOL-WATER MIXTURES

$R_1=R_5=H$, $R_2=O$, $R_4=Cl$. Results are averages of six determinations. R_M values were calculated from a linear fit of the R_M -concentration function.

Com- pound No.	R_3	R_F				R_M^*
		60% MeOH	65% MeOH	70% MeOH	75% MeOH	
1	H	0.52	0.66	0.71	0.83	-0.25
2	COCH ₃	0.44	0.60	0.70	0.81	-0.15
3	COCH ₂ CH ₃	0.36	0.53	0.67	0.81	-0.03
4	COCH(CH ₃) ₂		0.43	0.61	0.76	0.12
5	CO(CH ₂) ₂ CH ₃	0.23	0.40	0.43	0.77	0.17
6	CO(CH ₂) ₂ COOCH ₃	0.27	0.58	0.68	0.80	-0.03
7	COCH ₂ CH(CH ₃) ₂		0.32	0.50	0.71	0.34
8	COC(CH ₃) ₃		0.33	0.52	0.72	0.30
9	COCH(CH ₂ CH ₃) ₂		0.26	0.45	0.69	0.46
10	COCH(CH ₂) ₃ CH ₃		0.12**	0.28**	0.55	0.88
	↓					
	CH ₂ CH ₃					
11	COCH ₂ Ph		0.33	0.54	0.76	0.32
12	COCH ₂ CH ₂ Ph	0.11	0.24	0.42	0.69	0.50
13	COCH(CH ₃)CH ₂ Ph		0.19	0.39	0.63	0.64
14	COCHClCH ₂ Ph		0.20	0.41	0.65	0.60
15	COCHBrCH ₂ Ph***		0.18	0.35	0.63	0.65
16	COC(CH ₃) ₂ CH ₂ Ph		0.17	0.34	0.58	0.69
17	CO(CH ₂) ₃ Ph		0.19	0.36	0.64	0.65

* 65% methanol.

** Tailing of the spots occurred.

*** Partial decomposition during chromatography.

TABLE II

 R_F AND R_M VALUES OF 3-ACYLOXY-1,4-BENZODIAZEPINES

Results are average values of six determinations in 65% methanol.

Substituent					R_F	R_M
R_1	R_2	R_3	R_4	R_5		
H	O	H	Cl	Cl	0.62	-0.21
H	O	COCH ₃	Cl	Cl	0.61	-0.19
H	O	COCH(CH ₃) ₂	Cl	Cl	0.48	0.04
H	O	COCH ₂ CH(CH ₃) ₂	Cl	Cl	0.39	0.20
H	O	COC(CH ₃) ₃	Cl	Cl	0.39	0.20
H	O	COCH(CH ₂ CH ₃) ₂	Cl	Cl	0.30	0.36
H	O	COCH ₂ CH ₂ Ph	Cl	Cl	0.29	0.39
H	O	COCH(CH ₃)CH ₂ Ph	Cl	Cl	0.24	0.49
H	O	COCH ₂ Cl	Cl	H	0.59*	-0.16
H	O	COCHCl ₂	Cl	H	0.58*	-0.14
CH ₃	O	COCH ₃	Cl	H	0.49	0.01
H	O	COCH ₃	NO ₂	H	0.61	-0.20
—	NHCH ₃	COCH ₃	Cl	H	0.34	0.29
(CH ₂) ₂ COOEt	O	COCH ₃	Cl	H	0.45	0.08
CH ₂ COOEt	O	COCH ₃	Cl	H	0.49	0.01
(CH ₂) ₂ COOH	O	COCH ₃	Cl	H	0.67	-0.31

* Partial hydrolysis during chromatography.

Table II gives the R_F values of the other 3-acyloxy-1,4-benzodiazepines measured with a methanol concentration of 65%.

A regular increase in the carbon number of the acyl moiety resulted in a linear increase in R_M , as can be seen in Fig. 2. Compounds with an ω -phenyl substituent in the acyl moiety give a separate line. Early investigations¹¹ indicated a possible interaction between two aromatic systems united by a methylene chain, when varying π -increments of the successive methylene units are found. This is not the

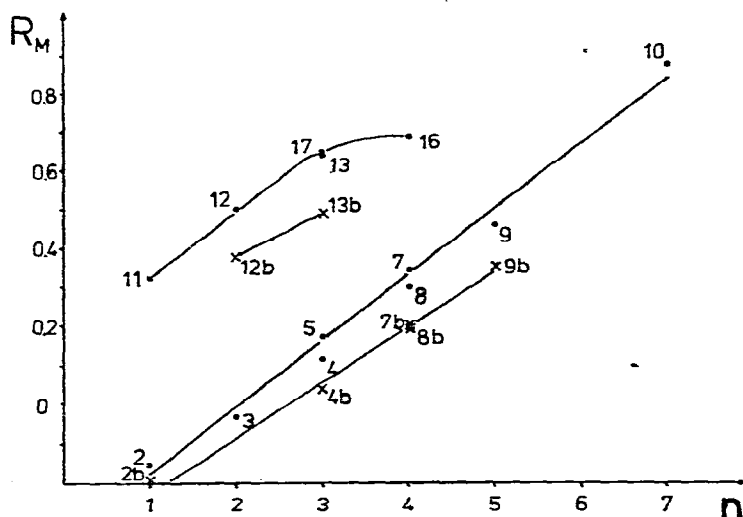


Fig. 2. Relationship between carbon number of acyl moiety (n) and R_M for oxazepam esters (compounds 2-17) and lorazepam esters (compounds 2b-13b).

case with ω -phenyl-substituted esters, because these compounds have similar ΔR_M increments per methylene unit.

Linearity of R_M values with increasing carbon number is similar to that found for aliphatic amines¹² and for the log P values of barbiturates¹³. Branching results in a decrease in R_M ^{4,12} which is characteristic of α,α -dimethyl- β -phenylpropionyl oxazepam (compound 16 in Fig. 2). The slopes in Fig. 2 are similar, indicating that ω -phenyl or 5-(2'-chloro) substitution does not affect the dependence on n , but causes a constant change in hydrophobicity manifested by a vertical shift of the lines.

Halogen substitution in the α -position (compounds 14 and 15) causes a similar change to that of methyl substitution, as ΔR_M is proportional to the partial molar volume of the groups¹⁴.

The effect of ring substituents was also investigated, maintaining the acyl moiety constant (acetyl esters). Table III gives the R_M values of 3-acetoxy-1,4-benzodiazepines bearing some pharmacologically potent substituents. Lipophilicity is increased by N¹-alkyl substitution and substitution of the 2-oxo group for the methylamino group and is decreased by 5-(2'-chloro) substitution.

TABLE III

 R_M VALUES OF 3-ACETOXY-1,4-BENZODIAZEPINES

$R_2 = \text{COCH}_3$, $R_5 = \text{H}$. Results are average values of six determinations in 65% methanol.

Substituent			R_M
R_1	R_2	R_4	
CH ₃	O	Cl	0.01
H	O	NO ₂	-0.20
—	NHCH ₃	Cl	0.29
(CH ₂) ₂ COOEt	O	Cl	0.08
CH ₂ COOEt	O	Cl	0.01
(CH ₂) ₂ COOH	O	Cl	-0.31

ACKNOWLEDGEMENTS

The authors thank Mrs. E. Simon for supplying the lorazepam esters.

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