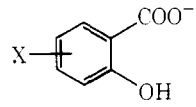
Structure–Activity Relationship in Synthetic Fibrinolytics. 2-Phenethynylcyclopropanecarboxylates[1]

Masafumi Yoshimoto,[2] Kurt N. von Kaulla, and Corwin Hansch*

Department of Chemistry, Pomona College, Claremont, California 91711, and Department of Medicine, University of Colorado Medical Center, Denver, Colorado 80220. *Received March 13, 1975*

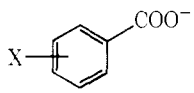
The fibrinolytic activity of nine 2-phenethynylcyclopropanecarboxylates was measured in the hanging clot test. The structure–activity relationship is given by log $1/C$ = 0.54 log P + 2.01 where P is the octanol–water partition coefficient of the carboxylate ion pair and C is the molar concentration of the drug. The equation obtained for the cyclopropanecarboxylates is compared with similar equations for benzoates, salicylates, and N-phenylanthranilates.

We have been interested in the structure–activity relationship of organic anions which have the capacity to dissolve blood clots[3] by activating their fibrinolytic enzyme system. The ability of such anions to dissolve clots is highly dependent on their lipophilic character (defined by log P where P is the octanol–water partition coefficient). Quantitative structure–activity relationships (QSAR) have recently been formulated[4] for three types of anions acting in the hanging clot test.[5] C in eq 1–3 is the molar concentration of anion which dissolves a standard clot of human plasma in 24 hr, n is the number of congeners upon which the equation is based, r is the correlation coefficient, s is the standard deviation, and the figures in parentheses are the 95% confidence limits. The coefficient with the log P term is essentially 0.5, indicating the same dependence of fibrinolytic activity on lipophilicity for each set of congeners.



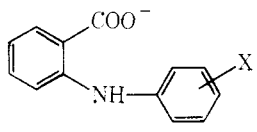
$$\log 1/C = 0.52\,(\pm 0.10)\log P + 1.98\,(\pm 0.14) \quad (1)$$

n	r	s
22	0.928	0.248



$$\log 1/C = 0.48\,(\pm 0.15)\log P + 0.44\,(\pm 0.24)\,E_s + 1.36\,(\pm 0.25) \quad (2)$$

n	r	s
16	0.885	0.210



$$\log 1/C = 0.47\,(\pm 0.19)\log P + 2.43\,(\pm 0.10) \quad (3)$$

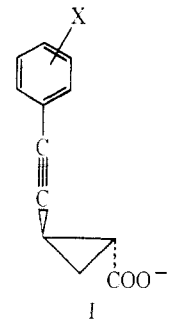
n	r	s
17	0.812	0.165

In our first studies of lipophilic anions causing fibrinolysis, log P for the un-ionized form of acid was used.[3b,c] This type of correlation is satisfactory for the analysis of a single set of congeners since, to a first approximation, log P_{ion} = log P − constant. However, when one wishes to make comparisons between different sets of congeners, log P for the biologically active form should be used. We have redone our early work using log P for the sodium salts of the acids;[4] that is, partitioning was done between 0.1 N NaOH and octanol. It is assumed that it is the ion pair which is partitioning.[6] Since the value of log P of ions is dependent on the counterion (Na^+ in this case), we have standardized on 0.1 N NaOH for weak acids and 0.1 N HCl for weak bases. Log P for the ion at infinite dilution has been used.[6]

We have restudied[4] our first analysis[3c] of the fibrinolytic activity of the benzoic acids and obtained eq 2. Equation 2 is based on two new data points. One old point (the most lipophilic compound) was dropped. This yields an equation linear in log P which can be better compared with eq 1, 3, and 4. In reformulating eq 2, it was found that a term in E_s was needed to account for ortho substitution. To compare eq 2 with eq 1 and 3, the E_s value of 1.24 for hydrogen is substituted. Then, solving for the intercept yields a value of 1.91 which holds for the case when no ortho substituents are present. This indicates that activities of benzoates and salicylates in the hanging clot test are identical for isolipophilic compounds when no steric effects are present.

Equation 3 has an intercept which is about 0.48 log unit higher than the mean value of eq 1 and 2. Since the antilog of 0.48 is 3, we can say that the intrinsic activity of the anthranilates is about three times that of the benzoates and salicylates.

In seeking anions of greater intrinsic activity, we have tested a set of *trans*-2-phenethynylcyclopropanecarboxylates[7] (I) in the hanging clot test.



I

Equation 4 has been formulated from the data in Table I. Although eq 4 is not a sharp correlation as judged by r, it is highly significant in terms of the F statistic: $F_{1,7}$ = 20.0; $F_{1,7;\alpha\,0.005}$ = 16.2. Adding terms in E_s, σ, or (log P)^2 to eq 4 did not improve the correlation.

$$\log 1/C = 0.538\,(\pm 0.28)\log P + 2.006\,(\pm 0.18) \quad (4)$$

n	r	s
9	0.861	0.112

The slope and intercept of eq 4 are within experimental error, identical with eq 1 and that calculated for eq 2. No special effect is observed for the phenylethynylcyclopropyl group which suggests that the geometry of the aromatic ring with respect to the carboxyl group is not very critical since this geometry would be quite different from that of the benzoates, salicylates, or N-phenylanthranilates.

Equations 1–4 can be of help in the search for more potent fibrinolytic agents. Three or four well-chosen deriva-

Table I. Constants Used for Deriving Eq 4

No.	X	Log 1/C Obsd	Log 1/C Calcd[a]	Δ log 1/C	Log P[b]
1	4-OMe	1.70	1.67	0.03	−0.63
2	H	1.70	1.68	0.02	−0.61
3	4-F	1.74	1.75	0.01	−0.47
4	4-Me	1.82	1.98	0.16	−0.05
5	2-Me	1.92	1.98	0.06	−0.05
6	4-Cl	1.92	2.06	0.14	0.10
7	3-Me	2.05	1.98	0.07	−0.05
8	3-Cl	2.22	2.06	0.16	0.10
9	4-Br	2.22	2.14	0.08	0.25

[a]Calculated using eq 4. [b]The value of compound **2** was determined and the others were calculated from **2** using the π constant; see C. Hansch, A. Leo, S. Unger, K. H. Kim, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973). In the determination, 0.1 *N* NaOH was used as the aqueous phase and the experimental values obtained were extrapolated to infinite dilution.

tives of a parent anion can be made and tested to find log $1/C$ in the hanging clot test; by well chosen, it is meant that a range of 2–3 units in log P should be present. Also, since it is understood that log $1/C$ will be parabolically dependent on log P in the most general sense,[8] log P should be in the range −2.0 to +2.0 for the initial study. Equations 1–4 indicate that one can expect linearity between log P and log $1/C$ in this range in the standard hanging clot test. Since log P values can generally be estimated within an absolute value of ±0.5, it would not be necessary to measure log P values in the preliminary phases of the work; one might measure that of each parent molecule. One could obtain the slope and intercept for each set of congeners from the plot of log $1/C$ vs. log P. Only those cases with intercepts significantly higher than that of eq 3 would merit in-depth study.

Equation 2 indicates that steric effects can be significant in fibrinolytic activity and no doubt further study will show how electronic effects are important. Indeed, it is the stereoelectronic character of the *N*-phenylanthranilate moiety which gives it a higher activity than the salicylates. Without much more experimental effort it would be pointless at this time to speculate on what the ideal stereoelectronic characteristics of the fibrinolytic anions are. This is also true of their mechanism of action; at present it can only be said that the activity is highly dependent on lipophilic character as operationally defined by log P and that it is rather insensitive to steric and electronic changes in the parent structure.

Acknowledgment. We wish to thank Drs. Y. Kishida and T. Hiraoka of the Sankyo Co. for the helpful discussions on the synthesis of the cyclopropanecarboxylic acids.

References and Notes

(1) This research was supported by Grant CA-11110 from the National Cancer Institute.
(2) Visiting Scientist from the Sankyo Co., Tokyo, Japan.
(3) (a) K. N. von Kaulla, "Chemistry of Thrombolysis: Human Fibrinolytic Enzymes", Charles C Thomas, Springfield, Ill., 1963, p 261; (b) J. M. Schor, "Chemical Control of Fibrinolysis–Thrombolysis", Wiley-Interscience, New York, N.Y., 1970, pp 1, 245; (c) C. Hansch and K. N. von Kaulla, *Biochem. Pharmacol.*, **19**, 2193 (1970).
(4) C. Hansch and K. N. von Kaulla in "Synthetic Fibrinolytic Thrombolytic Agents. Chemical, Biochemical, Pharmacological and Clinical Aspects", K. N. von Kaulla and J. F. Davidson, Ed., Charles C Thomas, Springfield, Ill., 1975, p 227.
(5) K. N. von Kaulla, *J. Med. Chem.*, **8**, 164 (1965).
(6) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(7) M. Yoshimoto, N. Ishida, and Y. Kishida, *Chem. Pharm. Bull.*, **19**, 863 (1971); **20**, 2593 (1972).
(8) C. Hansch and J. M. Clayton, *J. Pharm. Sci.*, **62**, 1 (1973).

Benzoxocin and Benzoxonin Derivatives. Novel Groups of Terpenophenols with Central Nervous System Activity. A Correction

Shlomo Houry, Raphael Mechoulam,*

Department of Natural Products, Pharmacy School, The Hebrew University of Jerusalem, Israel

and Bernard Loev

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101.
Received November 18, 1974

The structure of a compound previously reported as 2,3,4,5,6,7-hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-pentyl-3,7-methano-1-benzoxonin (**1**) is shown to be actually 3,4,5,6-tetrahydro-7-hydroxy-2-methyl-5-isopropyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (**2a**).

In a recent publication[1] we reported the synthesis of a series of terpenophenols with central nervous system activity. One of the compounds obtained on condensation of olivetol with pinene (or limonene) was assigned the tentative structure 2,3,4,5,6,7-hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-pentyl-3,7-methano-1-benzoxonin (**1**) (compound **15a** in the previous paper). On reexamination of the spectral data we concluded that they were more consistent with the structure 3,4,5,6-tetrahydro-7-hydroxy-2-methyl-5-isopropyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (**2a**), a cannabinoid whose synthesis by another route has been reported[2] (see Scheme I).

In the earlier publication[2] the structure was unequivocally shown to be **2a** by several chemical correlations. Thus dihydrocannabidiol (**3**), obtained on hydrogenation of cannabidiol (**4**), was cyclized with ease to **2a**; it was also obtained as one of the isomers in the hydrogenation of the isocannabinoid **5**, which was the product of three different cyclization sequences. The isocannabinoid **5** has also been obtained by Crombie[3] and by Razdan.[4] Samples of com-