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[1] Sutherland, E. W., and Rall, T. W., *Pharmacol. Revs.*, **12**, 265 (1960).
[2] Hammermeister, K. E., Yunis, A. A., and Krebs, E. G., *J. Biol. Chem.*, **240**, 986 (1965).
[3] Chance, B., Williamson, J. R., Jamieson, D., and Schoener, B., *Biochem. Z.* (in the press).
[4] Williamson, J. R., and Jamieson, D., *Nature*, **206**, 364 (1965).
[5] Williamson, J. R., *J. Biol. Chem.*, **239**, 2721 (1964).
[6] Posner, J. B., Hammermeister, K. E., Bratvold, G. E., and Krebs, E. G., *Biochemistry*, **3**, 1040 (1964).
[7] Butcher, R. W., and Sutherland, E. W., *J. Biol. Chem.*, **237**, 1244 (1962).
[8] Williamson, J. R., *J. Biol. Chem.* (in the press).
[9] Murad, F., Chi, Y.-M., Rall, T. W., and Sutherland, E. W., *J. Biol. Chem.*, **237**, 1233 (1962).
[10] Hess, M. E., Shanfeld, J., and Haugaard, N., *Biochem. Pharmacol.*, **11**, 1031 (1962).
[11] Ellis, S., *Pharmacol. Revs.*, **11**, 469 (1959).
[12] Fischer, E. H., Graves, D. J., Crittenden, E. R. S., and Krebs, E. G., *J. Biol. Chem.*, **234**, 1698 (1959).
[13] Danforth, W. H., and Helmreich, E., *J. Biol. Chem.*, **239**, 3133 (1964).
[14] Nayler, W. G., *Amer. Heart J.*, **65**, 404 (1963).
[15] Shanes, A. M., in *Transfer of Calcium and Strontium across Biological Membranes*, 359 (Academic Press, New York).
[16] Williamson, J. R., *Nature*, **206**, 473 (1965).

Chemical Structure and Biological Activity on *m*- and *p*-Disubstituted Derivatives of Benzene

IN an earlier paper on this topic[1] we proposed a four-parameter equation (1), which expresses the quantitative relationship between the structure of *p*-disubstituted derivatives of benzene and the magnitude of their biological activity, for example intravenous LD_{50}. This report presents our results on a group of compounds of the type  , where X, Y = H, CH_3, Cl, OH, NO_2, NH_2. The series includes all possible combinations of groups X and Y, with the exception of three substances which were not soluble enough even in 20 per cent aqueous polyvinylpyrrolidone solution to make LD_{50} measurements possible. The experimental results fitted equation (1):

$$\log \frac{[LD_{50}]_{HH}}{[LD_{50}]_{XY}} = b_X + b_Y + e_X e_Y \qquad (1)$$

Constants b_X and e_X were obtained by statistical treatment of experimental data under the presumption of the validity of equation (1). Fig. 1 shows the correlation obtained; the values of the substituent constants b_X and e_X are given in Table 1.

Table 1

	NO_2	Cl	OH	CH_3	H	NH_2
b_X	0·601	0·248	0·260	0·149	0·004	0·015
e_X	0·90	−0·49	−0·13	−0·22	−0·06	−0·41

Table 2

	NO_2	Cl	OH	CH_3	H	NH_2
b_X	0·516	0·295	0·294	0·191	0·014	0·015
$(e_X)_m$	0·84	−0·45	−0·04	−0·13	0·00	−0·37
$(e_X)_p$	0·68	−0·04	0·57	0·07	0·00	−0·83

A comparison of the constants b_X for the *m*-substituted compounds with the values of b_X found for the *p*-substituted compounds[1] showed that for the given group of compounds $\Delta b_X < 0{\cdot}1$, where $\Delta b_X = (b_X)_p - (b_X)_m$. We considered it advantageous to recalculate the b_X constants basing them on all data from both groups. Fig. 2 shows the results of this treatment; the constants b_X, $(e_X)_m$ and $(e_X)_p$ are given in Table 2.

In our further work we intend to test the relationship between the given equation and linear free energy relationships (L.F.E.R.)[2,3] which have been already applied to biological problems, especially in papers by Zahradník[4,5] and lately by Hansch[6–8]. This effort is supported by the surprising fact that the constants bX are linearly dependent on the constants of f_i' obtained in the study of the thyroxine-like activity of 3,3′,5,5′-substituted analogues of thyroxine[9]. The constants f_i' are also linearly dependent on the σ_m-constants.

At present the *o*-disubstituted derivatives of benzene are being studied in the same way, and simultaneously the number of substituents in the *p*-series is being extended to a more complete set of substances.

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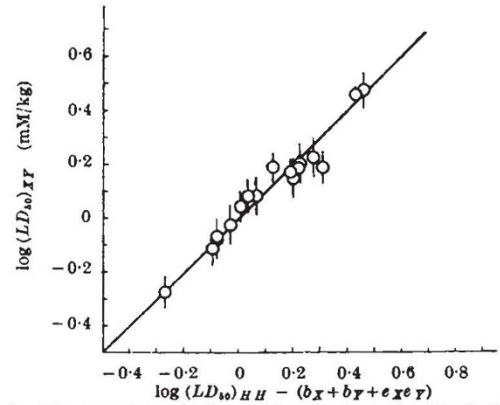

Fig. 1. LD_{50} were determined on white mice (weighing 20 ± 2 g) by the Thompson method. The substances were administered intravenously in a 20 per cent aqueous polyvinylpyrrolidone solution

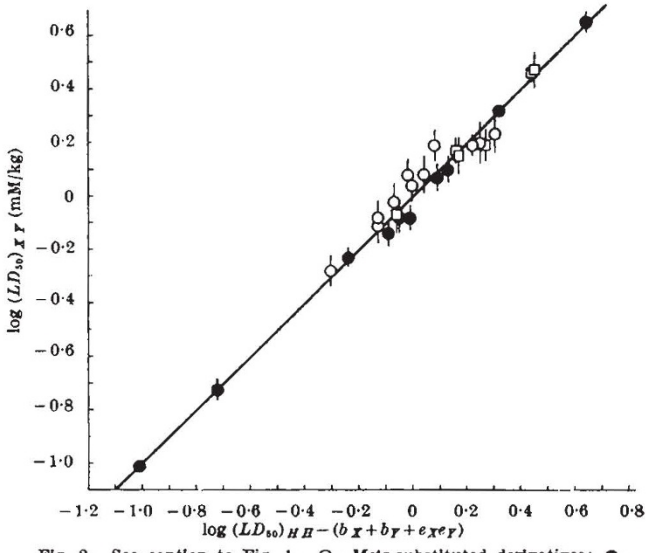

Fig. 2. See caption to Fig. 1. ○, *Meta*-substituted derivatives; ●, *para*-substituted derivatives; □, mono-substituted derivatives. Hydroquinol and resorcinol are omitted. If they are included the relationship between structure and biological activity becomes more complicated

[1] Boček, K., Kopecký, J., Krivucová, M., and Vlachová, D., *Experientia*, **20**, 667 (1964).
[2] Hammett, L. P., *Physical Organic Chemistry* (McGraw-Hill, New York, 1940).
[3] Taft, jun., R. W., *J. Amer. Chem. Soc.*, **75**, 4231 (1953).
[4] Zahradník, R., *Experientia*, **18**, 534 (1962).
[5] Zahradník, R., *Arch. Int. Pharmacodyn.*, **135**, 311 (1962).
[6] Hansch, C., Maloney, P. P., Fujita, T., and Muir, R. M., *Nature*, **194**, 178 (1962).
[7] Hansch, C., Muir, R. M., Fujita, T., Maloney, P. P., Geiger, F., and Streich, M., *J. Amer. Chem. Soc.*, **85**, 2817 (1963).
[8] Hansch, C., and Fujita, T., *J. Amer. Chem. Soc.*, **86**, 1616 (1964).
[9] Bruice, T. C., Kharasch, N., and Winzler, R. J., *Arch. Biochem. Biophys.*, **62**, 305 (1956).