Minimal Statistical Data for Structure–Function Correlations

PAUL N. CRAIG,

Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania 19101

CORWIN H. HANSCH,

Pomona College, Claremont, California 91711

JAMES W. MCFARLAND,

Pfizer Medical Research Laboratories, Groton, Connecticut 06340

YVONNE C. MARTIN,

Abbott Laboratories, Chemical Pharmacology Department, North Chicago, Illinois 60064

WILLIAM P. PURCELL,

University of Tennessee Medical Units, Memphis, Tennessee 38103

AND RUDOLPH ZAHRADNÍK

Czechoslovak Academy of Sciences, Prague, Czechoslovakia

Received December 18, 1970

In recent years, the number of publications which include results of regression analysis has mushroomed. Since there are many formats for presenting such results, and since the statistical parameters employed will vary with the type of analysis, it is sometimes difficult for the reader to assess the significance of the work from the data presented.

Accordingly, we urge that the following data be presented in each paper submitted to this journal which reports Free–Wilson type analyses or Hansch multiple parameter analyses.

A. Free–Wilson Analyses.—It is imperative that the complete structure matrix used in the analysis be presented. In addition, the correlation coefficient r, or r^2, the $F_{k,n}$, and the group constants obtained, are sufficient to enable the reader to assess and to duplicate the work presented. For predictions, $m\mu$, the overall average, should be given.

B. Hansch Multiple Parameter Analyses.—A complete table of the compounds studied, the log $1/c$ values (or other biological data) and all parameter values used for every molecule should be listed. It is especially important to explain estimated or calculated values used. The results of each regression analysis should be accompanied by either 90 or 95% confidence intervals for each term, or a t test value for each term should be given. Whenever applicable, the maximum or minimum π value (or any other optimal value obtainable by differentiation of a quadratic equation) should be given, together with confidence intervals. [See discussion by Hansch, *et al.*[1]]

n (the number of compounds included in a particular regression), s (the standard deviation), and r or r^2 (the correlation coefficient) should also be given for each equation.

In comparing two equations which differ only by one term, the F test should be applied to test the significance of adding the new term to the simpler equation. If compounds are dropped from consideration (for whatever reason), they should be identified.

(1) C. Hansch, A. R. Steward, S. M. Anderson, and R. Bentley, *J. Med. Chem.*, **11**, 1 (1968).

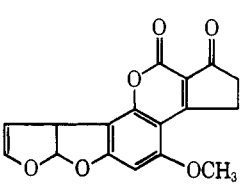
Synthesis and Toxicology of 5,7-Dibenzyloxycyclopentenone[2,3-*c*]coumarin.[1] A Model Compound of Aflatoxin B_1

CHING YUNG WANG AND PAUL F. PARKS*

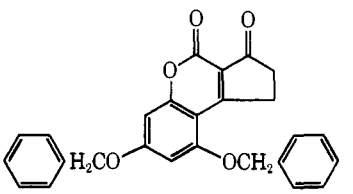
Department of Animal Science, Agricultural Experiment Station, Auburn University, Auburn, Alabama 36830

Received August 31, 1970

Aflatoxins (aflatoxin B_1, I), metabolites of *Aspergillus flavus*, are extremely toxic and carcinogenic to ducklings[2–6] and rats.[7–11] Acute intoxication of aflatoxins produces liver necrosis, degeneration, and bile duct proliferation in ducklings and rats. One model compound of aflatoxin B_1, 5,7-dimethoxycyclopentenone[2,3-*c*]coumarin, has been synthesized.[12] We have synthesized 5,7-dibenzyloxycyclopentenone[2,3-*c*]coumarin (II) and determined its toxicity in ducklings and rats.



I



II

The cyclopentenone coumarin moiety of II constitutes a major part of the aflatoxin structure. Compound II, synthesized in an attempt to place a benzene ring in the vicinity of the dihydrofurofuran rings of aflatoxin, was used to study the biological specificity of the dihydrofurofuran ring of aflatoxin B_1. The synthesis of II was accomplished in 3 steps. Condensation of phloroglucinol and ethyl methyl β-ketoadipate yielded 5,7-dihydroxy-4-(2-methoxycarbonylethyl)coumarin, which was cyclized to 5,7-dihydroxycyclopentenone[2,3-*c*]-coumarin. Benzylation of the product gave II.

The acute toxicity of II was determined in 1-day-old Pekin ducklings, and the chronic toxicity and carcinogenicity were studied in weanling rats. Forty-nine

(1) The authors acknowledge the guidance and advice of Dr. C. D. Blanton, Jr., in the synthesis of this compound.

(2) R. Allcroft, in "Mycotoxins in Foodstuffs," G. N. Wogan, Ed., MIT Press, Cambridge, Mass., 1965, p 153.
(3) F. D. Asplin and R. B. A. Carnaghan, *Vet. Rec.*, **73**, 1215 (1961).
(4) W. H. Butler, *Pathol. J. Bacteriol.*, **88**, 189 (1964).
(5) R. B. A. Carnaghan, *Nature (London)*, **208**, 308 (1965).
(6) P. M. Newberne, W. W. Carlton, and G. N. Wogan, *Pathol. Vet.*, **1**, 105 (1964).
(7) J. M. Barnes and W. H. Butler, *Nature (London)*, **202**, 1016 (1964).
(8) W. H. Butler, *Brit. J. Cancer*, **18**, 756 (1964).
(9) S. M. Epstein, B. Bartus, and E. Farber, *Cancer Res.*, **29**, 1045 (1969).
(10) M. C. Lancaster, F. P. Jenkins, and J. McL. Philp, *Nature (London)*, **192**, 1059 (1961).
(11) W. D. Salmon and P. M. Newberne, *Cancer Res.*, **23**, 571 (1963).
(12) T. Asao, G. Buchi, M. M. Abdel-Kader, S. B. Chang, E. L. Wick, and G. N. Wogan, *J. Amer. Chem. Soc.*, **87**, 882 (1965).