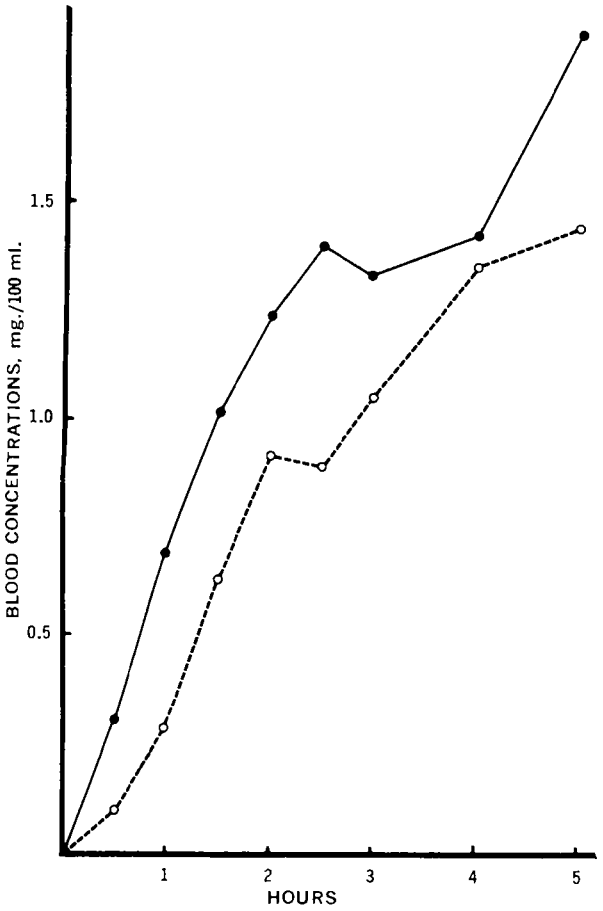

Figure 1—*Blood concentrations of free sulfathiazole following oral administration of 1 g. sulfathiazole crystals. Key: ○, in presence of FD&C Blue No. 1; and ●, in absence of FD&C Blue No. 1.*

enediamine dihydrochloride (6). Spectrophotometric measurements were carried out on the final colored solutions at a wavelength of 543 nm., and comparisons were made with an appropriate standard. Blanks prepared from control blood samples, from each subject, were used for appropriate corrections.

Table I shows blood concentrations of sulfathiazole obtained following administration in the absence and in the presence of Blue No. 1. From these results, it is apparent that, in the first 3 hr., the sulfathiazole concentrations in the presence of the dye were lower than those in the absence of the dye for all three subjects. Figure 1 presents the blood concentration curves as a function of time obtained from the mean values presented in Table I. The data obtained in this study are in excellent accord with the *in vitro* dissolution rate data (1, 2). This agreement suggests that such a small concentration of FD&C Blue No. 1 could delay significantly the absorption of sulfathiazole through dissolution inhibition.

It should be stressed, however, that the limited data presented in this report on sulfathiazole crystals and Blue No. 1 cannot exclude the possibility that other dyes can exert similar effects on the absorption of crystalline drugs with poor solubility. More extensive studies are desirable with regard to absorption kinetics in the presence of certified dyes.

(1) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **59**, 56(1970).

(2) R. Tawashi and J. Piccolo, *Pharm. Acta Helv.*, **45**, 653(1970).

(3) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **60**, 59(1971).

(4) *Ibid.*, **60**, 1818(1971).

(5) A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, **128**, 537(1939).

(6) H. Varley, "Practical Clinical Biochemistry," 2nd ed., William Heinemann Medical Books Ltd., London, England, 1960, p. 579.

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Fagaronine, a New Tumor Inhibitor Isolated from *Fagara zanthoxyloides* Lam. (Rutaceae)

Keyphrases □ *Fagara zanthoxyloides* Lam.—isolation, identification of fagaronine, antitumor activity □ Fagaronine—isolation, identification from *Fagara zanthoxyloides* Lam., antitumor activity □ Antitumor activity—fagaronine, isolated from *Fagara zanthoxyloides* □ Medicinal plants—isolation, identification of fagaronine from *Fagara zanthoxyloides* Lam., antitumor activity

Sir:

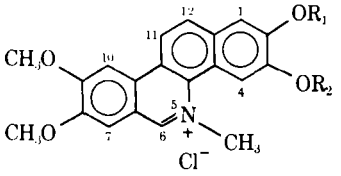
During a phytochemical investigation of *Fagara zanthoxyloides*[1], we isolated a new alkaloid for which we have assigned the trivial name fagaronine. Fagaronine has been shown to elicit a high order of activity against the P-388 leukemia in mice, giving prolongations of life on the order of 265, 210, and 190% T/C at doses of 100, 50, and 25 mg./kg., respectively. A compound is active if it exhibits a T/C of ≧125% (1)[2]. Several leukemic mice treated with fagaronine were considered as "cures."

Fagaronine crystallized as the chloride (from a mixture of ethyl acetate–methanol) as bright-yellow needles, exhibiting m.p. 202° followed by solidification and melting again at 255°[3]. A UV absorption spectrum of λ_{max} 233 (log ϵ 4.29), 272 (4.55), 305 (4.44) (sh), and 328 nm. (4.44) indicated that fagaronine belonged to the benzophenanthridine class of alkaloids; in particular, this spectrum resembled that of nitidine (2). The UV spectrum of fagaronine in 0.01 *N* HCl showed no change; however, in 0.01 *N* NaOH, a bathochromic shift to λ_{max} 346 nm. (log ϵ 4.31) was observed, suggest-

[1] The plant material was collected in Ghana by Mr. O. B. Dokosi, University of Ghana. A voucher specimen (SP-280) was identified by Mr. Dokosi as *F. zanthoxyloides* Lam. (Rutaceae) and is deposited in the Herbarium of the Department of Pharmacognosy and Pharmacology, University of Illinois at the Medical Center, Chicago, Ill. The roots were the parts used.

[2] The antitumor tests were performed through the Drug Research and Development Branch, National Cancer Institute, Bethesda, Md.

[3] Details of the isolation of fagaronine will be published.



Ia: $R_1 = H$, $R_2 = CH_3$
Ib: $R_1 = CH_3$, $R_2 = H$

ing the presence of a phenolic group in the molecule. The presence of a phenolic hydroxyl group was also indicated by a broad absorption band at 3500–3200 cm.$^{-1}$ in the IR spectrum. A lack of peaks at 1480 and 940 cm.$^{-1}$ in the IR spectrum was suggestive of the absence of the methylenedioxy function in the molecule, which was confirmed by a negative Labat's test and by a lack of absorption in the area of 6 p.p.m. in the NMR spectrum.

An NMR spectrum of fagaronine (I*a*) in dimethyl sulfoxide, with tetramethylsilane as the internal standard, showed peaks for $-N^+-CH_3$ (δ in p.p.m., singlet at 5.11), three $-OCH_3$ (singlets at 4.24, 4.11, and 4.04), 6-position proton (singlet at 9.97), protons at positions 11 and 12 (doublets centered at 8.86, J = 9 Hz., and 8.16, J = 9 Hz.), and protons at positions 1, 4, 7, and 10 (singlets at 7.66, 7.94, 8.13, and 8.36). At this point, Structures I*a* and I*b* were suggested for fagaronine.

A molecular ion, M^+, was observed at *m/e* 350 in the mass spectrum of fagaronine, followed by peaks at *m/e* 349 (M^+-1), 348, 335 (base peak, $M-15$), 334, 320, 306, 292, and a doubly charged species at *m/e* 167.5. The formation of these ions can be explained by the mode of fragmentation proposed for such compounds by Torto and Mensah (3) and Slavik *et al.* (4). Structure I*a* is favored over I*b* for the structure of fagaronine because of the more favorable formulation of the peak at *m/e* 349 ($M^+ - 1$) (9%).

Final proof of the structure of fagaronine by synthesis is in progress.

(1) Anon., *Cancer Chemother. Rep.*, **1962**, 1.
(2) F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.*, **23**, 67 (1971).
(3) F. G. Torto and I. A. Mensah, *Phytochemistry*, **9**, 911(1970).
(4) J. Slavik, L. Dolejš, V. Hanuš, and A. D. Cross, *Collect. Czech. Chem. Commun.*, **33**, 1619(1962).

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BOOKS

REVIEWS

Handbook of Experimental Pharmacology, Volume 28, Part 2, Concepts in Biochemical Pharmacology. Edited by B. B. Brodie and J. R. Gillette. Springer-Verlag New York, Inc., 175 Fifth, Ave., New York, NY 10010, 1971. xx + 778 pp. 16.5 × 25 cm. Price $75.00.

This work completes Volume 28. Part 1 [reviewed in *J. Pharm. Sci.*, **60**, 1765(1971)] covered the subjects of absorption, tissue distribution, and excretion of drugs, while Part 2 addresses the topics of analytical techniques for the study of drug metabolism and the significance of microsomal and nonmicrosomal enzymatic metabolism of drugs to pharmacological action. The completed volume is well suited to serve as a single reference work on all aspects of drug disposition. The organization, indexing, and general arrangement will make this volume useful to the nonspecialist with a casual interest in drug disposition as well as to the graduate student and experienced investigator because of the encyclopedic nature of the coverage. Although each of the major topics treated in Part 2 (*e.g.*, analytical methods for drugs and drug metabolites, pathways of drug metabolism, cytochrome P-450, and enzyme induction) has been adequately and extensively reviewed elsewhere, never has this information been brought together in a single work focused upon the specific question of the significance of these topics to drug action.

In any book which is the product of the collaborative efforts of 46 authors, it is to be expected that coverage of each topic will not be uniform with respect to scope and depth. This does not appear to be a serious deficiency of the present volume since the authors have provided extensive referencing (in convenient tabular form in many chapters) to take the reader beyond the material covered in the text. The brevity of some chapters does, however, leave the reader unsated. Regrettably, this is the case with some of the more technically sophisticated and newer methods of analysis such as immunoassay (4-page chapter), enzymatic assays (12 pages), and radioisotope derivative methods (3 pages).