# Mechanism of Thermal Rearrangement and Decarboxylation of Procaine

*Sir:*

A recent paper (1) has described a new and interesting reaction of procaine (I) which may be of pharmacological importance. The controlled pyrolysis of I at 225–235° (20–25 mm.) results, among other things, in the evolution of carbon dioxide and the production of *N*-phenyl-*N'*,*N'*-diethylethylenediamine (II) as shown in Scheme I.

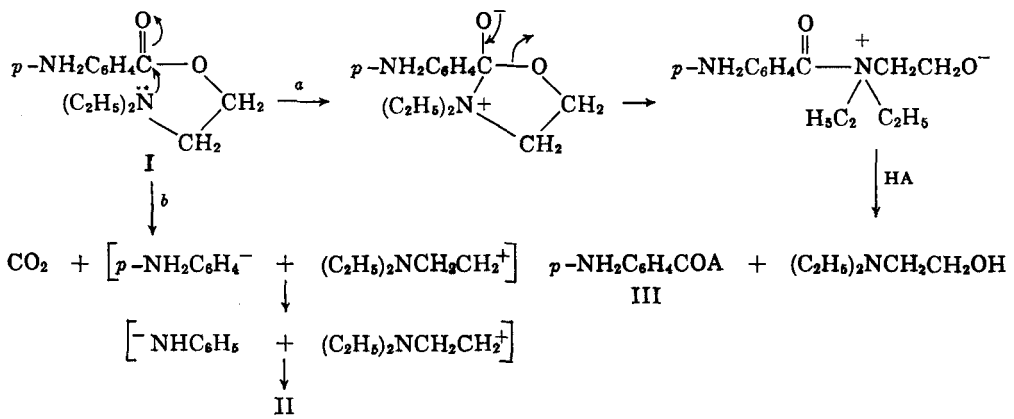
$$p\text{-}NH_2C_6H_4CO_2CH_2CH_2N(C_2H_5)_2 \rightarrow$$
$$\text{I}$$
$$CO_2 + C_6H_5NHCH_2CH_2N(C_2H_5)_2$$
$$\text{II}$$

Scheme I

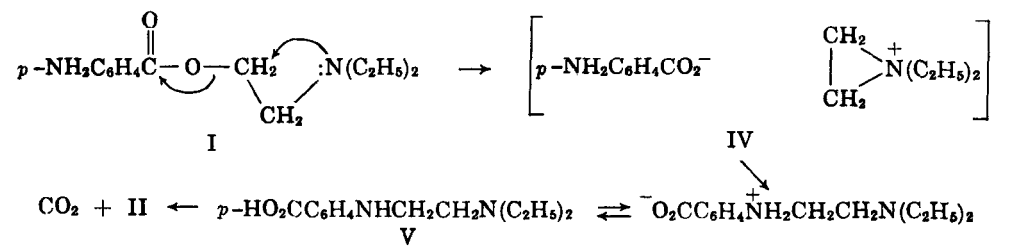
Certain aspects of the mechanism proposed (1) for this transformation (Scheme I) are deserving of comment. While it is true that the diethylamino group is admirably situated to render intramolecular nucleophilic assistance (2) to reactions at the carboxyl function, it is difficult to rationalize the decarboxylation by the interaction pictured by Grier (1), for which adequate analogy does not exist. Attack of the tertiary amino nitrogen on the carbonyl carbon atom would result, almost certainly, in solvolytic cleavage as illustrated in Scheme II*a* rather than, as suggested (1), in the sequence II*b*, involving the highly energetic primary carbonium ion–phenylcarbanion ion pair.

In the present case, the role of HA in Scheme II*a* could be played by the *p*-amino group of I. *N*,*N*-Diethyl ethanolamine was indeed a product of this thermolysis as was a polyamide which gave rise to *p*-aminobenzoic acid on hydrolysis. The polyamide would, of course, ensue from III by repetition of the same sequence.

In order to account for the production of II and carbon dioxide, it is suggested that the diethylamino group participates by assisting oxygen-alkyl fission resulting in the formation of an ethyleniminium salt (IV). (Scheme III.) Such a process has ample precedence among the 2-halogenoethyl amines (3), and a similar cleavage has been advanced to account for the racemization of L(+)-2$\alpha$-tropyl acetate (4). Re-




Scheme II




Scheme III

combination of the ion pair IV by attack of the *p*-amino function on the three-membered heterocyclic ring leads directly to the zwitterionic form of the amino acid V. Decarboxylation of V is then unexceptional, being facilitated, in fact, by the presence of the *p*-amino group (5).

Finally, it seems pertinent to point out that this scheme might be substantiated by at least two methods. On the one hand, a salt corresponding to IV could conceivably be prepared and its decomposition products studied; and, on the other hand, advantage could be taken of the fact that in IV the two methylene groups in the three-membered ring lose their identity in contrast to their behavior in Scheme II*b*. Thus, the pyrolysis of a suitably labeled sample of I would be critical.

(1) Grier, N., *J. Pharm. Sci.*, **53**, 1208(1964).
(2) Capon, B., *Quart. Rev.*, **18**, 45(1964).
(3) Triggle, D. J., *J. Theoret. Biol.*, **7**, 241(1964).
(4) Archer, S., *et al.*, *J. Am. Chem. Soc.*, **83**, 2386(1961).
(5) Noller, C. R., "Chemistry of Organic Compounds," 2nd ed., W. B. Saunders Co., Philadelphia, Pa., 1957, p. 518.

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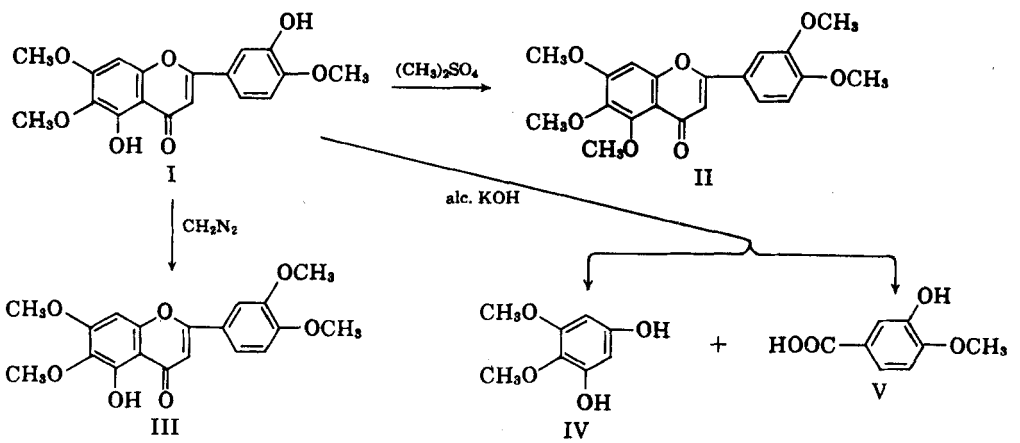
# Tumor Inhibitors VIII. Eupatorin, New Cytotoxic Flavone from *Eupatorium semiserratum*

*Sir:*

In the course of our continuing search for tumor inhibitors from plant sources, an alcoholic extract of *Eupatorium semiserratum* DC[1] was found to have reproducible activity against human carcinoma of the nasopharynx carried in cell culture (KB).[2] This communication reports the fractionation of the active extract and the isolation and structure elucidation of a new cytotoxic flavone, eupatorin.

The preliminary fractionation of the alcoholic extract (A) is summarized in Fig. 1. The mixed flavonoid band (H) was divided into sodium carbonate-soluble (I, 16.2 Gm.), sodium hydroxide-soluble (J, 20.6 Gm.), and nonacidic (K, 10 Gm.) fractions by partitioning with chloroform. Fraction J was chromatographed on silicic acid, and a band eluted by 5% methanol in chloroform was fractionally crystallized from ethyl acetate and from dioxane–water to yield eupatorin (I), m.p. 196–198°, $\lambda_{max.}^{alc.}$ 243 mμ (ε 17,400), 254 mμ (ε 19,300), 274 mμ (ε 19,800), 342 mμ (ε 27,700).

The empirical formula, $C_{15}H_7O_4(OCH_3)_3$, was assigned for eupatorin on the basis of elemental and methoxyl analysis. Methylation of eupatorin with dimethyl sulfate yielded II, m.p. 175–176°, $\lambda_{max.}^{alc.}$ 240 mμ (ε 25,900), 265 mμ (ε 16,500), 328 mμ (ε 28,600), characterized by comparison of its physical properties with those reported for 3′,4′,5,6,7-pentamethoxyflavone (1). Methylation of eupatorin with diazomethane gave 5-hydroxy-3′,4′,6,7-tetramethoxyflavone,




[1] Stems, leaves, and flowers were gathered in Florida, September 1963. The authors acknowledge with thanks receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the U.S.D.A. by the Cancer Chemotherapy National Service Center.

[2] Cytotoxicity was assayed, under the auspices of the CCNSC, against Eagle's KB strain of human epidermoid carcinoma. The procedures were those described in *Cancer Chemotherapy Rept.*, **25**, 1(1962).