LETTERS TO THE EDITORS

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Structure of Colchicine

THE suggestion of Dewar[1] that ring *C* of colchicine is 7-membered is interesting, and the arguments which he advances in favour of this merit consideration. I cannot, however, accept his statement that "Cohen, Cook and Roe have now provided evidence that ring *B* must be 7-membered". The paper[2] to which Dewar refers merely makes a tentative suggestion that ring *B might* be 7-membered. The only legitimate evidence that ring *B* of a degradation product of colchicine (namely, deaminocolchinol methyl ether) is 7-membered is provided by experiments described in a paper by Barton, Cook and Loudon, recently submitted for publication in the *Journal of the Chemical Society* (and received by the Society on February 1). Consequently, Dewar's assumption in respect of the structure of this part of the colchicine molecule is based on unwarranted speculation. Incidentally, the work of Barton, Cook and Loudon fully establishes the methoxylation pattern of deaminocolchinol methyl ether, and hence probably also the orientation of the substituents in colchicine.

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[1] Dewar, M. J. S., *Nature*, **155**, 141 (1945).
[2] Cohen, A., Cook, J. W., and Roe, E. M. F., *J. Chem. Soc.*, 194 (1940).

MY communication on this subject was written in ignorance of the work of Barton, Cook and Loudon, which was partly disclosed at a meeting of the Chemical Society, but is still unpublished. In relation to the facts known when I wrote, my remarks on the nature of ring *B* in colchicine can scarcely be described as unduly speculative. In any event I reserve any possible discussion for the time when all the facts are available. This question of the structure of ring *B* is, of course, important, but it can be settled by application of routine methods of alkaloid chemistry. On the other hand, the suggestion I have ventured to make regarding ring *C* is quite novel in this field.

Confirmation of the tropolone structure of ring *C* has now been obtained by the degradation suggested by me. Dr. I. Berenblum very kindly provided a small specimen of colchicine and this was converted to crude hexahydrocolchiceine and submitted to lead tetra-acetate oxidation. About 0·6 molecules of lead tetra-acetate were rapidly consumed and considerable further oxidation took place more slowly. This behaviour would be expected in an unsaturated cyclic α-glycol[1]. The oxidation product was aldehydic and gave an amorphous mixture of dinitrophenylhydrazones. Although lack of material prevented purification of the hexahydrocolchiceine or isolation of a definite oxidation product, it seems fairly certain that hexahydrocolchiceine must indeed be an α-diol. If so, confirmation is provided for the tropolone structure of colchicine.

Previously[2] resonance chelation was postulated to explain the aromatic nature of the tropolone ring. Calculation shows that in such a structure the O—O distance would be about 2·51 A. and that the O—H bond would be stretched. It is possible, therefore, that the resonance is an ionic one of the type postulated for colchicine[3] and that tropolone forms a tautomeric system of high mobility. On the other hand, the great solubility in water of colchicine, in contrast to colchiceine or stipitatic acid, is better explained if in it alone an ionic resonance (implying a semi-zwitterion structure) occurs.

It may be noted that puberulic acid[4] is probably one of the three possible monohydroxystipitatic acids, and puberulonic acid the corresponding 'tropoloquinone'. This relationship was pointed out by Birkinshaw, Chambers and Raistrick[5], and the existing evidence is insufficient for further comment on the structures of those acids.

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University, Oxford.

[1] Crigee, *Ber.*, **64**, 265 (1931).
[2] Dewar, *Nature*, **155**, 50 (1945).
[3] Dewar, *Nature*, **155**, 141 (1945).
[4] Birkinshaw and Raistrick, *Biochem. J.*, **26**, 441 (1932). Barger and Dorrer, *ibid.*, **28**, 11 (1934).
[5] Birkinshaw, Chambers and Raistrick, *Biochem. J.*, **36**, 242 (1942).

Metabolism of 3,4-Benzpyrene in Mice

IF 3,4-benzpyrene is introduced into a mouse, it is eventually excreted as the phenol 8-hydroxybenzpyrene[1,2]. It has been established that this transformation proceeds by various steps[3,4]. Four different benzpyrene derivatives have now been separated from extracts of various fresh tissues; they are provisionally termed X_1, X_2, F_1 and F_2, because they are responsible for the 'BPX' and 'BPF' fluorescences that Peacock[5] and Chalmers[6] discovered in the liver, bile, intestine and fæces of various animals after application of benzpyrene. The separation of X_1, X_2, F_1 and F_2 has been effected by fluorescence chromatography and selective extraction, using alumina and silica as adsorbents and acetone, benzene, xylene, petroleum ether, methyl, ethyl and amyl alcohols and water as solvents. X_1 and X_2 occur *in vivo* not only in the liver and digestive system but also in the lung, kidney cortex, subcutaneous tissue, skin (after painting with benzpyrene), and in the mammary glands as evidenced by the milk of mice; F_1 and F_2 occur in the large intestine and fæces, and occasionally in the lungs. The amount of fresh uncontaminated mouse urine did not suffice for a definite analysis, but there were indications of the presence of the X derivatives. *Post mortem*, all X-bearing tissues show slowly increasing amounts of the F derivatives unless they are kept in formol. The 3,4-benzpyrene-5,8-quinone that Berenblum and Schoental[2] discovered in the fæces never appeared in fresh tissues.

The sequence of the metabolic conversion can best be seen by following the products through the digestive system. In the liver, X_1 is formed almost exclusively, and enters with the bile into the small intestine, where it is converted slowly to X_2 in the tissue of the wall. However, the bulk of the X_1 is changed to F_1 after its passage through the ileocaecal valve. In the later stages of the metabolism, more and more F_2 appears in the fæces. This sequence can be summarized by the scheme:

$$Bp \xrightarrow{(1)} X_1 \xrightarrow{(2)} F_1 \xrightarrow{(3)} F_2 \xrightarrow{(4)} HO\text{-}Bp$$
$$X_1 \xrightarrow{(2')} X_2$$