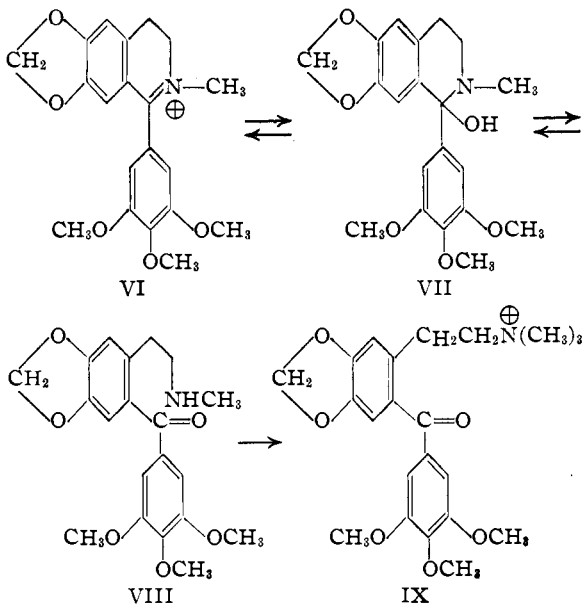

corresponding carbinol-amine (VII), which is in equilibrium with the amino-ketone (VIII). In the presence of methyl sulfate and alkali the quaternary ammonium compound IX would be formed, and would then be decomposed to the vinyl compound V in a normal Hofmann exhaustive methylation process. That compound VI may be the first-formed intermediate in the conversion is demonstrated by the production of the vinyl compound in over 80% yield on treatment of the methosulfate of VI (m. p. 193.8–194.3°. *Anal.* Calcd. for $C_{21}H_{25}O_9NS$: N, 3.0. Found: N, 3.0, 3.0) with excess alkali and methyl sulfate.

Work on the synthesis of picropodophyllin or podophyllotoxin from the keto-acid is under way.

DEPARTMENT OF CHEMISTRY
BOSTON UNIVERSITY WALTER J. GENSLER
BOSTON, MASS. CARLOS M. SAMOUR

RECEIVED MAY 27, 1950

OXYGEN ATOM TRANSFER IN THE REACTION OF CHLORATE WITH SULFITE IN AQUEOUS SOLUTION[1]

Sir:

In a large class of oxidation–reduction reactions, the oxidizing agent undergoes a loss of oxygen, and the reducing agent gains in oxygen content. When a change of this type takes place in the absence of any other source of oxygen, oxygen is of necessity transferred from oxidizing agent to reducing agent. However, when the change occurs in an oxide labile solvent such as water, the possibility exists that the oxygen appearing on the reducing agent is derived from the environment. A program of research has been begun, using labeled oxygen as a tracer, to distinguish between the two types of mechanism: one involving oxygen atom transfer between the reactants, the other involving electron transfer only, the medium acting as a sink and source for oxide. We are reporting the results of some experiments completed for the reaction system in water

$$ClO_3^- + 3\Sigma SO_3^- = Cl^- + 3\Sigma SO_4^-$$

For the tracer technique to be applicable, the oxidizing agent, and the product resulting on oxidation of the reducing agent must both possess the property that they do not exchange oxygen rapidly with the environment. This requirement is fulfilled by the present system: the product SO_4^- is known[2,3] to exchange with water only slowly; observations published for ClO_3^- suggest,[3] and experiments we have done show that it also exchanges only slowly under the conditions of the oxidation–reduction reaction.

Data have been obtained using O^{18} enriched ClO_3^- with normal SO_3^- and water (part A of the table) and using normal ClO_3^- in O^{18} enriched SO_3^- and water (part B of the table). Analyses were made by removing SO_4^- as $BaSO_4$, and reducing it with carbon (utilizing an induction furnace) under conditions such that principally carbon dioxide was produced. Isotopic analysis of this product was made by means of a mass spectrometer.

Summary of Tracer Experiments

N_x represents the ratio $O^{18}/\Sigma O$ in the substance of formula X. n is calculated from the data, and represents the number out of every three oxygens on the ClO_3^- which are transferred to the reducing agent. The temperature was 25°, except in experiment #28 in which it was 50°.

PART A

$N_{ClO_3^-} = 14.61 \times 10^{-3}$, $N_{SO_3^-} = 2.00 \times 10^{-3}$

No.	Conditions[a]	n
2	SO_2 into 0.096 M $KClO_3$*	2.3
6	SO_2 into 0.062 M $KClO_3$* and 1.0 M HCl	2.1
12	1 ml. ~0.1 M SO_2 mixed with 1 ml. 0.096 M $KClO_3$* and 0.1 M HCl	2.9

PART B

$N_{ClO_3^-} = 2.00 \times 10^{-3}$, $N_{SO_3^-} = 14.9 \times 10^{-3}$

No.	Conditions[a]	n
16	1 ml. ~0.1 M SO_2* mixed with 0.5 ml. of 0.15 M HCl and 0.38 M $KClO_3$	2.6
28	1 ml. ~0.1 M SO_2* mixed with 0.5 ml. of pH 5 acetate buffer	1.9

[a] Sulfite and water are in isotopic equilibrium.

The results prove that direct transfer of oxygen from chlorate to sulfite does take place. The deviations of n from the maximum value of 3 are outside of experimental error, which is estimated to be ±0.2 in n. We suggest tentatively that the effect arises in the last stage of reduction of ClO_3^-:ClO^- to Cl^-. Hypochlorite can be expected to exchange rapidly with water (by way of the chlorine hydrolysis equilibrium, for example) and may exchange partly before being reduced.

(1) This work was supported by funds from the Office of Naval Research under contract N6-Ori-02026.

(2) Mills, THIS JOURNAL, **62**, 2833 (1940).

(3) Hall and Alexander, *ibid.*, **62**, 3455 (1940).

Experiments on this system and related systems are being continued and will be reported in greater detail later.

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RECEIVED MAY 18, 1950

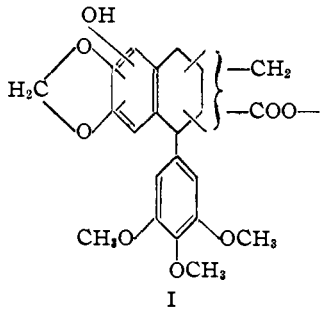
(4) A. E. C. Pre-doctoral Fellow.

COMPONENTS OF PODOPHYLLIN. IV. THE CONSTITUTION OF PODOPHYLLOTOXIN[1,2]

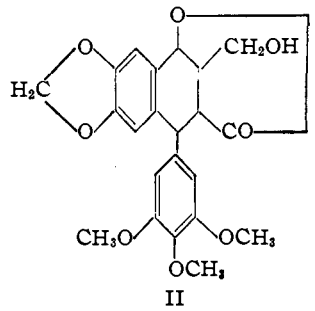
Sir:

Certain aspects of the chemistry of the peltatins (β-peltatin = I)[2] indicated that the accepted formula for podophyllotoxin (II)[3] might require revision. Like the two peltatins,[2] podophyllotoxin forms[4] an isomeric product (picropodophyllin, III) when treated with basic reagents; and, when acetylated with acetic anhydride containing sodium acetate, it yields an acetate differing from the acetate obtained with acetic anhydride alone.

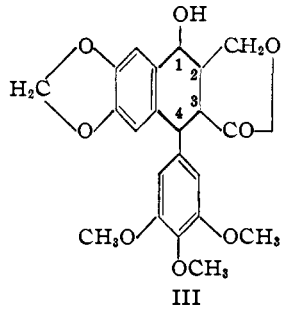
The peltatin acetates of one series were readily converted into those of the other series by refluxing with sodium acetate in ethanol.[2] These results could be explained only by epimerization through enolization at the carbon atom α to the carbonyl group. The same explanation had to be considered for podophyllotoxin, and it appears from the present work to be correct. When acetylpodophyllotoxin or benzoylpodophyllotoxin[5] was refluxed with sodium acetate in various solvents, the corresponding derivative of picropodophyllin was obtained in good yield. These reactions can likewise be satisfactorily explained only by inversion through enolization, and demonstrate that podophyllotoxin and picropodophyllin are C_3-epimers. It is proposed, therefore, that these two compounds are not structural isomers but diastereoisomers represented by III and differing only in configuration about C_3.



I



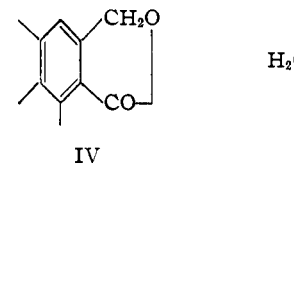
II



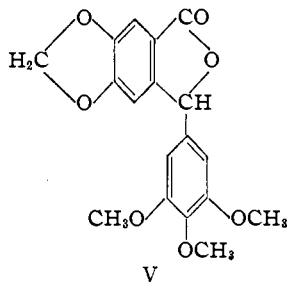
III

Proof of the attachment of the lactone ring at C_2:C_3 as in III has been afforded[6] by the synthesis of a compound represented by partial formula IV and by its identification with dehydroanhydropicropodophyllin, prepared by dehydration and dehydrogenation of picropodophyllin (III).[7]

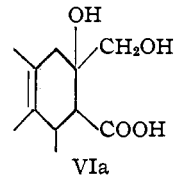
The following evidence is presented for the assignment of the hydroxyl group at C_1. The location of the hydroxyl group at C_4 has been eliminated[8] by the production of the lactone, V, by permanganate oxidation of podophyllic acid (partial formulas VI). The necessity for the presence of an enolizable hydrogen atom at C_3 eliminates this position from consideration. Since periodate oxidation of podophyllic acid was found to yield no formaldehyde, a 1,2-glycol structure (VIa, hydroxyl group at C_2) is ruled out. There remains the only other alternative, VIb (and, hence, III).



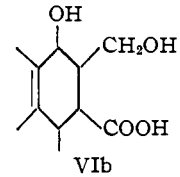
IV



V



VIa



VIb

The action of acetyl chloride or phosphorus trichloride on podophyllotoxin yielded a crystalline chloride, m. p. 190–191° (†), which was readily hydrolyzed in aqueous acetone to a new stereoisomer of podophyllotoxin, m. p. 159–161°, $[\alpha]_D$ −75° (chloroform). Since the latter product, on

(1) This paper was presented before the Medicinal Chemistry Division of the American Chemical Society, in Philadelphia, April 10, (1950).

(2) Paper III, Hartwell and Detty, THIS JOURNAL, **72**, 246 (1950).

(3) Borsche and Niemann, *Ann.*, **499**, 59 (1932); *Ber.*, **65**, 1633, 1790 (1932); Späth, Wessely and Nadler, *ibid.*, **65**, 1773 (1932).

(4) Podwyssotzki, *Arch. exp. Path.*, **13**, 29 (1881); Borsche and Niemann, *Ann.*, **494**, 126 (1932); Robertson and Waters, *J. Chem. Soc.*, 83 (1933).

(5) The preparation of the benzoates of podophyllotoxin and picropodophyllin was according to Edward H. Price, Ph.D. thesis, 1949, University of Maryland, which was kindly made available by Professor Nathan L. Drake.

(6) Haworth and Richardson, *J. Chem. Soc.*, 348 (1936).

(7) Späth, Wessely and Kornfeld, *Ber.*, **65**, 1536 (1932).

(8) Borsche and Niemann, *Ann.*, **499**, 59 (1932); Späth, Wessely and Nadler, *Ber.*, **66**, 125 (1933).