purines in this experiment indicates that the activity of the thymine methyl carbon is close to the expected activities of the 2- and 8-positions of the purines.[7]

When α-labeled glycine was fed 90% of the activity was again present in the methyl group. This finding makes it unlikely that the methyl carbon was introduced together with carbon 5 of the pyrimidine ring, since α-labeled glycine gives rise to α,β-labeled serine[8] or to equally labeled acetate.[9] It appears that the methyl group of thymine is derived from a one-carbon intermediate[7,8] by methylation of a pyrimidine nucleus. This is in accord with the suggestion that the conversion of N^{15}-cytidine to thymine in the rat proceeds by a direct conversion to thymidine.[10]

It is difficult to reconcile the activities of thymine and DNA purines reported here with the concept of "biochemical stability" of DNA proposed on the basis of experiments with N^{15}-labeled adenine.[11]

The reported role of folic acid and vitamin B_{12} in the synthesis of labile methyl groups,[12] and the common origin of the methyl groups of choline[2] and thymine and the 2- and 8-positions of uric acid,[7] suggest an explanation for the known replacibility of folic acid[13] or vitamin B_{12}[14] by thymidine, and of *p*-aminobenzoic acid by thymine, purines and methionine, in certain deficient microörganisms.[15]

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(7) This is based on the finding that following administration of serine to pigeons the activity of the 2- and 8-positions accounted for 90% of the total activity of excreted uric acid (Elwyn and Sprinson, *J. Biol. Chem.*, **184**, 465 (1950)).

(8) Sakami, *ibid.*, **178**, 519 (1949).

(9) Sprinson, *ibid.*, **178**, 529 (1949).

(10) Hammarsten, Reichard and Saluste, *ibid.*, **183**, 251 (1950).

(11) Furst, Roll and Brown, *ibid.*, **183**, 251 (1950).

(12) Bennett, *Science*, **110**, 589 (1949).

(13) Shive, *et al.*, THIS JOURNAL, **70**, 2299 (1948).

(14) Snell, *et al.*, *J. Biol. Chem.*, **175**, 473 (1948).

(15) Lampen, Jones and Roepke, *ibid.*, **180**, 423 (1949).

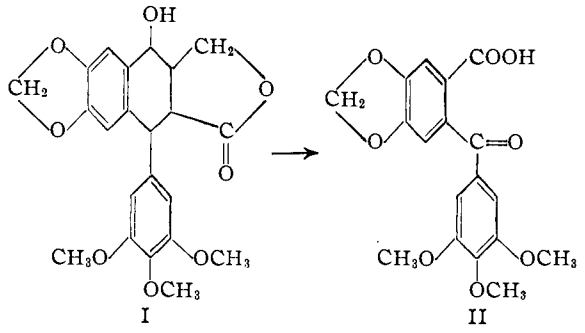
(16) Life Insurance Medical Research Student Fellow, 1949-1950.

SYNTHESIS OF A DEGRADATION PRODUCT FROM PICROPODOPHYLLIN[1]

Sir:

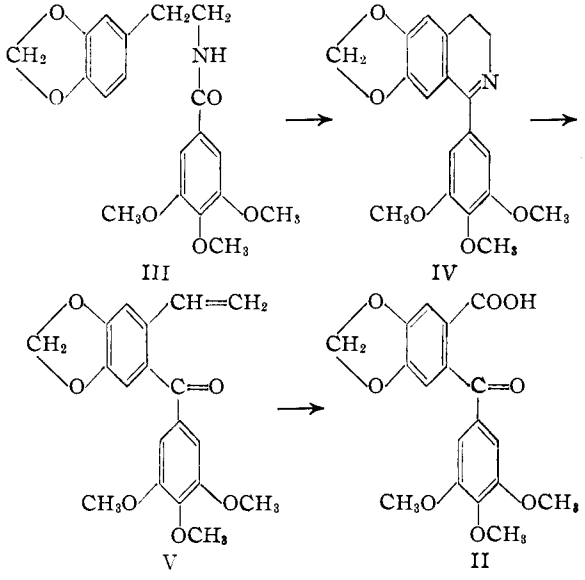
One of the oxidation products of picropodophyllin (I[2]) is considered, on the basis of degradative evidence, to have the structure of trimethoxybenzoylpiperonylic acid (II).[3] We wish to report the synthesis of this compound and thereby confirmation of the assigned structure.

Reaction of homopiperonylamine (prepared by reduction of piperonylidenenitromethane with



I II

lithium aluminum hydride) with trimethoxybenzoyl chloride leads to amide III, m. p. 135.2–135.7°, in 80% yield. (*Anal.* Calcd. for $C_{19}H_{21}$-



III IV V II

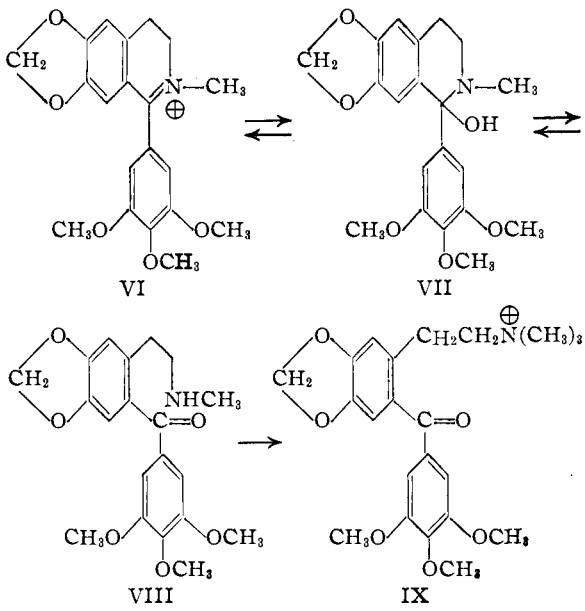
O_6N: N, 3.9. Found: N, 3.9, 3.9.). Heating the amide with phosphorus oxychloride in toluene results in cyclization (93%) to 1-trimethoxyphenyl - 6,7 - methylenedioxy - 3,4 - dihydroisoquinoline (IV), m. p. 160.2–160.6°. (*Anal.* Calcd. for $C_{19}H_{19}O_5N$: N, 4.1. Found: N, 4.1, 4.2). This compound, on treatment with excess methyl sulfate and aqueous alcoholic alkali, is transformed to the vinylbenzophenone derivative (V), m. p. 139.2–139.8°, in 80% yield. (*Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.68; H, 5.26. Found: C, 66.5, 66.6; H, 5.3, 5.4). Finally, oxidation of V with permanganate furnishes the desired keto-acid (II), m. p. 215.2–215.7°, in 50–70% yield (*Anal.* Calcd. for $C_{18}H_{16}O_8$: C, 60.02, H, 4.44. Found: C, 59.8, 60.0; H, 4.5, 4.6). The mixed melting point with the keto-acid obtained from picropodophyllin[3] shows no depression.

The novel one-step conversion of isoquinoline IV to the vinyl compound V must proceed through several intermediate stages. It is likely that the first step involves formation of a dihydroisoquinolinium cation (VI). On treatment with alkali, such compounds are known to yield the

(1) This work has been supported by American Cancer Society Grant-in-aid No. CBC-6 as recommended by the Committee on Growth of the National Research Council.

(2) Borsche and Niemann, *Ann.*, **499**, 59 (1932).

(3) Späth, Wesely and Nadler, *Ber.*, **66**, 125 (1933).



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.

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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).