Podophyllic Acid "Trihydrate"[1]

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Hydrolysis of picropodophyllin opens the lactone ring and gives podophyllic acid.[2] The acid, crystallized from a two-phase mixture of chloroform and water, was reported as a trihydrate.[3] Closer examination of this material has now shown that it is not a hydrate but is instead a nonstoichiometric combination with chloroform.

The effect of chloroform in inducing crystallization of podophyllic acid is striking. In the absence of chloroform, crystallization of podophyllic acid from water, if possible at all, is difficult, and usually gels are obtained. However, addition of chloroform promptly and smoothly precipitates the crystalline chloroform complex. Drying this material at 110° gives solvent free podophyllic acid, presumably the same as that reported before.[3]

EXPERIMENTAL[4]

Podophyllic acid "trihydrate," prepared essentially according to Borsche and Niemann,[3,5] showed melting points dependent on the rate of heating. Material recrystallized three times from water and chloroform melted at 153.5–154.5° (dec.) when the temperature was raised about 5° per minute. A slower rate of heating (*ca.* 1°/min.) tended to cause shrinking around 150° and fusion to a glass at 190–196° (dec.). When the temperature was raised very slowly, no change was apparent at the 154° region, and the solid melted at 203°. Loss of chloroform of solvation as well as relactonization could be responsible for this melting point behavior.

Anal. Calc'd for $C_{22}H_{24}O_9 \cdot 0.329(CHCl_3)$: C, 56.85; H, 5.20; Cl, 7.42; $CHCl_3$, 8.33. Found: C, 56.39; H, 5.02; Cl, 7.12; wt. loss on heating *in vacuo* overnight at 110°: 7.51.

Solution of the dried material in aqueous bicarbonate showed that lactonization did not occur. The melting point taken with a temperature increase of 1°/min. was 203–208° (dec.).

Anal. of the dried material. Calc'd for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.2; H, 5.6.

Other experiments furnished additional analytical data.

(A) Calc'd for chloroform complex, $C_{22}H_{24}O_9 \cdot 0.11(CHCl_3)$: C, 59.59; H, 5.45; Cl, 2.64; $CHCl_3$, 2.96. Found: 59.60; H, 5.42; Cl, 2.94; wt. loss on drying to constant weight at 110°, 2.84, 3.21. *Anal.* for the dried material: Found: C, 61.43; H, 5.56; Cl, 0.0.

(B) Calc'd for chloroform complex, $C_{22}H_{24}O_9 \cdot 0.176(CHCl_3)$: C, 58.74; H, 5.38; Cl, 4.13; $CHCl_3$, 4.64. Found: C, 59.19; H, 4.91; Cl, 4.13; wt. loss on drying at 110°, 4.72, 4.84. *Anal.* for the dried material: Found: C, 61.83; H, 5.68; Cl, 0.0.

The chlorine-free material as a mull in mineral oil showed an infrared absorption band at 5.91 μ. The specific rotation in absolute alcohol (0.864 g. per 100 ml.) was $(\alpha)_D^{25}$ −96.0.

Approximately 0.1 g. of chlorine-free podophyllic acid was dissolved in 15 ml. of almost boiling water. Filtration removed a small amount of solid. A very small amount of solid developed on standing at room temperature, and more appeared during refrigeration for three days. The solids formed in the cold mixture melted at 212–214° (dec.) and were insoluble in bicarbonate (picropodophyllin?). Addition of chloroform to the clear filtrate at room temperature resulted in immediate precipitate formation.

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(2) Kelly and Hartwell, *J. Nat. Cancer Inst.*, **14**, 967, 989 (1954).

(3) Borsche and Niemann, *Ann.*, **494**, 126 (1932).

(4) Analyses were performed by Dr. S. M. Nagy at Massachusetts Institute of Technology Microchemical Laboratory, and by Dr. C. K. Fitz, 115 Lexington Avenue, Needham Heights 94, Massachusetts.

(5) *Cf.* Hartwell and Schrecker, *J. Am. Chem. Soc.*, **73**, 2909 (1951).

Some Indole Derivatives Tested for Antitubercular Activity

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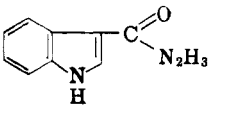
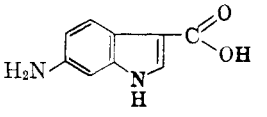
During the course of synthesis of indole derivatives in this laboratory interest in the compounds 3-indolecarboxylic acid hydrazide (I), 6-amino-3-indolecarboxylic acid (II), and 6-amino-3-indolecarboxylic acid hydrazide (III) arose because of the similarities of their structures to those of the known antitubercular compounds *p*-aminosalicylic acid (IV),[1] and isonicotinic acid hydrazide (V).[2]



I



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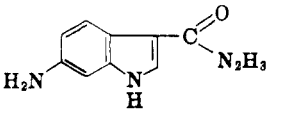
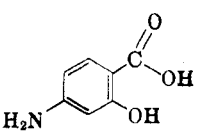
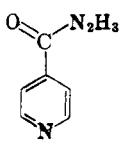


III



IV



V

Indole derivatives previously reported in connection with antitubercular activity are 3-indoleacetic acid hydrazide[3] and 3-indolecarboxaldehyde thiosemicarbozone.[4] The latter compound possesses high *in vitro* and *in vivo* activity against tubercle bacilli.

(1) Lehmann, *Lancet*, **250**, 15 (1946).

(2) Grunberg, Schnitzer, Leiwant, D'Ascensio, and Titsworth, *Quart. Bull. Sea View Hosp.*, **13**, 3 (1952).

(3) Yale, Losee, Martins, Perry, and Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).

(4) Weller, Sell, and Gottshall, *J. Am. Chem. Soc.*, **76**, 1959 (1954).