While folinic acid accounts for the major portion of the activity of extracts of hog liver, another factor with similar physical and biological properties occurs in these extracts. At least two other substances possessing activity in the assay have been detected by means of paper chromatography. Consequently, it appears that a group of compounds, the folinic acid group, possess activity similar to that of folinic acid.

Since the folinic acid group is utilized more effectively than folic acid for several organisms, the possibility exists that it may be more active than folic acid in the treatment of sprue, nutritional and pernicious anemia, and other nutritional deficiencies related to the folic acid and vitamin B_{12} groups.

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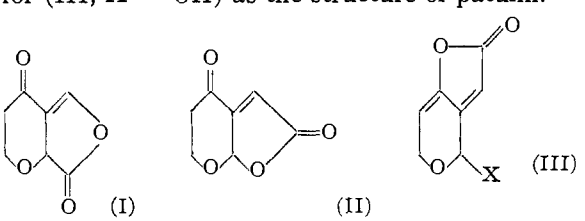
THE STRUCTURE OF PATULIN

Sir:

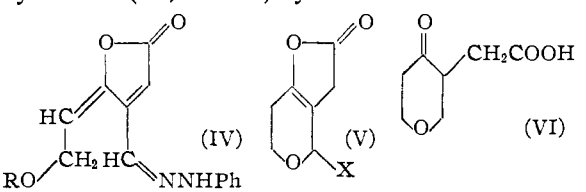
Recent evidence has required revision of the accepted structure (I)[1] of the antibiotic mold metabolite, patulin, and two new formulations, (II)[2] and (III, X = OH),[3] have been advanced. The following data now afford additional strong support for (III, X = OH) as the structure of patulin.



(I) (II) (III)

Structure (III, X = OH) possesses three structural characteristics: free hydroxyl group, lactal ring and doubly-unsaturated lactone system. Presence of a free O–H band (2.73μ), in the infrared spectrum of patulin and its absence in patulyl acetate (III, X = OAc) and in patulyl chloride (III, X = Cl), retention of the characteristic double bond ultraviolet and infrared spectra of patulin in these derivatives (Patulin: u.v., 275 mμ, log ϵ 4.22; ir., 5.58μ, 5.94μ, 6.11μ. Acetate: u.v., 277 mμ, log ϵ 4.24; ir., 5.58μ, 5.93μ, 6.11μ. Chloride: u.v., 277 mμ, log ϵ 4.18; ir., 5.61μ, 5.94μ, 6.13μ), and conversion of each in high yield to patulin phenylhydrazone by aqueous phenylhydrazine indicate the presence of a non-enolic hydroxyl group and exclude occurrence of enolization or isomerization during their preparation.

Patulin shows reactions (negative Schiff, positive Tollens, positive Fehling)[1] characteristic of a lactal ring. Lactal ring opening by phenylhydrazone formation usually unmasks a hydroxyl group and the conversion of patulin phenylhydrazone (IV, R = H) by treatment with sodium



(IV) (V) (VI)

acetate–acetic anhydride to patulin phenylhydrazone acetate (IV, R = Ac), m. p. 143° (calcd. for $C_{15}H_{14}O_4N_2$: C, 63.00; H, 4.93. Found: C, 63.40; H, 5.27) fits this interpretation. Infrared spectra of patulin phenylhydrazone (5.86μ, 6.04μ, 6.23μ) and its acetate (5.84μ, 6.00μ, 6.22μ) indicate retention of the doubly-unsaturated lactone system in these derivatives. Demonstration of a lactone ring in the phenylhydrazone and its acetate is shown by consumption of 1.05 and 1.92 equivalents, respectively, of sodium hydroxide. Dihydropatulin (V, X = OH) phenylhydrazone[4] contains only a singly-unsaturated lactone system (u.v., 380 mμ, log ϵ 4.55; 1.07 equivalents sodium hydroxide).

Treatment of patulin with warm excess thionyl chloride followed by sublimation furnishes unstable patulyl chloride (III, X = Cl) in 78% yield, m. p. 92–94° (calcd. for $C_7H_5O_3Cl$: C, 48.70; H, 2.92; Cl, 20.55. Found: C, 48.94; H, 2.63; Cl, 20.43); structural evidence given above. Patulyl chloride in anhydrous dioxane with palladium–barium sulfate catalyst absorbs 2.0 of moles hydrogen in two hours to give a neutral fraction which furnishes on distillation oily dihydrodesoxypatulin (V, X = H) in 34% yield, b. p. 90–95° (0.5 mm.). (Calcd. for $C_7H_8O_3$: sapon. equiv. 140.1. Found: 141.2); immediate Legal test; u.v., at 212 mμ, log ϵ 3.93; ir., 5.57μ, 6.01μ. Accordingly, dihydrodesoxypatulin contains a β,γ-unsaturated-γ-lactone system and its exact structure is established by hydrolysis in aqueous alcoholic sodium hydroxide to dihydrodesoxypatulinic acid (VI), identified by its well-known derivatives[2,3,4,5]: 2,4-dinitrophenylhydrazone, m. p. 193–195°; methyl ester 2,4-dinitrophenylhydrazone, m. p. and m. m. p. 149–150° (calcd. for $C_{14}H_{16}O_7N_4$: C, 47.70; H, 4.58. Found: C, 47.50; H, 5.02); *p*-phenylphenacyl ester, m. p. 124–127°.

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