lic acid trihydrate is 163–165° (dec.)[2,3] at which temperature picropodophyllin (I) is reformed. The melting point of the anhydrous acid[3] is not recorded.

The present synthesis is unambiguous with the exception of one step. Cyclization of dibasic acid V could lead to a compound isomeric with VI in which the trimethoxyphenyl ring is part of the tetralin system and the methylenedioxyphenyl ring is a substituent. However, this possibility was excluded by conversion of the dihydroxy acid VII (treatment with boiling water or boiling 10% aqueous sulfuric acid) to *dl*-β-apopicropodophyllin the structure of which is accepted[7] as VIII. The identity of the synthetic apo compound [m.p. 215–216°; *Anal.* Calcd. for $C_{22}H_{20}O_7$: C, 66.7; H, 5.1. Found: C, 66.7; H, 5.3] was demonstrated by the infrared absorption curve, which was indistinguishable from that of "natural" β-apopicropodophyllin, and by the ultraviolet absorption curve, which showed a maximum and a minimum of the same intensities and wave lengths as those reported[7,8] for the "natural" material.

Further work on the relation of the synthetic dihydroxy acid VII to podophyllic acid, and to picropodophyllin and podophyllotoxin is under way.

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(8) N. L. Drake and E. H. Price, *ibid.*, **73**, 201 (1951).

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

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HIGH STREPOGENIN POTENCY OF SYNTHETIC OXYTOCIN AND OF PURIFIED VASOPRESSIN

Sir:

The bacterial and animal growth factor strepogenin, which is a peptide-like substance liberated during partial hydrolysis of certain proteins,[1,2] has previously not been isolated in pure condition. Consequently, considerable doubt and confusion has prevailed about its nature and biological functioning. The application of ion-exchange chromatography under very carefully controlled conditions, and of countercurrent distribution, has now resulted in the isolation from partial hydrolysates of insulin (concd. HCl, 37°, 24 hours)[3] of eight peptides, each of which exhibited very high strepogenin activity for *Lactobacillus casei*. These peptides behaved as homogeneous substances in several highly selective fractionation procedures, but no final claim of their purity is being made. The most active one was 780 times as potent as the standard liver extract[2] and thus gave half-maximal growth at 0.09 γ per cc. This peptide yielded on hydrolysis cystine, glutamic acid, glycine, serine, valine and the leucines. The other peptides which ranged in potency from 100 to 600 times the liver extract standard each contained these same amino acids with the following modifications. Some contained tyrosine and some lacked one or two of serine, glycine and isoleucine.

The amino acid composition of these peptides was being investigated when the synthesis of oxytocin was announced by du Vigneaud, *et al.*[4] The similarity in amino acid composition of our peptides to oxytocin was readily seen. Through the kindness of Dr. du Vigneaud and co-workers samples of synthetic oxytocin and related peptides were obtained. Assays showed that oxytocin was 300 times as active as the liver extract standard. It was, thus, far more potent than any protein digest,[2] and approached the activity of our best isolated peptide. The fact that the oxytocin was synthetic showed clearly that a polypeptide could have high strepogenin activity. So long as isolated compounds were the only ones with high potency it could be argued that the strepogenin activity resided in some constituent other than those generally recognized to occur in proteins. Such a belief is no longer tenable.

The cystine residue of oxytocin was vital to its strepogenin potency. S,S-Dibenzyloxytocin was practically inactive (potency less than 6), as was also performic-acid-oxidized oxytocin. Several of the smaller synthetic peptides representing sequences in oxytocin or in vasopressin[4,5,6] were inert also. This was true of L-isoleucyl-L-glutaminyl-L-asparagine, L-phenylalanyl-L-glutaminyl-L-asparagine and L-glutaminyl-L-asparagine. However, some variation in the amino acid composition was compatible with high strepogenin potency, as shown by assay of the structurally related polypeptide vasopressin. A sample of purified arginine-vasopressin (300 pressor units per mg.), free of oxytocin, was kindly provided by Dr. du Vigneaud for this test. It had a strepogenin activity of 150. Clearly, high strepogenin activity for *L. casei* did not reside in a single structure. However, since many polypeptides, even those containing glutamic acid[7] and cystine have proven to be almost inert, some specificity of structure obviously is involved.

FROM THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK
D. W. WOOLLEY[8]
R. B. MERRIFIELD

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