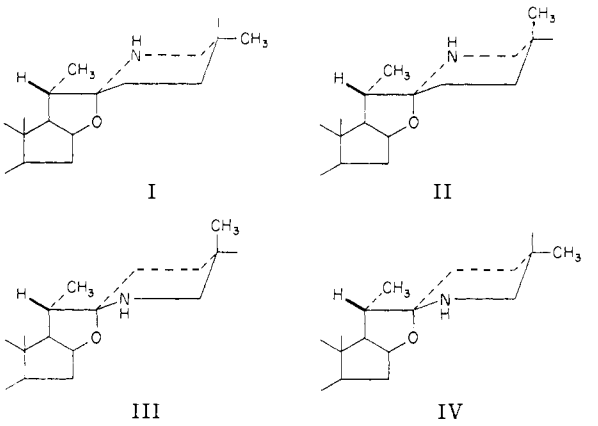
respectively, to enantiomorphic forms of 2-methylglutaric acid which have been correlated with D- and L-glyceraldehyde, the "D" configuration at C-25 in the case of solasodine has, accordingly, been established. Furthermore, the partial synthesis of 5β-solanidan-3β-ol from sarsasapogenoic acid[8] serves to establish the "L" configuration at C-25 in this octahydropyrrocoline solanum alkaloid, and in its congeners, including demissidine, 5α-solanidan-3β-ol, which was recently shown to be the end-product of a series of transformations of tomatidine.[9] Since neither of these partial synthetic sequences would be expected to lead into version at C-25, the "L" configuration at this position in tomatidine may be assigned and the alkamine recently prepared from pseudosarsasapogenin[6] designated as the 5β-epimer of the tomato alkaloid.

We have now confirmed this formulation for tomatidine by synthesis from neotigogenin, a sapogenin originally encountered as a companion substance to tigogenin in *Chlorogalum pomeridianum*[10] and more recently isolated from the mother liquors accumulated subsequent to the crystallization of hecogenin from *Agave sisalana*.[11] Neotigogenin was shown[11] to yield L-2-methylglutaric acid following chromic acid oxidation of an appropriate derivative and to afford tigogenin on prolonged maintenance under reflux in ethanolic acid solution.

Pseudoneotigogenin,[12] m.p. 174–178°, has been transformed, following successive treatment with *p*-toluenesulfonyl chloride in pyridine and sodium iodide in diethyl ketone, to the C-27 phthalimido derivative, m.p. 98–100° (calcd. for $C_{35}H_{47}NO_4$: C, 77.02; H, 8.68; N, 2.57. Found[13]: C, 76.90; H, 9.02; N, 2.58) which, on treatment with hydrazine in ethanol, followed by phosphoric acid, has afforded tomatidine, m.p. 205–207° (calcd. for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.69; H, 10.83; N, 3.24), mixed melting point and infrared spectrum identical with that displayed by a sample of naturally occurring tomatidine[14]; hydrochloride, m.p. 265–270°; $[\alpha]^{25}D$ −5.3° (*c* 0.254 in methanol); calcd. for $C_{27}H_{46}NO_2Cl$: C, 71.73; H, 10.26; N, 3.10. Found: C, 71.35; H, 10.02; N, 3.11.

It is not possible, on the basis of the experimental evidence available at the present time, to unequivocally assign total spatial representations to rings E and F of the aminoketal alkaloids. As a consequence of the recent rather extensive discussion[7,15,16] of the stereochemical relationships at C-20, C-22 and C-25 in the spiroketal sapogenins, there appears to be general argeement that in those sapogenin isomers which are stable to moderately vigorous acid conditions, the C-21 methyl group may be assigned to the α-position. This consideration, together with the demonstration of the specific orientations at C-25, limits the configurational possibilities to formulations I and III for solasodine and to II and IV for tomatidine. If arguments advanced[16] in the sapogenin field may be considered germane to the case of the alkaloids, the partial expressions I for solasodine and II for tomatidine appear most probable.



I II III IV

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(12) This substance will be fully described by Drs. Callow and James in a forthcoming publication. We wish to thank Dr. Callow of the National Institute for Medical Research, London, for the gift of a quantity of neotigogenin.

(13) Microanalyses and spectroscopic determinations by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology, Cambridge, Mass.

(14) We are indebted to Dr. T. D. Fontaine, U. S. Department of Agriculture, Philadelphia, for a specimen of naturally occurring tomatidine.

(15) M. E. Wall, C. R. Eddy and S. R. Serota, THIS JOURNAL, **76**, 2849 (1954); M. E. Wall and S. R. Serota, *ibid.*, **76**, 2850 (1954); J. B. Ziegler, W. E. Rosen and A. C. Shabica, *ibid.*, **76**, 3865 (1954).

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GLUCOSIDES FROM THE RHIZOMES OF *PODOPHYLLUM PELTATUM* LINN.

Sir:

It has long been known that podophyllotoxin (Ia)[1] is the most important component of the resin fraction obtained from the rhizomes of the North American *Podophyllum peltatum* Linn. and the Indian *Podophyllum emodi* Wall. (*Berberidaceae*). It is only recently, however, that this compound has gained in interest following the discovery of its ability to inhibit the growth of certain tumors. In both species of podophyllum a number of other compounds have been encountered which are similar both in chemical structure and in biological activity to podophyllotoxin. The Indian variety, for example, also contains 4′-demethyl-podophyllotoxin (Ib),[2] while the American variety contains α-peltatin (IIb) and β-peltatin (IIa).[3] Recently, we have been able to show that the two compounds podophyllotoxin and demethyl-podophyllotoxin, which are present in the resin fraction, also occur

(1) V. Podwyssotzki, *Arch. Exp. Path.*, **13**, 29 (1880); *Ber.*, **15**, 377 (1882). Regarding the constitution, see in particular: J. L. Hartwell and A. W. Schrecker, THIS JOURNAL, **73**, 2909 (1951).

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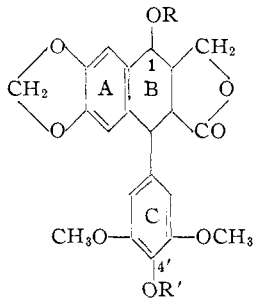
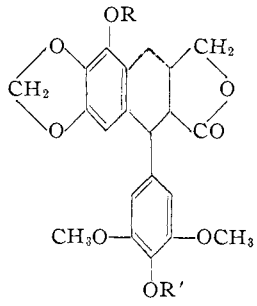
(3) J. L. Hartwell, *ibid.*, **69**, 2918 (1947); J. L. Hartwell and W. E. Detty, *ibid.*, **70**, 2833 (1948); **72**, 246 (1950).

in the plant as glucosides (Ic, Id).[4,5] In both glucosides, the alcoholic hydroxyl group in ring B is connected with a D-glucose residue. The two substances differ from their aglucones in having a certain solubility in water; both are biologically active.



Ia, R = H; R′ = CH_3
Ib, R = R′ = H
Ic, R = glucose residue; R′ = CH_3
Id, R = glucose residue; R′ = H



IIa, R = H; R′ = CH_3
IIb, R = R′ = H
IIc, R = glucose residue, R′ = CH_3

Since the two peltatins which are present in the American podophyllum together with podophyllotoxin also contain either one or two free hydroxyl groups,[6] it seemed possible that these compounds might also be found in the plant in the form of glycosides.

We have now succeeded in isolating from the rhizomes of *Podophyllum peltatum* the glucoside of β-peltatin in addition to podophyllotoxin glucoside previously isolated from the Indian drug. The two glucosides resemble one another very closely in their properties, so that a complete separation was possible only by means of chromatography and a number of partition procedures. A further difficulty in the preparation of pure homogeneous compounds lay in the fact that neither β-peltatin glucoside nor podophyllotoxin glucoside showed any tendency to crystallize.

The **podophyllotoxin-β-D-glucoside** (Ic) which we were able to separate from the mixture of the two glucosides isolated from the American drug was obtained as a white powder melting at 152–154° and having a specific rotation $[\alpha]^{20}D$ −76° (*c* 0.5) in methanol. The amorphous preparation yields a crystalline tetra-acetyl derivative which melts at 134°, and on treatment with mild alkalies it readily undergoes rearrangement to the crystalline picropodophyllin glucoside which is characterized by having a double melting point at 235° and 252°. The amorphous glucoside thus agrees in its properties with podophyllotoxin glucoside.[4] The yield from *P. peltatum* Linn. is, however, smaller than that from *P. emodi* Wall.

After repeated partition chromatography it was possible to obtain β-peltatin glucoside free from podophyllotoxin glucoside, also in the form of a white powder. It melts at 156–159° and has a specific rotation $[\alpha]^{20}D$ −123° (*c* 0.5) in methanol and $[\alpha]^{20}D$ −169° (*c* 0.5) in pyridine. The analysis corresponds to an empirical formula $C_{28}H_{32}O_{13}$ (Calcd.: C, 58.33; H, 5.60; OCH_3, 16.15. Found: C, 58.42; H, 5.79; OCH_3, 16.30). The ultraviolet absorption spectrum exhibits a characteristic maximum at 280 mμ (log ε = 3.44) and a minimum at 260 mμ (log ε = 3.12). The glucoside is readily soluble in alcohols, acetone and ethyl acetate. Its solubility in water is similar to that of podophyllotoxin glucoside.

The new glucoside is rapidly decomposed by β-glucosidase (emulsin), giving a quantitative yield of a crystalline aglucone having the composition of $C_{22}H_{22}O_8$ (Calcd.: C, 63.76; H, 5.35; OCH_3, 22.47. Found: C, 63.76; H, 5.51; OCH_3, 22.43). After crystallization from absolute alcohol, the aglucone melts at 238 to 241° and it exhibits an optical rotation $[\alpha]^{20}D$ −122.9° (*c* 0.5) in chloroform. The ultraviolet absorption spectrum shows a maximum at 275 mμ (log ε = 3.26) and a minimum at 262 mμ (log ε = 3.17). Acetylation results in a monoacetyl derivative melting at 231–232°. The aglucone obtained by enzymatic cleavage of the new glucoside thus agrees in its properties with β-peltatin.[3] A mixed melting point with a sample of β-peltatin obtain from the resin fraction from *P. peltatum* rhizomes gave no depression.

The sugar split off on enzymatic cleavage could be identified via the α-methyl-D-glucoside<1.5> (m.p. 168–169°) as D-glucose.

These results indicate that the new glucoside is **8-*O*-(β-D-glucopyranosyl)-β-peltatin** (IIc). The yield from the rhizomes of *P. peltatum Linn.* is approximately 0.1 to 0.5%.

The two glucosides obtained from *Podophyllum peltatum* Linn. differ from one another in the position of the hydroxyl group carrying the glucose residue. In podophyllotoxin glucoside, the hydroxyl group is alcoholic, whereas in β-peltatin glucoside it is phenolic. In the American plant both types of glucosides are encounted side by side. Like podophyllotoxin glucoside, β-peltatin glucoside also exerts an inhibiting effect on mitosis. A detailed account of the separation of the two compounds and the properties of the new glucoside will be published shortly in *Helvitica Chimica Acta.*

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