tane or ergostane series are more stable in the 14α-configuration (C/D *trans*),[9] the reverse stability relationship (14$\alpha \rightarrow$ 14β) exists in 15-ketones of the spirostan series[3,4] and in 15,20-diketones of the pregnane series. It is obvious that subtle stereochemical effects can completely alter the relative stabilities of such fused hydrindane systems and that at the present time each case should be examined rigorously, rather than basing stereochemical assignments on analogy.

The smooth side chain degradation[2] of digitogenin offers a path to a variety of 15-hydroxylated steroids and experiments are now under way to prepare steroidal 15-ketones with different C-17 substituents in order to determine the effect of size and type of such substituents upon the stability of the C/D ring structure.

Two of us (C. D. and L. B. H.) are indebted to the American Cancer Society through the Committee on Growth of the National Research Council) for a research grant.

[9] C. S. Barnes, D. H. R. Barton and C. G. Laws, *Chem. and Ind.* 616 (1953).

JOINT CONTRIBUTION FROM
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RECEIVED JUNE 10, 1955

PODOPHYLLOTOXONE, PICROPODOPHYLLONE, AND DEHYDROPODOPHYLLOTOXIN[1]

Sir:

Assignment of a secondary alcohol grouping at the 1-position of podophyllotoxin (Ia) rests on the formation of stereoisomers in, and on the relative ease of, displacement reactions at the alcohol-bearing carbon.[2] The production of ketones (II) corresponding to podophyllotoxin and to picropodophyllin[3] now makes direct corroboration of this assignment possible.

Treatment of podophyllotoxin (Ia) with freshly prepared manganese dioxide[4] furnished (58%) the oxidation product, podophyllotoxone (IIa), m.p. 191–192° (softens 187°) and $[\alpha]^{25}$D −125°. *Anal.* Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 64.0; H, 5.0. Ultraviolet absorption maxima were observed at 235, 277 and 316 mμ (log ϵ 4.64, 4.09 and 3.96). Peaks in the infrared at 5.62 and 5.99 μ corresponded to lactone and ketone carbonyls. No hydroxyl absorption was evident. Manganese dioxide oxidation of picropodophyllin (Ib) gave (57%) picropodophyllone (IIb), m.p. 153–154° and $[\alpha]^{25}$D −142°. Anal. Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 64.1; H, 5.0. Maxima appeared at 240, 279 and 324 mμ (log ϵ 4.42, 3.95 and 3.91) in the ultraviolet, and at 5.66 μ and 5.98 μ—but not in the 2.5–3.0 μ region—in the infrared. The ultraviolet absorption curves of IIa and IIb, as well as of synthetic keto-ester IV[5] (λ_{max} at 236, 275 and 320 mμ, and log ϵ 4.45, 3.94 and 3.87) although differing somewhat in position and extinction of their respective maxima, are quite similar in general contour. Likewise the 5.95 μ ketone carbonyl absorption of keto-ester IV falls close to the corresponding absorption in IIa and IIb.

No rearrangement occurred in the manganese dioxide oxidations, since reduction of the two ketones, IIa and IIb, with zinc borohydride[6] regenerated the respective starting materials, podophyllotoxin (94%) and picropodophyllin (35%).

Dehydrogenation of podophyllotoxone or of picropodophyllone with selenium dioxide furnished the same product, dehydropodophyllotoxin (III) melting (in evacuated sealed capillary) at 286–288° (dec.) with preliminary softening at 275°. The melting point behavior depended on the rate of heating. *Anal.* Calcd. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.2; H, 4.4. Absorption maxima were evident at 226, 263, 323 and 356 mμ (log ϵ 4.49, 4.62, 4.02 and 3.72), and in the infrared at 2.91 and 5.69 μ. Although this α-naphthol derivative III gave no color with ferric chloride and was not soluble in 10% sodium hydroxide solution, the presence of hydroxyl was substantiated by formation of an acetate, m.p. 259–260° (dec.) with softening at 258°. *Anal.* Calcd. for $C_{24}H_{20}O_9$: C, 63.71, H, 4.46. Found: C, 63.7, H, 4.6.

The above conversions show unequivocally that the hydroxy group in podophyllotoxin and picropodophyllin (Ia and b) cannot be tertiary, and therefore cannot be at the 2, 3 or 4 positions. Also, since manganese dioxide oxidation occurs smoothly only with allylic or benzylic alcohols,[7] it follows that the free hydroxy group must be placed on the 1 position as in I, and not on the exocyclic position as in V. The facts that the ultraviolet absorptions of compounds IIa, IIb and IV are similar, and that compounds IIa and IIb can be oxidized to naphthol III provide further support for I as opposed to V, for these facts indicate that carbonyl compounds IIa and IIb are ***ketones*** and not aldehydes.

Kofod and Jørgensen[8] recently isolated a compound from podophyllin, which they named "dehydropodophyllotoxin," and to which they assigned the structure of compound III. Dr. Kofod

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[1] This work has been supported by grants-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

[2] J. L. Hartwell and A. W. Schrecker, THIS JOURNAL, **73**, 2909 (1951).

[3] Earlier attempts to prepare these ketones have not been rewarding; see footnote 19 of ref. 2.

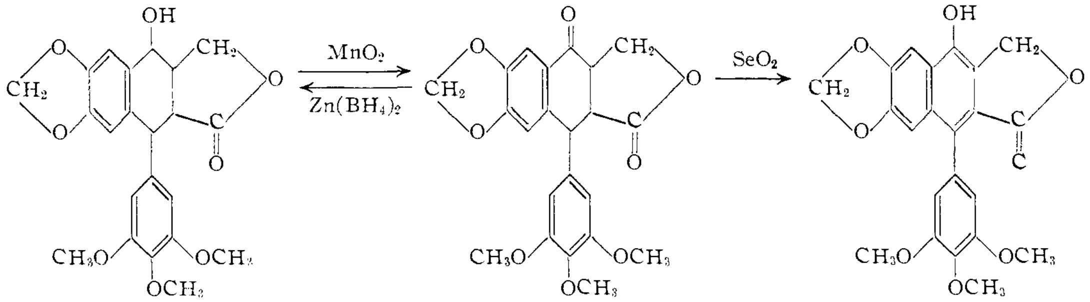
[4] *E.g.*, podophyllotoxin (5.0 g.) is exposed to manganese dioxide (30 g.)in boiling chloroform (300 ml.) for one and one-quarter hours. Solvent is removed from the filtrate, and the residue is crystallized from benzene. *Cf.* D. L. Turner, THIS JOURNAL, **76**, 5175 (1954); J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

[5] W. J. Gensler, C. S. Samour and Shih Yi Wang, THIS JOURNAL, **76**, 315 (1954).

[6] *Cf.* E. Wiberg and W. Henle, *Z. Naturforsch.*, **7b**, 579 (1952); G. D. Barbaras, *et al.*, THIS JOURNAL, **73**, 4585 (1951); E. Wiberg, *Angew. Chem.*, **65**, 16 (1953). Ether-soluble zinc borohydride, which can be prepared from sodium borohydride and zinc chloride, may prove of special value in the reduction of alkali sensitive compounds. In our work, for example, reduction with sodium borohydride was not clean cut, and gave a product of as yet undetermined structure from both IIa and IIb.

[7] S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, **42**, 516 (1948); F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953); M. Harfenist, A. Bavley and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

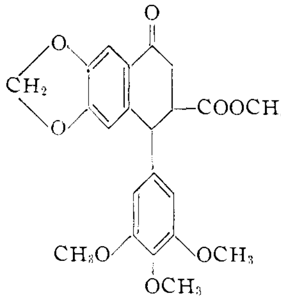
[8] H. Kofod and Chr. Jørgensen, *Acta Chem. Scand.*, **8**, 1296 (1954).



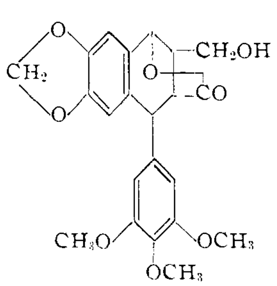
I
a, podophyllotoxin
b, picropodophyllin

II
a, podophyllotoxone
b, picopodophyllone

III
dehydropodophyllotoxin



IV



V

very kindly carried out direct comparisons of his dehydropodophyllotoxin with our compound III. He reports that the two materials are the same.

Ketones IIa and IIb should prove of value in elaborating structural and stereochemical derivatives of podophyllotoxin.

BOSTON UNIVERSITY WALTER J. GENSLER
BOSTON, MASSACHUSETTS FRANCIS JOHNSON

RECEIVED MAY 7, 1955

POLYTHIOLSTYRENE—A NEW OXIDATION-REDUCTION ION EXCHANGE RESIN

Sir:

Oxidation–reduction polymers of the dihydroxybenzene type have been described by Cassidy[1] and Manecke.[2] We wish to report on a new oxidation–reduction resin of the thiophenol type.

Polystyrene (mol. wt. 30,000) was nitrated[3] to form polynitrostyrene, which was reduced by hydrogenation using a palladium catalyst to polyaminostyrene. Calcd. for C_8H_9N: N, 11.75. Found: N, 11.25.

Diazotization of polyaminostyrene with nitrous acid to form the diazonium chloride, followed by treatment with potassium ethylxanthate, gave insoluble polystyrene xanthate. Calcd. for $C_{11}H_{12}OS_2$: S, 28.58. Found: S, 26.96. Conversion to the polythiol was by hydrolysis with base, then acidification with acid to give polythiolstyrene. Calcd. for C_8H_8S: 23.50. Found: 21.77.

The resin was obtained as large brown granules; these were ground to a powder which was insoluble in all common solvents and swelled about 25% in alkaline solutions. Cross-linking probably occurred during decomposition of the diazo polymer.

The reducing capacity of the resin was determined in columns containing 0.1–0.4 g. of resin. Reductions were carried out using excess amounts of 0.5–2 *M* solutions of either sodium hydrosulfite, sodium sulfide or thioglycolic acid (at *p*H 8). The resin was then oxidized with known amounts of standard 0.1 *N* iodine in 0.25 *N* potassium iodide in a phosphate buffer (*p*H 8). The reducing capacity as calculated from back-titrations of the iodine effluent was 6.6 ± 0.4 meq./g. of resin for about ten consecutive cycles each on two columns. The theoretical capacity based on the sulfur analysis is 6.79 meq./g.

This new resin is a very strong reducing agent. In the oxidized state it can be reduced only by very strong reducing agents, not by weaker agents as acid-iodide. It is apparently stable to all but strong oxidizing agents such as permanganate. It is also highly specific toward metals which form mercaptides. Detailed experiments will be reported upon later.

This investigation was supported in part by the Office of Naval Research and by a research grant, RG 2934(C3), from the Division of Research Grants of the National Institutes of Health, Public Health Service. One of us (D.D.) was supported by the Boris Kidric Foundation, to which he wishes to express his thanks.

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[1] H. G. Cassidy, *et al.*, THIS JOURNAL, **75**, 1615 (1953).

[2] G. Manecke, *Z. Elektrochem. Ber. Bunsenges. physik. Chem.*, **58**, 369 (1954).

[3] A. Skogseid, Dissertation, Oslo, 1948.

THE SYNTHESIS OF POLY-*p*-THIOLSTYRENE, AN OXIDATION REDUCTION POLYMER

Sir:

We wish to report the successful synthesis of pure poly-*p*-thiolstyrene. This polymer and its copolymers are of both practical and theoretical interest because of the reversible oxidation reduction system of a thiol group and a disulfide group which is the basis for the activity of a number of proteolytic enzymes. In this system disulfide formation provides a labile cross-link. These polymers are also of a potential use as prophylactics for ionizing radiation which are not rapidly excreted from the body.

p-Aminoacetophenone (I) was converted to the xanthate by diazotization followed by reaction with