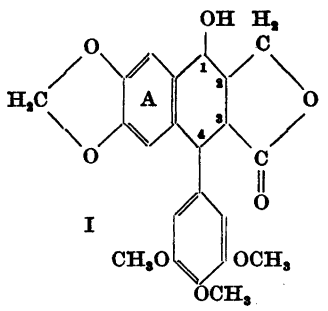
Bromopodophyllotoxin

HELMER KOFOD and CHR. JØRGENSEN

Danmarks farmaceutiske Højskole, Org.-kem. Laboratorium, Copenhagen, Denmark

It has been postulated [1] that podophyllotoxin (I) is unreactive toward bromine, and this appears to be generally believed. In recent X-ray work, for instance, during which the introduction of a bromine atom in the molecule was desirable, this has been done indirectly by bromoacetylation of the hydroxy-group [2].

We find, however, that a solution of podophyllotoxin in chloroform virtually consumes approximately 2 equivalents of bromine per molecule, when shaken with an acidified aqueous bromide-bromate solution.



Podophyllotoxin $C_{22}H_{22}O_8$
trans 1:2, trans 2:3, cis 3:4.

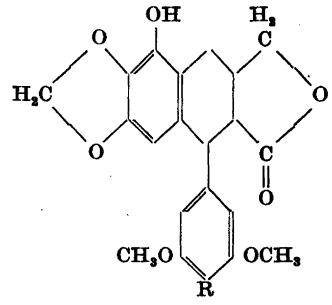
(Hartwell *et al.*)

From the reaction mixture a product has been isolated in good yield as colourless needles (from benzene) melting at 182–183° C or at 155° C. The substance is dimorphous, the lower melting form is slowly converted into the higher melting one when heated to its melting point. It analyzed as monobromopodophyllotoxin, $C_{22}H_{21}O_8Br$ (493.3): Calc. C 53.5; H 4.3; Br 16.2; $3OCH_3$ 18.7.
Found. 53. 6, 53.8; 4.4, 4.5; 16.3, 16.7; 18.7.

The bromine is firmly bound. The substance gave no precipitate of silver halide with alcoholic silver nitrate even on heating, and the bromine was not hydrolyzed by boiling alcoholic sodium hydroxide, which indicates that substitution has taken place in an aromatic ring. The nature of the carbon-bromine bond and the analyses prove the non-identity with the podophyllotoxin bromide $C_{22}H_{21}O_7Br$, m. p. 157.5–159°, (the hydroxy-group at C_1 replaced by bromine) prepared by Hartwell and Schrecker [3] by the action of phosphorus tribromide on podophyllotoxin. That the hydroxy-group is intact in our compound was finally proved by hydrogenation with Raney-nickel catalyst. This process, because simultaneous epimerization occurred in the alkaline medium, yielded picropodophyllin, identified by its melting point and by paper chromatography [4].

Degradation studies with the aim of locating the bromine substituent are in progress. Paper-chromatographic examination of the oxidation products seems to indicate that the bromine atom occupies one of the two free positions in ring A.

Picropodophyllin, which according to Hartwell *et al.*[3] is an epimer of I with the configuration *trans 1 : 2, cis 2 : 3, trans 3 : 4*, also consumes *ca.* 2 equivalents of bromine under similar conditions. The configurations of this and the foregoing bromoderivative are being examined. The peltatins (II, III) consume approximately 4 equivalents of bromine per molecule. This too is contrary to previous reports [1].



II R = OH α–Peltatin
III R = OCH_3 β–Peltatin

(Hartwell *et al.*)

Analyses by Mr. P. Hansen, Chemical Laboratory, University of Copenhagen, and by Chr. Jørgensen.

1. Hartwell, J. L. and Detty, W. E. *J. Am. Chem. Soc.* **72** (1950) 247.
2. Pepinsky, R. and Perdok, W. G., *Troisieme Congres International, Union Internationale de Cristallographie*, Paris 1954, p. 40. (Preliminary communication.)
3. Hartwell, J. L. and Schrecker, A. W. *J. Am. Chem. Soc.* **73** (1951) 2911.
4. Kofod, H. and Jørgensen, Chr. *Acta Chem. Scand.* **8** (1954) 941.

Received August 9, 1954.

Simplified Preparation of 6-Hydroxytropinone

POUL NEDENSKOV AND NIELS CLAUSON-KAAS

Centrallaboratoriet, Sadolin & Holmblad A/S, Copenhagen, Denmark

6-Hydroxytropinone (IV) has been prepared by Sheehan and Bloom [1] from 2,5-dimethoxy-2,5-dihydrofuran(I)through a four-step reaction (yield 7 %) and by Stoll, Becker and Jucker [2] from the corresponding ethoxy compound through a three-step reaction (yield probably about 15 %).

If an acid solution of dimethoxydihydrofuran is left standing for some time at room temperature, neutralized and added to a buffered solution of methylamine and acetonedicarboxylic acid, 6-hydroxytropinone is formed in a 55 % yield. Apparently malealdehyde (II), which is formed very rapidly by hydrolysis of dimethoxydihydrofuran, adds one mole of water whereby malaldehyde (III) is formed, which then condenses with methylamine and acetonedicarboxylic acid to hydroxytropinone.

Experimental. (Microanalyses by E. Boss.) *6-Hydroxytropinone (IV).* I[3] (0.65 g, 0.005 mole) was dissolved in hydrochloric acid (3 *N*, 12.5 ml) and the mixture left standing for 18 hours. The yellowish-brown solution was neutralized with a solution of sodium hydroxide (6 *N*, 6.2 ml) and added to a solution of acetonedicarboxylic acid (1.47 g, 0.01 mole), methylamine hydrochloride (0.68 g, 0.01 mole) and sodium acetate (3.4 g) in water (80 ml). The mixture (pH 4.3) was left standing for 2 days, whereby the acidity decreased to pH 4.9. Potassium carbonate (25 g) and sodium chloride (25 g) were dissolved in the light-brown reaction mixture and the solution continuously extracted with ether. The etheral extract was evaporated in a vacuum, leaving white crystals of hydroxytropinone embedded in a brown oil. By addition of a hot solution of picric acid (1.0 g) in ethanol (9 ml) the picrate of hydroxytropinone was obtained. The yield was 1.05 g (55 %), m. p. 199—200° (dec.) (Hershberg app., corr.), previously found [2] 199° (dec.). (Found: C 43.9; H 4.1; N 14.6. Calc. for $C_{14}H_{16}O_9N_4$ (384.3): C 43.8; H 4.2; N 14.6).

The free base was prepared from the picrate (250 mg) in the usual way and purified by sublimation. The yield of sublimed hydroxytropinone was 82 mg (82 %), m. p. 121—122°, previously found [1] 122.5—123.5°. (Found: C 61.7; H 8.5; N 8.8. Calc. for $C_8H_{13}O_2N$ (155.2): C 61.9; H 8.4; N 9.0).

1. Sheehan, J. C. and Bloom, B. M. *J. Am Chem. Soc.* **74** (1952) 3825.
2. Stoll, A., Becker, B. and Jucker, E. *Helv. Chim. Acta* **35** (1952) 1263.
3. Clauson-Kaas, N., Limborg, F. and Glens, K. *Acta Chem. Scand.* **6** (1952) 531.

Received August 14, 1954.