[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Synthesis of Dehydropodophyllotoxin Acetate

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Reaction of 2,3-dialkoxycarbonyl-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone with formaldehyde in the presence of alkali afforded a product which apparently consisted primarily of dehydropodophyllotoxin. Acetylation gave the acetate of dehydropodophyllotoxin. Hydrogenation gave 1-hydroxy-2-hydroxymethyl-3-carboxy-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-5,6,7,8-tetrahydronaphthalene lactone, from which an acetate was prepared.

Dehydropodophyllotoxin was isolated recently from podophyllin,[1] and has been prepared from podophyllotoxone and picropodophyllone by dehydrogenation.[2] The purpose of this paper is to report a direct synthesis of the acetate of this natural product III from keto-diester II. An earlier paper[3] described the unambiguous synthesis of II and presented data which confirmed the tetralone structure of this compound.

Compound II was hydrolyzed with dilute alkali and the warm solution was treated with formaldehyde. Acidification subsequently afforded crystalline material which decomposed in the temperature range 270–280°. The infrared spectrum of the material had new bands at 2.97 and 5.70 μ, indicating the presence of hydroxyl and lactone groups, respectively. Analysis and microscopic examination indicated that the material was a mixture, but attempts to separate pure components in the limited amount of material available were not promising. However it was found at a later time that the ultraviolet spectrum of the crystalline mixture was almost identical with the spectrum of dehydropodophyllotoxin.[2,4] In view of these facts it appears likely that the formaldehyde reaction product consisted primarily of dehydropodophyllotoxin. This conclusion was borne out by results in further experiments. Acetylation of the formaldehyde reaction product with acetic anhydride afforded pure dehydropodophyllotoxin acetate III, identical with the acetate of the natural product,[5] as determined by mixture melting point, ultraviolet spectra and infrared spectra (see Experimental section).

Further evidence bearing on the nature of the formaldehyde reaction product was obtained from hydrogenation experiments. Hydrogenation of that material in the presence of palladium–charcoal in acetic acid at 80° gave a hydroxylactone, m.p. 230–232°, from which an acetate, m.p. 175–177°, was prepared by treatment with acetic anhydride. Structure IV is assigned to the hydrogenation product on the basis of analytical figures obtained for it and for the acetate, and also for the following reasons. The infrared spectrum of the acetate of IV resembled that of dehydropodophyllotoxin acetate in having a single, intense peak at 5.65–5.68 μ, apparently due to both the naphthol acetate and phthalide groups, while the intense triplet in the 6.65–6.85 μ region, which is seen in the spectra of podophyllotoxin, picropodophyllin, and their desoxy compounds,[6] was absent in the spectra of IV and the acetate. If the acetate of IV possessed aromatic A and C rings and a saturated B-ring, the acetoxy and lactone bands would be expected to appear at about 5.80 and 5.60 μ, respectively. Furthermore, the ultraviolet spectrum of IV acetate was very similar to that of the closely related compound, 6,7-methylenedioxy-1-(3′,4′,5′-trimethoxyphenyl)-3-hydroxymethyl-5,6,7,8-tetrahydro-2-naphthoic acid lactone[6] (V) and dissimilar to ultraviolet spectra of compounds in this series having aromatic A and C rings and saturated B-ring, as in VI.

It is not surprising that IV was formed from dehydropodophyllotoxin under the conditions used here, since Schrecker and Hartwell obtained V by hydrogenation of β-apopicropodophyllin and dehydroanhydropicropodophyllin under the same conditions.[6] The apparent great tendency toward aromatization of the B-ring in these compounds helps to explain the formation of a fully aromatic system from the tetralone II under the mild conditions used here, although the exact course of the change is still in question. Possibly air-oxidation occurred during the formaldehyde reaction, or alternatively, a small fragment may have been eliminated from a highly substituted intermediate to yield, finally, the aromatic structure. The properties of II, especially the presence of a strong 6.01 μ ketone band in the infrared spectrum and the fact that hydrolysis and decarboxylation lead to 3-carboxy-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone[3,7] exclude the possibility that II, prepared as described earlier,[3] is a naphthol, rather than a tetralone, derivative. The transformation of II to a naphthol with formaldehyde and alkali contrasts strongly with 2,2-bis-methylol substitution of other 3-carboxy-1-tetralones unsubstituted at positions 2 and 4, as experienced by Campbell.[8] Whether or not the tendency toward aromatization also prevails in simpler tetralones of type II remains to be seen from model studies which are in progress.

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

(2) W. J. Gensler and F. Johnson, THIS JOURNAL, **77**, 3674 (1955).

(3) G. N. Walker, *ibid.*, **75**, 3390 (1953).

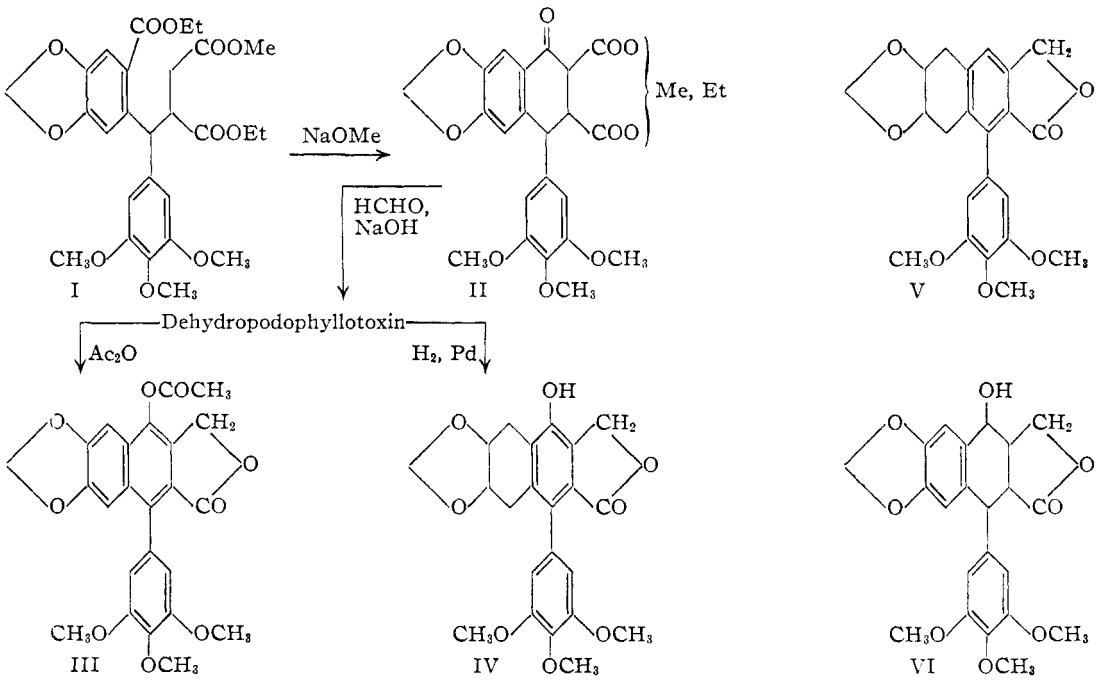
(4) D. H. Kofod very kindly furnished a copy of the ultraviolet spectral curve of dehydropodophyllotoxin (unpublished).

(5) Dr. W. J. Gensler very kindly supplied a sample of the acetate and informed me that its identity with Dr. H. Kofod's specimen of the same compound has been established.

(6) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **75**, 5916 (1953).

(7) *Cf.* W. J. Gensler, C. M. Samour and Shih Yi Wang, *ibid.*, **76**, 315 (1954), for an independent synthesis of this compound. Dr. Gensler compared samples of the methyl ester of this acid, prepared by the different routes, and reports that they are identical (private communication).

(8) K. N. Campbell, J. A. Cella and B. K. Campbell, *ibid.*, **75**, 4681 (1953).



In view of the fact that podophyllotoxin and picropodophyllin have been converted to III by methods[2] which exclude the reasonable possibility of alterations in the carbon ring skeleton, the present synthesis of III constitutes an independent demonstration of the correct structure, VI, for these compounds.

Experimental[9,10]

Methyl Ethyl Diester of 2,3-Dicarboxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone (II).—The Dieckmann cyclization of the required triester I was modified by using sodium methoxide in place of sodium, with some improvement in the yield of tetralone. A solution of 22.3 g. of triester I, prepared as described earlier,[3] in 100 ml. of dry toluene was added to a stirred suspension of dry sodium methoxide, freshly prepared from 1.1 g. of sodium, in 100 ml. of dry toluene. The mixture was refluxed and stirred for 2 hours. Water (200 ml.) and ethyl acetate (300 ml.) were added to the cooled suspension, and, after shaking the mixture, the layers were separated. The dark-colored organic solution was washed with 2 portions of 5% sodium hydroxide solution and 2 portions of water, and was dried over magnesium sulfate. Evaporation of the solvents and trituration of the gummy residue with methanol gave 4.2 g. (20%) of tan crystals, m.p. 214–220°. Recrystallization from methanol–ethyl acetate (Norit) afforded colorless crystals, m.p. 222–225°. The mixed m.p. with a sample of the compound prepared as described previously[3] was 221–225°. The infrared spectra of the samples (chf) were identical, having intense peaks at 5.79 and 6.01 μ and a weak band at 6.19 μ. The ultraviolet spectrum of the compound (chf.) had λ_{max} 242, 279, 304, 317, 350 and 363 mμ (log ϵ 4.38, 4.70, 4.06, 3.94, 3.55 and 3.57, respectively). This rather abnormal spectrum may be due in part to contributions from enolic forms of II. In view of the possibility that ester exchange may have occurred during cyclization, the previous assignment[3] of methyl and ethyl ester groups in this compound is now regarded as uncertain.

Hydrolysis of II and Reaction with Formaldehyde.—A mixture of 0.6 g. of II and 50 ml. of 2.5% sodium hydroxide solution was refluxed for a half-hour. Formaldehyde (1 ml.) was added, and the solution was warmed on a steam-cone for a half-hour. The cooled solution was diluted to 200 ml., filtered and acidified with dilute hydrochloric acid at ice temperature. The crystalline product was collected, washed with cold water and triturated with one portion of methanol. There was obtained 0.45 g. of slightly discolored crystals. Although this material could be recrystallized from methanol–ethyl acetate, a trace of color was retained, even when Norit was added. Attempts to purify the material by chromatography were not successful. The recrystallized material decomposed at 270–280°, after becoming brown gradually at temperatures above 240°. Microscopic examination revealed that two species of crystals (tiny needles and a few large rhombs) were present.

Anal. Calcd. for $C_{22}H_{18}O_8$: C, 64.4; H, 4.4. Found: C, 63.7; H, 4.7.

The material was not soluble in dilute alkali, and, unlike II, did not give a ferric chloride test[2] or react with 2,4-dinitrophenylhydrazine.[3] The infrared spectrum (Nujol) had peaks at 2.97, 5.70 and 6.16 μ. The ultraviolet spectrum (chf.) had λ_{max} 265, 323 and 357 mμ (log ϵ 4.63, 4.00 and 3.68, respectively) and a shoulder at 313 mμ (log ϵ 3.98). These values are very close to those reported[2] for dehydropodophyllotoxin.

Dehydropodophyllotoxin Acetate (III).—The product obtained in the preceding experiment (0.25 g.) was refluxed with acetic anhydride (30 ml.) for an hour. Evaporation of the excess reagent afforded crystalline material, trituration of which with methanol gave 0.18 g. of product, m.p. 261–265° dec.[11] Recrystallization from ethyl acetate gave colorless crystals, m.p. 265–268° dec. (reported[2] m.p. 259–260° dec.).

Anal. Calcd. for $C_{24}H_{20}O_9$: C, 63.71; H, 4.46. Found: C, 63.85; H, 4.50.

A sample of dehydropodophyllotoxin acetate received from Dr. W. J. Gensler was found in this Laboratory to have m.p. 263–266° dec. The mixed m.p. of the samples was 265–268° dec. The infrared spectra of the samples (chf.) were identical, with a strong carbonyl band at 5.65–5.68 μ. This band evidently represents both lactone and ester carbonyl groups, and cannot be resolved. The ultraviolet spectra (ethanol) were also identical, having maxima at 260, 313 and 350 mμ (log ϵ 4.74, 4.02 and 3.71, respectively).

(9) Melting points are corrected.

(10) Analyses were carried out by Dr. William C. Alford and his staff. Spectra were measured by Mrs. Iris Siewers and Mrs. H. F. Byers of the Instrument Laboratory.

(11) Melting points of this compound were taken on a Kofler hot-stage. Samples were heated rapidly to 240°, then 5° per minute to 250° and 3° per minute to the melting point. The m.p. (dec.) of this substance is strongly dependent upon rate of heating, as was also observed by Drs. Gensler and Kofod (private communication from Dr. Gensler).

Compound IV and Acetyl Derivative.—A mixture of 0.4 g. of the product from alkaline formaldehyde treatment of II, 1.0 g. of 10% palladium–charcoal catalyst, and 50 ml. of glacial acetic acid was shaken under hydrogen (40 lb.) at 80° for 1.5 hours. Filtration of the catalyst and evaporation of the solvent gave glassy material which crystallized partly in the presence of methanol. Trituration with this solvent afforded 0.2 g. of colorless crystals, m.p. 227–230°. Recrystallization from methanol-ether gave pure material, m.p. 230–232°.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 63.76; H, 5.35. Found: C, 63.98; H, 5.40.

Acetylation with refluxing acetic anhydride (2 hours), evaporation of excess reagent, and recrystallization from methanol gave colorless crystals, m.p. 175–176.5°. After drying the material at 80°, a hemihydrate was obtained.

Anal. Calcd. for $C_{24}H_{24}O_3 \cdot {}^1/_2H_2O$: C, 61.93; H, 5.41. Found: C, 61.83; H, 5.49.

After further drying at 100°, a weight loss of 1.4% (calcd.: 1.93%) was detected, and anhydrous material was obtained.

Anal. Calcd. for $C_{24}H_{24}O_3$: C, 63.15; H, 5.30. Found, C, 63.44; H, 5.25.

The infrared spectrum (chf.) had an intense peak at 5.65–5.68 μ. The ultraviolet spectrum (ethanol) had λ_{max} 294 mμ (log ϵ 3.58) with an inflection at 235 mμ (log ϵ 4.30) and a valley at 283 mμ (log ϵ 3.56), and was in all respects very similar to the spectrum of compound V.[6]

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Addition Reactions of 1-Methyl-2-naphthol with Unsaturated Ketones[1]

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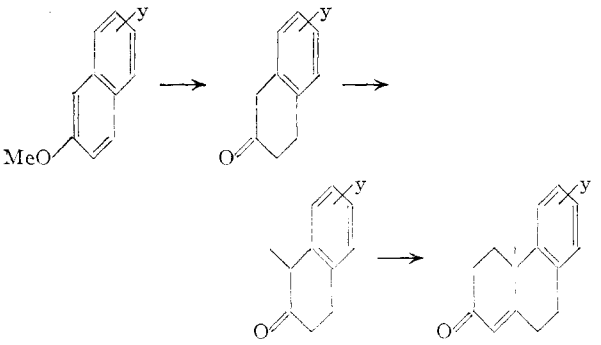
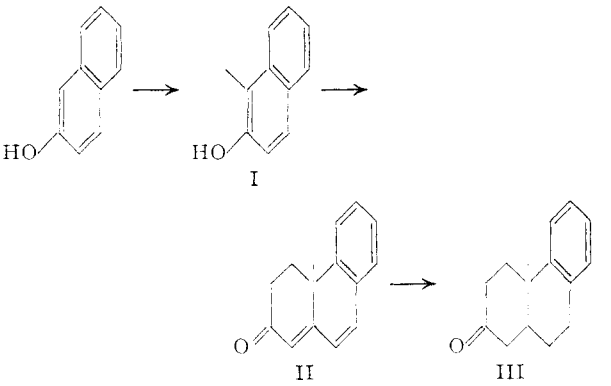
The base- and acid-catalyzed addition reactions of methyl vinyl, methyl β-chlorovinyl and methyl ethynyl ketones with 1-methyl-2-naphthol are described. The structure and stereochemistry of the products are elucidated. A new synthetic route to hydrophenanthrones is presented.

As part of their later total synthesis of the steroid nucleus,[3] Cornforth and Robinson introduced in 1946[4] a simple, attractive method for the conversion of a naphthol derivative into a hydrophenanthrone. Formally this process involved a reduction followed by two alkylations

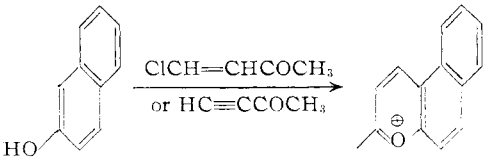


While the introduction of only one alkyl group at a time into the intermediate tetralone had caused some difficulty at first, this obstacle has been overcome by the utilization of a heterogeneous reaction process[5] and perhaps more interestingly by the prior transformation of the tetralone into its ene-amine.[6]

In connection with a contemplated terpene and/or steroid synthesis it was of interest to ascertain whether the above reaction sequence could be reversed, *i.e.*, the alkylations to precede the reduction. For this purpose the introduction of a butanone



side chain into 1-methyl-2-naphthol (I) came under consideration. Various cases of *ortho*-alkylation of phenols *via* their β-addition to α,β-unsaturated ketones are already on record. The acid-catalyzed version of this reaction is the usual synthetic route to benzopyrrylium salts, *e.g.*, by the use of methyl β-chlorovinyl[7] and methyl ethynyl ketones[8]



Base-catalyzed addition reactions, Michael reactions, have been reported also, *e.g.*[9,10]

(1) Part of this work was presented at the Symposium on the Chemistry of Natural Products, Technion, Haifa, Israel, June 28–29, 1955.

(2) National Science Foundation Predoctoral Fellow, 1953–1955.

(3) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(4) J. W. Cornforth and R. Robinson, *ibid.*, 676 (1946).

(5) C. A. Grob and W. Jundt, *Helv. Chim. Acta*, **31**, 1691 (1948).

(6) G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954); and private communicaton from Professor Stork.

(7) A. N. Nesmeyanov, N. Kochetkov and M. Rybinskaya, *Isvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.*, 479 (1953) [*C. A.*, **48**, 10015 (1954)]; *Doklady Akad. Nauk. S.S.S.R.*, **93**, 71 (1953) [*C. A.*, **49**, 3953 (1955)].

(8) A. W. Johnson and R. Melhuish, *J. Chem. Soc.*, 346 (1947).

(9) S. A. Miller and R. Robinson, *ibid.*, 1535 (1934); F. J. McQuillin and R. Robinson, *ibid.*, 586 (1941).

(10) N. K. Kochetkov, M. Rybinskaya and A. N. Nesmeyanov, *Doklady Akad. Nauk. S.S.S.R.*, **79**, 799 (1951) [*C. A.*, **46**, 6102 (1952)].