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AN INTRAMOLECULAR DIELS-ALDER REACTION. A SIMPLE SYNTHESIS OF γ-APOPICROPODOPHYLLIN.

L.H. Klemm and K.W. Gopinath
Department of Chemistry, University of Oregon,
Eugene, Oregon, U. S. A.

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γ-APOPICROPODOPHYLLIN (II) was isolated as a secondary degradation product resulting from dehydration of the naturally occurring, tumor-necrotizing compound podophyllotoxin.[1] II was found to be identical with a compound previously synthesized by Haworth and Richardson[2] by a multiple-step procedure, which was investigated further by Schrecker and Hartwell.[3] Interest in general syntheses of II and its analogous lignans of the 4-aryltetrahydronaphthalene type[4] has led us to investigate the possibility of effecting a simple intramolecular Diels-Alder condensation between two open-chain unsaturated Ar-C-C-C units (lignan building blocks), joined together at the γ-carbons in order to facilitate close proximity of these units. Needed to form II by such a scheme is

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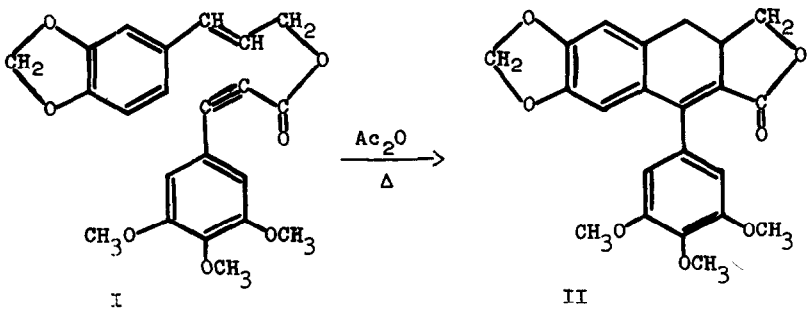
[1] A.W. Schrecker and J.L. Hartwell, J. Amer. Chem. Soc. 74, 5676 (1952).

[2] R.D. Haworth and T. Richardson, J. Chem. Soc. 348 (1936).

[3] A.W. Schrecker and J.L. Hartwell, J. Amer. Chem. Soc. 74, 5672 (1952).

[4] W.M. Hearon and W.S. MacGregor, Chem. Rev. 55, 957 (1955).



I II

the ester 3,4-methylenedioxycinnamyl 3,4,5-trimethoxyphenylpropiolate (I).

Methyl 3,4,5-trimethoxycinnamate (III) was prepared by esterification of the corresponding acid (Aldrich Chemical Co.) with methanolic hydrogen chloride. The crude dibromo ester (m.p. 105-108°, 87% yield), resulting from treatment of a chloroform solution of III with bromine, was dehydrobrominated with alcoholic potassium hydroxide to form 3,4,5-trimethoxyphenylpropiolic acid (IV), m.p. 141.5-142°, υ_{max} (nujol) at 1655 and 2140 cm.$^{-1}$, 37% yield from III (Found: C, 61.00; H, 5.26. Calc. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12). Treatment of IV with purified thionyl chloride at room temperature and then refluxing with equimolar amounts of pyridine and 3,4-methylenedioxycinnamyl alcohol (available from lithium aluminum hydride reduction of ethyl 3,4-methylenedioxycinnamate) gave I, m.p. 130-131°, υ_{max} (nujol) at 1690 and 2220 cm.$^{-1}$, 44% yield (Found: C, 66.78; H, 5.21. Calc. for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09). Refluxing I with acetic anhydride for six hours gave a 48% yield of racemic II, m.p. 252-253°, υ_{max} ($CHCl_3$) at 1750 cm.$^{-1}$ (no band at 2220), identical in m.p., mixture m.p., infrared and ultraviolet absorption

spectra with a sample of bona fide γ-apopicropodophyllin kindly furnished to us from the stock of Schrecker and Hartwell. Cyclization to II was also effected in smaller yield by slow evaporative distillation of I at 240° and 0.3 mm.

In a similar fashion was prepared the enynic ester 3,4-methylenedioxycinnamyl 3,4-dimethoxyphenylpropiolate (V), m.p. 142-143°, υ_{max} (nujol) at 1710 and 2240 cm.$^{-1}$, 36% yield (Found: C, 68.71; H, 5.19. Calc. for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95). This was cyclized with acetic anhydride to produce 1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-6,7-methylenedioxy-3,4-dihydro-2-naphthoic acid lactone (VI), m.p. 222-223°, υ_{max} ($CHCl_3$) at 1750 cm.$^{-1}$ (no band at 2240), (Found: C, 68.39; H, 5.02). As for II, VI has an NMR absorption band at 7.1τ (methylene protons at the 4-position) but none at 2.4τ (expected for the β-proton in the system ArCH=C-C=O,[5] which would result if Diels-Alder cyclization involved the ArC≡C- group acting as a diene and the C=C group acting as a dienophile). The cinnamyl cinnamate (dienic) esters corresponding to I and V,[6] on the other hand, show NMR bands at 2.4τ and none at 7.1τ .

Work on these and analogous cyclizations is continuing in our laboratory.

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[5] M.F. Zinn, T.M. Harris, D.G. Hill, and C.R. Hauser, J. Amer. Chem. Soc. 85, 71 (1963).

[6] Unpublished work from this laboratory.