Tetrahedron Letters No.43, pp. 3213-3216, 1964. Pergamon Press Ltd.
Printed in Great Britain.

ACTION OF N,N-DICYCLOHEXYLCARBODIIMIDE ON PHENYLPROPIOLIC ACIDS: SYNTHESIS OF DEHYDRO-OTOBAIN

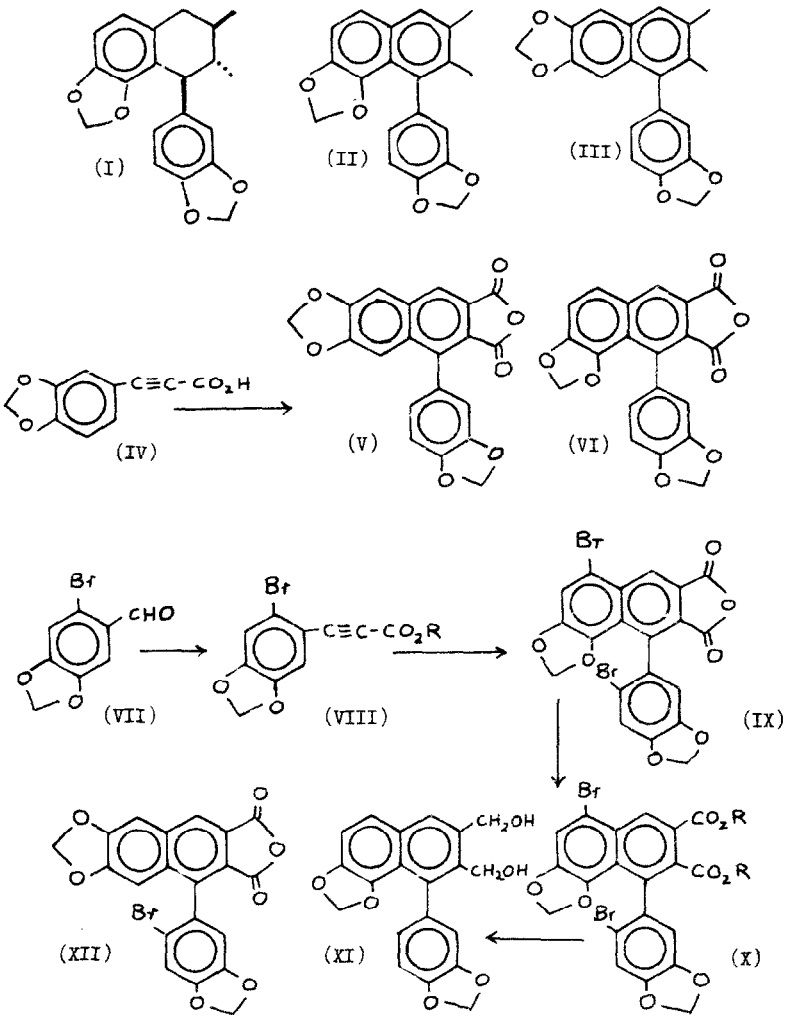
Derek Brown and Robert Stevenson

Department of Chemistry, Brandeis University, Waltham, Massachusetts

(Received 28 August 1964)

The constitution of the lignan, otobain(I)[1-3] rests largely on interpretation of nuclear magnetic resonance spectra and the fact that the dehydrogenation product, dehydro-otobain (II) differs from the known 2,3-dimethyl-6,7-methylenedioxy-1-(3',4'-methylenedioxyphenyl) naphthalene(III). We have sought confirmation of this by a synthesis of II.

The conversion of phenylpropiolic acid to the anhydride of 1-phenylnaphthalene-2,3,-dicarboxylic acid by the action of acetic anhydride was first observed by Michael and Bucher.[4] The early history of this reaction has been reviewed[5] and the generality demonstrated.[6] In particular, Haworth and Kelly[7] reported that piperonylpropiolic acid(IV), on heating under reflux with acetic anhydride, yielded 6,7-methylenedioxy-1-(3',4'-methylenedioxyphenyl)naphthalene-2,3-dicarboxylic anhydride(V). Subjection of 2-bromo-4,5-methylenedioxyphenylpropiolic acid(VIII, R=H) to similar treatment in the hope of obtaining the analogue (IX) gave no identifiable crystalline products. We have observed, however, that piperonylpropiolic acid(IV) under very mild conditions, namely treatment with dicyclohexylcarbodiimide in dimethoxyethane solution below 0°, undergoes anhydride formation and ring closure to yield V in excellent yield. Application of this procedure


(I)
(II)
(III)
C≡C-CO₂H
(IV)
(V)
(VI)
Br
CHO
(VII)
C≡C-CO₂R
(VIII)
(IX)
CH₂OH
CH₂OH
CO₂R
CO₂R
(X)
(XI)
(XII)

to VIII (R=H) has now permitted isolation of IX, readily converted to dehydro-otobain (II).

Bromination of piperonal readily gave 6-bromopiperonal[8](VII) which on treatment with triethyl phosphonoiodoacetate (the Wadsworth-Emmons acetylenic acid synthesis[9]) yielded ethyl 2-bromo-4,5-methylenedioxyphenylpropiolate(VIII, R=C_2H_5) [$C_{12}H_9O_4Br$, m.p. 100-101°, λ 4.53(C≡C), 5.90μ (ester)] . The corresponding 2-bromo-4,5-methylenedioxyphenylpropiolic acid(VIII,R=H) [$C_{10}H_5O_4Br$, m.p. 181-183°(dec.)[10], λ 3.4 broad (carboxyl-OH), 4.53(C≡C), 5.96μ (carbonyl >C=O)] obtained by alkaline hydrolysis, on treatment with N,N-dicyclohexylcarbodiimide in dimethoxyethane yielded two major products,a dibromo and a monobromo anhydride, separated by crystallization and purified by chromatography on silica gel.

The dibromoanhydride, obtained as yellow plates, is 5-bromo-7,8-methylenedioxy-1-(2'-bromo-4',5'-methylenedioxyphenyl) naphthalene-2,3-dicarboxylic anhydride(IX) [$C_{20}H_6O_7Br_2$, m.p. 255-258°, λ 5.45 and 5.63μ (anhydride carbonyl), C≡C absent] . Alkaline hydrolysis of IX gave the dicarboxylic acid (X,R=H), which can be reconverted to IX on heating. Esterification of the acid with diazomethane gave the dimethyl ester (X, R=CH_3) [$C_{22}H_{14}O_8Br_2$, m.p. 185-186°,λ 5.80μ(ester)] , whose nuclear magnetic resonance spectrum showed singlet peaks of correct intensity at δ 3.65 and 3.94 (two CH_3 groups as carbomethoxyls), 5.83 and 5.96 (two methylenedioxy groups) and 6.73, 6.98, 7.54 and 8.90 (four aromatic protons). Reduction of the ester (X, R=CH_3) with lithium aluminum hydride - aluminum chloride in ether solution proceeded with debromination and yielded the diol, 2,3-bishydroxymethyl-7,8-methylenedioxy-1-(3'4'-methylenedioxyphenyl)naphthalene (XI) [$C_{20}H_{16}O_6$, m.p. 200-203°, λ 3.0μ (hydroxyl), carbonyl absent] . Hydrogenolysis of the diol with 10% palladium-carbon catalyst in ethyl acetate solution gave 2,3-dimethyl-

7,8-methylenedioxy-1-(3',4'-methylenedioxyphenyl)naphthalene (m.p. and mixed m.p. 184-185°) identified as dehydro-otobain(II) by infrared comparison with authentic specimen[2](m.p. 185-187°).

The monobromoanhydride, obtained as pale yellow crystals from the carbodiimide reaction, is shown to be 6,7-methylenedioxy-1-(2'-bromo-4', 5'-methylenedioxyphenyl) naphthalene-2,3-dicarboxylic anhydride (XII) [$C_{20}H_9O_7Br$, m.p. 263-266°, λ 5.45 and 5.63 μ (anhydride carbonyl)] by its conversion (by the same pathway as IX→X→XI→II) to III(dehydro-epigalbacin)[2].

Satisfactory analyses have been obtained for all new compounds.

Acknowledgment. The award (to R. S.) of a research grant (G-14528) from the National Science Foundation is gratefully acknowledged.

References

1. R. Stevenson, Chem. Ind. (London), 270 (1962).

2. N. S. Bhacca and R. Stevenson, J. Org. Chem., 28, 1638 (1963).

3. T. Gilchrist, R. Hodges and A. L. Porte, J. Chem. Soc., 1780 (1962).

4. A. Michael and J. E. Bucher, Ber., 28, 2511 (1895).

5. A. W. Johnson, Acetylenic Compounds, Vol. II, p. 77, Arnold, London, (1950).

6. F. G. Baddar, J. Chem. Soc., 224 (1947) and subsequent papers in series.

7. R. D. Haworth and W. Kelly, J. Chem. Soc., 745 (1936).
F. G. Baddar, H. A. Fahim, and M. A. Galaby, J. Chem. Soc., 465 (1955) claim, without experimental detail, that the isomer (VI) can be "obtained in very small amount". In our hands, only V could be isolated by Haworth's procedure.

8. A. Oelker, Ber., 24, 2592 (1891).

9. W. S. Wadsworth and W. D. Emmons, J. Amer. Chem. Soc., 83, 1733(1961).

10. This melting-point point refers to the crude specimen, precipitated by acidification of the reaction mixture. There was a general lowering and divergence of m.p. on crystallization.