comparison of the infrared spectrum with that of the product obtained from the zinc chloride dehydration of spiro-[4,5]decan-1-ol according to the procedure of Mayer,[14] which has been shown to yield this olefin as the major product. The by-products present were 7% of a presumably rearranged acetate (determined by micro saponification), which exhibited a weak absorption band at 1740 cm.$^{-1}$, and weak bands appeared in both samples at 3070 and 743 cm.$^{-1}$ which possibly is indicative of olefinic material with a double bond exocyclic to one of the ring systems.

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF KANSAS, LAWRENCE, KANS., AND THE UNIVERSITY OF WISCONSIN, MADISON, WIS.]

A Stereospecific Synthesis of D(−)-Shikimic Acid[1,2]

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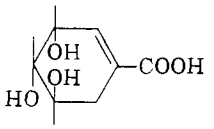
A stereospecific synthesis of *dl*-shikimic acid (I) from the Diels–Alder adduct of *trans,trans*-1,4-diacetoxy-1,3-butadiene (II) and methyl acrylate is reported. The optical resolution also was effected.

Naturally occurring shikimic acid was first isolated in 1885.[3] Fischer and Dangschat reported its structure to be I.[4] No total synthesis of shi-

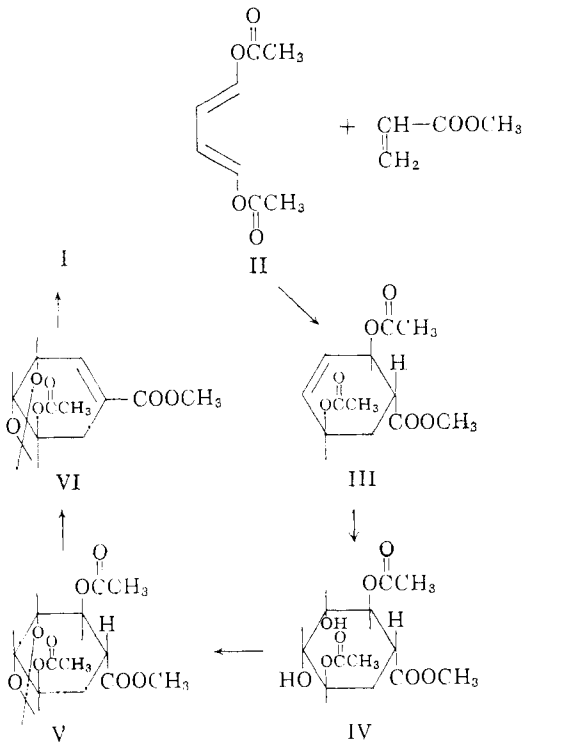


I

kimic acid had previously been described, although Grewe and co-workers had reported the synthesis of quinic acid[5] which Fischer and Dangschat had previously converted to shikimic acid.[6] This acid has been shown to be the biological precursor of phenylalanine, tyrosine and tryptophan,[7] which, in turn, are the parents of the majority of plant alkaloids. It is also involved in the biosynthesis of lignin,[8] one of the major constituents of wood, flavonoids,[9] and of other important aromatic compounds.[10] The enzymatic synthesis of shikimic acid from D-erythrose-4-phosphate and phosphoenolpyruvate was reported by Srinivasan, Katagiri and Sprinson.[11]

Since the acid has been shown to be an important link in aromatic biogenesis, it was desirable to devise a complete synthetic scheme whereby carbon-14 could be introduced into specific positions of the molecule. If this could be accomplished, the pathways of formation of various naturally occurring aromatic compounds could be followed.

The route to shikimic acid which proved successful was based on a Diels–Alder reaction of *trans,trans*-1,4-diacetoxy-1,3-butadiene[12,13] (II) with methyl acrylate to afford methyl 2β,5β-diacetoxy-3-cyclohexene-1α-carboxylate (III) in 93% yield. Although attempted hydroxylation of the double bond in III with potassium permanganate led to a mixture of compounds, *cis*-hydroxylation *anti* to the two acetoxy groups was successfully achieved by employing osmium tetroxide. The product obtained in this reaction was designated as methyl 2β,5β-diacetoxy-3α,4α-dihydroxycyclohexane-1α-carboxylate (IV). The stereochemical assignment of the carbomethoxy function at 1 differs from that proposed by McCrindle, Overton and Raphael,[2] but is in accord with the results of pyrolysis of the corresponding acetonide V.



(1) This work was supported in part by grants from the National Institutes of Health, National Science Foundation, and Research Corporation.

(2) This work was initially reported in a Communication to the Editor, *J. Am. Chem. Soc.*, **81**, 2909 (1959), and was later corroborated by R. McCrindle, K. H. Overton and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960), utilizing a similar synthesis.

(3) J. F. Eykman, *Rec. trav. chim.*, **4**, 32 (1885).

(4) H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **17**, 1200 (1934); **18**, 1211 (1935); **20**, 708 (1937).

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(6) H. O. L. Fischer and G. Dangschat, *Biochim. Biophys. Acta*, **4**, 199 (1950).

(7) B. D. Davis, *J. Biol. Chem.*, **191**, 315 (1951); *J. Bacteriol.*, **64**, 729, 749 (1952).

(8) F. F. Nord and W. J. Schubert, *Experientia*, **15**, 245 (1959).

(9) E. W. Underhill, J. E. Watkins and A. C. Neish, *Can. J. Biochem. and Physiol.*, **35**, 219 (1957).

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(11) P. R. Srinivasan, M. Katagiri and D. B. Sprinson, *J. Am. Chem. Soc.*, **77**, 4943 (1955).

(12) W. Reppe, G. Schlichting, K. Klager and T. Toepel, *Ann.*, **560** 1 (1948).

(13) H. H. Inhoffen, J. Heimann-Trosien, H. Muxfeldt and H. Kramer, *Chem. Ber.*, **90**, 187 (1957).

Pyrolysis of IV resulted not in the formation of the desired methyl 3-O-acetylshikimate but in the production of a mixture of aromatic hydroxy esters and acids. Since protection of the free hydroxyl groups was obviously necessary, the acetonide V was prepared.

Base-catalyzed elimination of acetic acid from V would be expected to occur readily if the C-1 hydrogen and the 2-acetoxy group were *trans* and diaxial to each other. If, on the other hand, a *cis* relationship existed, elimination should take place more readily on pyrolysis. In point of fact, V failed to undergo elimination or epimerization utilizing base under a variety of conditions, including treatment with potassium carbonate in refluxing benzene or toluene and potassium hydroxide or sodium ethoxide in ethanol. However, on pyrolysis V was converted to *dl*-methyl 3-O-acetylshikimate acetonide (VI) in 95% yield. Thus, the stereochemistry of V, and hence of IV and III, is assigned correctly as shown, in contrast to the interpretation of McCrindle, Overton and Raphael, who proposed the opposite configuration for the C-1 hydrogen (C-1 carboxy group) on the basis that elimination was found to occur (in unspecified yield) by treatment of V with sodium methoxide. These workers also reported, however, that at 290°, in the presence of magnesium oxide, V was converted to VI in 80% yield. The conditions of pyrolysis described herein differ only in that an evacuated tube was employed rather than an acetic acid scavenger.

On hydrolysis of the acetonide ester VI, *dl*-shikimic acid was obtained in 65% yield. Resolution was accomplished by means of (−)-α-phenylethylamine, with which D-(−)-shikimic acid (I) readily forms a sparingly soluble salt, which was identical in all respects with the salt of the naturally occurring compound.

Experimental

Methyl 2β,5β-Diacetoxy-3-cyclohexene-1α-carboxylate (III).—A solution of 3.87 g. (0.028 mole) of *trans,trans*-1,4-diacetoxy-1,3-butadiene and 2.0 g. (0.023 mole) of methyl acrylate (Eastman Organic Chemicals stabilized with hydroquinone) in 5 ml. of anhydrous xylene was heated slowly to reflux temperature. Small aliquots were removed from the reaction vessel every 5 hours and the optical extinction coefficient calculated at 250 mμ. After 37 hours the solution was concentrated *in vacuo* to give 5.9 g. of a brown oil. This oil showed no maximum in the 250 mμ region. The oil was chromatographed on a silicic acid column ultilizing chloroform as an eluant. On concentration of the eluate, 5.8 g. of a light brown oily substance was obtained. Distillation afforded 5.5 g. (93%) of methyl 2β,5β-diacetoxy-3-cyclohexene-1α-carboxylate which was obtained as a colorless liquid, b.p. 152–155° (3 mm.), $n^{25}D$ 1.4680, λ_{max}^{MeOH} 223 mμ (ε 1,000).

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.37; H, 6.32. Found: C, 56.24; H, 6.29.

Methyl 2β,5β-Diacetoxy-3-α,4α-dihydroxycyclohexane-1α-carboxylate (IV).—Eleven grams (0.043 mole) of methyl 2β,5β-diacetoxy-3-cyclohexene-1α-carboxylate (III) was dissolved in 50 ml. of anhydrous tetrahydrofuran and placed in a 1-l. flask. The flask was cooled to the temperature of a Dry Ice–trichloroethylene mixture. Eleven grams of anhydrous pyridine and 11 g. (0.043 mole) of osmium tetroxide were dissolved in 275 ml. of anhydrous tetrahydrofuran previously cooled to Dry Ice temperature. This solution was added to the flask and the mixture was stirred at −50° for 12 hours. The initial light yellow color of the mixture soon changed to dark brown, indicating the formation of an osmium complex. The brown osmium complex was precipitated by adding 400 ml. of anhydrous ether, the mixture filtered, and the residue washed with 50 ml. of anhydrous ether. The osmate ester was obtained in a yield of 20.4 g. (93%).

The osmate ester was cleaved by the method of Baran.[14] Pyridine (50 ml.) was added to the osmate ester. A solution of 19.6 g. (0.18 mole) of sodium bisulfite in 330 ml. of water and 300 ml. of pyridine was added to the pyridine solution of the osmate. On shaking the combined solutions, a dark brown oil separated and the solution became reddish-brown in color. After 1 hour, the solution was extracted with methylene chloride. The extract was washed with a small amount of water, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. A white powder remained, m.p. 166–167°, yield 6.13 g. (56%).

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.25; H, 6.22. Found: C, 49.04; H, 6.26.

Methyl 2β,5β-Diacetoxy-3α,4α-dihydroxycyclohexane-1α-carboxylate Acetonide (V).—Methyl 2β,5β-diacetoxy-3α,4α-dihydroxycyclohexane-1α-carboxylate (IV) (6.13 g., 0.021 mole) was dissolved in 150 ml. of anhydrous acetone. Anhydrous acetone saturated with dry hydrogen chloride was prepared and 5 ml. of this was added to the solution along with 5 g. of anhydrous calcium chloride. The reaction was allowed to proceed at room temperature for 36 hours with occasional shaking. At the end of this period, 10 g. of anhydrous sodium carbonate was added. The solvent was removed *in vacuo*. The residue was dissolved in a small volume of chloroform and chromatographed on Florisil. The column was eluted with chloroform and the eluate taken to dryness *in vacuo*. Crystallization from petroleum ether gave 3.23 g. (48%) of colorless needles, m.p. 143–144°.

Anal. Calcd. for $C_{15}H_{22}O_8$: C, 54.53; H, 6.71. Found: C, 54.52; H, 6.65.

***dl*-Methyl 3-O-Acetylshikimate Acetonide (VI).**—The acetonide of methyl 2β,5β-diacetoxy-3α,4α-dihydroxycyclohexane-1α-carboxylate (45 mg., 0.136 mmole) was placed in a Pyrex tube (8 mm. × 150 mm.) sealed at one end. This tube was evacuated to a pressure of 0.007 mm. and the tube completely sealed. It was then placed in an oven at 285° for 20 minutes after which it was removed and allowed to cool. The tube was opened and the contents dissolved in 3 ml. of chloroform. This solution was chromatographed using a silicic acid–chloroform column. The first band eluted was evaporated to dryness and yielded 35 mg. (95%) of a clear viscous oil.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.80; H, 6.66. Found: C, 58.20; H, 6.86.

Hydrolysis of *dl*-Methyl 3-O-Acetylshikimate Acetonide (VI) to *dl*-Shikimic Acid (I).—Fifty-four milligrams (0.2 mmole) of *dl*-methyl 3-acetylshikimate acetonide (V) in 5 ml. of 60% acetic acid was heated at 70° for 3 hours. After having cooled to room temperature, the solvent was removed *in vacuo*. The residue was dissolved in 8 ml. of 0.1 *N* alcoholic sodium hydroxide and allowed to stand for 15 hours at room temperature. The free acid was recovered by the use of an IR-120 cation exchange columns yield 24 mg. (65%), m.p. 193–195°.

Anal. Calcd. for $C_7H_{10}O_5$: C, 48.27; H, 5.79. Found: C, 48.02; H, 5.52.

Resolution of *dl*-Shikimic Acid.—To 0.0568 g. (0.33 mmole) of *dl*-shikimic acid was added 0.0392 g. (0.32 mmole) of (−)-α-phenylethylamine. This mixture was dissolved in hot absolute ethanol and allowed to stand at room temperature overnight. The white needles which formed were recrystallized using 1:1 ethanol–ethyl acetate until constant rotation was obtained. The salt exhibited a specific rotation $[\alpha]^{28.5}D$ −125°. The salt of the naturally occurring shikimic acid had a specific rotation $[\alpha]^{29.0}D$ −123°. The same procedure was utilized using (+)-α-phenylethylamine and the enantiomorph obtained.

(14) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).