315. *A Stereospecific Total Synthesis of* D-(—)-*Shikimic Acid.*

By R. McCrindle, K. H. Overton, and R. A. Raphael.

The Diels–Alder adduct derived from *trans-trans*-1,4-diacetoxybutadiene and acrylic acid has been elaborated to D-(—)-shikimic acid. An alternative route is also discussed.

THE lævorotatory shikimic acid, first isolated from the fruits of *Illicum religiosum*,[1] was shown by Fischer and Dangschat[2] to possess the constitution and stereochemistry (I; R = R′ = R″ = H). Since then this acid has been experimentally established as a biogenetic key link in the elaboration of aromatic amino-acids[3] and lignin[4] *in vivo*, and

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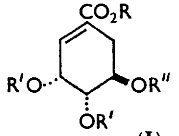
[1] Eykman, *Rec. Trav. chim.*, 1885, **4**, 32.

[2] Fischer and Dangschat, *Helv. Chim. Acta*, 1934, **17**, 1200; 1935, **18**, 1206; 1937, **20**, 705.

[3] Davis, in McElroy and Glass, " A Symposium on Amino Acid Metabolism," The Johns Hopkins Press, Baltimore, Maryland, 1955, p. 799.

[4] Acerbo, Schubert, and Nord, *J. Amer. Chem. Soc.*, 1958, **80**, 1990.

more recently its biosynthetic intermediacy has been invoked in a wider context, albeit on a speculative basis.[5]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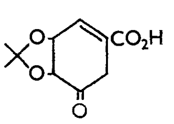
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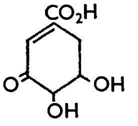
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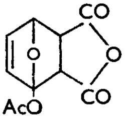
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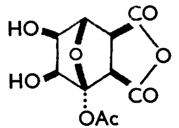
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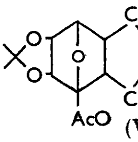
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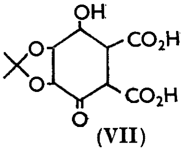
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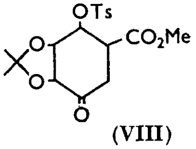
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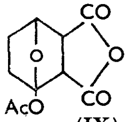
(IX)

Ts = p-$C_6H_4Me{\cdot}SO_2$

Consideration of its biological importance led us to undertake a synthesis of shikimic acid * in order to make possible the construction of a specifically labelled molecule and at the same time to confirm the constitution and stereochemistry revealed by Fischer and Dangschat's degradative work.

Our first approach envisaged the dehydroshikimic acid corresponding to (II) as an intermediary stage although, by analogy with the isomeric, naturally occurring dehydroshikimic acid[8] (III), we expected difficulties due to its potential ease of aromatisation. Hydroxylation by osmium tetroxide of the known adduct[9] (IV) of 2-acetoxyfuran and maleic anhydride afforded the diol (V), whose probable stereochemistry is assigned on the basis of precedents.[10] Treatment of this diol with acetone in the presence of anhydrous copper sulphate converted it smoothly into the crystalline isopropylidene derivative (VI). The next projected step was hydrolysis of the anhydride (VI) to the dicarboxylic acid (VII), to be followed by selective decarboxylation and subsequent β-elimination of the tosyloxy-ester (VIII) to the dehydroshikimic acid derivative (II). In practice we were unable to define conditions for the base-induced cleavage of the hemiketal acetate[11] (VI) which did not also result in aromatisation. Such a ring-opening was in fact accomplished in the course of model experiments with the related dihydro-adduct (IX) (see p. 1563) but only in circumstances which rapidly aromatised the isopropylidene derivative (VI).

The successful route to shikimic acid employed as starting material the Diels–Alder adduct (X) of *trans-trans*-1,4-diacetoxybutadiene[12] † and acrylic acid. Hydroxylation of the unsaturated acid (X) by osmium tetroxide furnished the *cis*-diol (XI; R = H), whose stereochemistry may be predicted with certainty on the basis of the Alder rules[13] and the assumption of hydroxylation at the less hindered face of the molecule (for a close stereochemical analogy see a synthesis of alloinositol[14]). With diazomethane the diol

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* The synthesis of quinic acid,[6] which had previously been transformed into shikimic acid,[7] already constitutes a formal synthesis of the latter.

† We are grateful to Professor R. Criegee, Karlsruhe, for making a quantity of this compound available to us in the initial stages of this work.

[5] Wenkert, *Experientia*, 1959, **15**, 165 and references cited therein; *Chem. and Ind.*, 1959, 906.

[6] Grewe, Lorenzen, and Vining, *Chem. Ber.*, 1954, **87**, 793.

[7] Fischer and Dangschat, *Biochim. Biophys. Acta*, 1950, **4**, 199.

[8] Salamon and Davis, *J. Amer. Chem. Soc.*, 1953, **75**, 5567.

[9] Clauson-Kaas and Elming, *Acta Chem. Scand.*, 1952, **6**, 560; Cava, Wilson, and Williams, *J. Amer. Chem. Soc.*, 1956, **78**, 2303.

[10] Woodward and Baer, *J. Amer. Chem. Soc.*, 1948, **70**, 1161; Kwart and Vosburgh, *ibid.*, 1954, **76**, 5400.

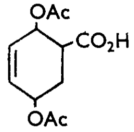
[11] Cf. Kritchevsky and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 184; Criegee, *Annalen*, 1948, **560**, 133; Heymann and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252.

[12] Reppe, Schlichting, Klager, and Toepel, *Annalen*, 1948, **560**, 1; Inhoffen, Heimann-Trosien, Muxfeldt, and Kramer, *Chem. Ber.*, 1957, **90**, 187.

[13] Alder, Schumacher, and Wolff, *Annalen*, 1950, **570**, 230.

[14] Criegee and Becher, *Chem. Ber.*, 1957, **90**, 2516.

(XI; R = H) gave the crystalline methyl ester which was converted into its isopropylidene derivative (XII; R = Me).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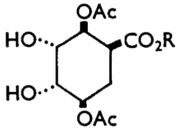
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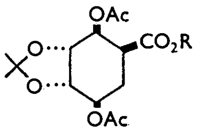
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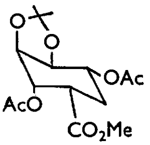
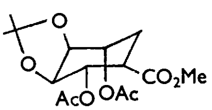

(XIIa)


(XIIb)

Base-promoted elimination of acetic acid could now be expected to occur in the desired manner, consequent upon activation provided by the methoxycarbonyl group.[15] Additionally, of the two chair conformations, (XIIa and b), which the ester can adopt, the former, preferred on the basis of non-bonded interactions, also affords the opportunity for *trans*-diaxial elimination.[16] Although the desired elimination could be effected partially by the conventional procedure (see p. 1565), protracted experimentation established that it could be made to occur in 80% yield by heating the diacetate (XII; R = Me) with magnesium oxide at 290°. When heated alone at 450°, this compound was recovered unchanged in quantitative yield. The racemate of the unsaturated monoacetate (I; R = Me, R' + R' = $>$CMe$_2$, R'' = Ac) obtained in this way crystallised when seeded with the (—)-form;[2] the ultraviolet and infrared film spectra of the two compounds were identical. Hydrolysis of the (±)-form afforded (±)-shikimic acid, m. p. 191—192°, whose ultra-violet and infrared (KCl disc) spectra were virtually identical with those of the natural acid.* Attempts to resolve the (±)-acid with a number of alkaloids were unsuccessful because of unfavourable solubility relationships. A satisfactory resolution was eventually effected on the triacetate (I; R = H, R' = R'' = Ac) *via* its quinine methohydroxy-salt whence the salt of (—)-tri-*O*-acetylshikimic acid, identical (m. p., mixed m. p., $[\alpha]_D$, ultraviolet and infrared spectra) with material prepared from natural shikimic acid, was obtained. Hydrolysis afforded D(—)-shikimic acid, identified by the same criteria with the naturally occurring material.

EXPERIMENTAL

M. p.s were taken on the Kofler block; $[\alpha]_D$ are in MeOH. Ultraviolet absorption spectra were determined for EtOH solutions with the Unicam S.P. 500 spectrophotometer, infrared spectra with the Perkin-Elmer 13 (by Dr. G. Eglinton and his colleagues) and the Infracord Spectrophotometer. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates. Chromatographic alumina was prepared and standardised by Brockmann's method.[18] Light petroleum refers to the fraction of b. p. 60—80° unless otherwise stated.

3-*Acetoxy*-3,6-*epoxy*-4,5-*dihydroxycyclohexane*-1,2-*dicarboxylic Anhydride* (V).—The adduct[9] (IV) (950 mg.; m. p. 138—140°) in dry redistilled dioxan (20 ml.) was added to osmium tetroxide (1 g.) in dry ether (10 ml.) and kept at room temperature for 20 hr. Excess of hydrogen sulphide was passed into the suspension, the osmium sulphide was filtered off after 4 hr. and extracted with warm ethyl acetate (3 × 10 ml.), and the filtrate and washings were combined. Removal of solvent afforded the anhydride (V) as a wax (1·08 g.), which was not further purified.

3-*Acetoxy*-3,6-*epoxy*-4,5-*isopropylidenedioxycyclohexane*-1,2-*dicarboxylic Anhydride*.—The above anhydride (1·08 g.), dissolved in dry acetone (40 ml.), was shaken with anhydrous copper sulphate (8 g.) for 80 hr. Separation of the copper sulphate and removal of acetone from the filtrate left a white residue, which was partly (350 mg.) insoluble in cold benzene (unchanged diol). Rapid filtration of the benzene extract through silica (20 g.) furnished on removal of solvent the *isopropylidene derivative* (VI) (755 mg.), needles (from benzene–light petroleum), m. p. 227—228° (Found: C, 52·1; H, 4·55. $C_{13}H_{14}O_8$ requires C, 52·35; H, 4·75%).

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* While the work here described was nearing completion, the synthesis of (±)-shikimic acid by an essentially identical route was disclosed in the form of a preliminary communication.[17]

[15] Linstead, Owen, and Webb, *J.*, 1953, 1211, 1218, 1225.

[16] Barton, *J.*, 1953, 1027.

[17] Smissman, Suh, Oxman, and Daniels, *J. Amer. Chem. Soc.*, 1959, **81**, 2909.

[18] Brockmann, *Ber.*, 1941, **74**, 73.

Attempted Cleavage of the Hemiketal Acetate (VI) *and its Derivatives.*—(*a*) The anhydride (10 mg.) in dry "AnalaR" pyridine (2 ml.) was kept at (i) 20° for 16 hr., (ii) 100° for 2 hr., and (iii) reflux for 5 hr. Removal of solvent in each case afforded a quantitative recovery of starting material.

(*b*) The anhydride (45 mg.) was kept with triethylamine (2 ml.) and methanol (3 ml.) at 20° for 3 days. Removal of solvent and treatment with ethereal diazomethane afforded the dimethyl ester corresponding to starting material.

(*c*) The *dimethyl ester* [needles from ethyl acetate–light petroleum; sublimed for analysis at 0·1 mm.; m. p. 206—207° (Found: C, 52·25; H, 5·55. $C_{15}H_{20}O_9$ requires C, 52·3; H, 5·85%)] (prepared from 300 mg. of anhydride) was dissolved in methanol (5 ml.) and treated with an excess of ethereal diazomethane for 3 days at 20°, in an attempt to bring about acetolysis (see Bredereck *et al.*[19]). The residue obtained on removal of solvents formed needles (from methanol), m. p. 127—128° (235 mg.) (Found: C, 52·45; H, 5·6; OAc, 17·25; OMe, 12·85. $C_{15}H_{20}O_9$ requires C, 52·3; H, 5·85; OAc, 18·0; OMe, 12·5%), and was an isomeric *dimethyl ester* (ultraviolet and infrared spectra). (For an analogy see Bergmann and Sprinzak [20].)

(*d*) The first dimethyl ester (98 mg.) in acetone (50 ml.) was treated with 0·02N-hydrogen chloride in acetone (0·5 ml.) for 16 hr. at 20°. Neutralisation with 0·01N-sodium hydroxide, removal of solvents, and extraction with ethyl acetate gave back starting material quantitatively.

(*e*) The dried disodium salt (from 95 mg. of anhydride), suspended in dry methanol (30 ml.), was refluxed with sodium methoxide (2 mol.) in methanol for 4 hr. Neutralisation with 0·02N-hydrochloric acid, removal of solvents, and extraction with ethyl acetate afforded a gum (63 mg.) which had almost continuous absorption in the ultraviolet region between 220 and 290 mμ and an intense band near 1600 cm.$^{-1}$ in the infrared spectrum.

When a suspension of the sodium salt was stirred with the same proportion of sodium methoxide in methanol as above for 7 days at 20°, a product having almost identical spectral properties was obtained. Methylation and chromatography over activated alumina (grade 5) afforded only fractions exhibiting marked aromatic absorption in the infrared region.

(*f*) The disodium salt was unaffected after it had been stirred in 1 : 1 methanol–dimethylformamide with an excess of ethereal diazomethane for 3 days.

(*g*) The anhydride (90 mg.) was treated at 20° with sodium hydroxide (36 mg.; 3 mol.) in absolute ethanol (30 ml.). The product obtained after 12 hr. showed $\lambda_{max.}$ 218, 260, and 295 mμ and gave a blue-green colour with ferric chloride (compare protocatechuic acid).

(*h*) The diol (85 mg.), dissolved in a 2% solution of potassium hydroxide in ethanol (5 ml.), was kept at 50° for 45 min. Removal of solvent, dissolution of the residue in saturated aqueous ammonium sulphate, and continuous extraction with ethyl acetate afforded an oil (32 mg.), $\lambda_{max.}$ 255—260 (ε 5000) and 290—292 mμ (ε 2200).

3-*Acetoxy*-3,6-*epoxycyclohexane*-1,2-*dicarboxylic Anhydride* (IX).—The adduct (IV) (2·0 g.) in "AnalaR" ethyl acetate (50 ml.) was shaken with Adams catalyst (50 mg.) in an atmosphere of hydrogen until one mol. had been absorbed (10 min.). Removal of catalyst and solvent afforded the saturated *anhydride* (IX) (1·86 g.), needles (from ethyl acetate), m. p. 165—166° (Found: C, 52·8; H, 4·7. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·45%).

2-*Hydroxy*-5-*oxocyclohexanecarboxylic Acid.*—The above anhydride (IX) (1·25 g., 0·0055 mole) in aqueous potassium hydroxide (2·8 g., 0·05 mole, in 10 ml.) was heated on the steam-bath for 1 hr. The cooled solution was acidified, saturated with sodium chloride, and constantly extracted with ethyl acetate for 16 hr. The yellow oily residue remaining on removal of solvent afforded on trituration with chloroform the *monocarboxylic acid* named (510 mg.), hexagonal plates (from chloroform), m. p. 140—141° (Found: C, 53·3; H, 6·2. $C_7H_{10}O_4$ requires C, 53·15; H, 6·35%).

Treatment of this acid (340 mg.) in methanol (5 ml.) with an excess of ethereal diazomethane afforded the oily methyl ester (360 mg.). When this was kept with recrystallised toluene-*p*-sulphonyl chloride (600 mg.) in the minimum of dry pyridine, the corresponding *toluene*-p-*sulphonate* separated as prisms; these, when washed successively with water and ethyl acetate and dried (460 mg.), had m. p. 176—178° (Found: C, 55·35; H, 5·5. $C_{15}H_{18}O_6S$ requires C, 55·2; H, 5·55%).

The toluene-*p*-sulphonyloxy-ester (160 mg.) and 2,4-dinitrophenylhydrazine (100 mg.) were heated together in pyridine (3 ml.) on the steam-bath for 1·5 hr. The pyridine was removed

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[19] Bredereck, Sieber, and Kamphenkel, *Chem. Ber.*, 1956, **89**, 1169.

[20] Bergmann and Sprinzak, *J. Amer. Chem. Soc.*, 1938, **60**, 1998.

at 0·05 mm. and the residue in chloroform (15 ml.) filtered through bentonite–kieselguhr (4 : 1). The *dinitrophenylhydrazone* so obtained (40 mg.) furnished orange needles (from ethanol), m. p. 166—168°, $\lambda_{max.}$ 360 mμ (ε 18,800) (Found: C, 50·05; H, 4·1; N, 16·45. $C_{14}H_{14}O_6N_4$ requires C, 50·3; H, 4·2; N, 16·75%).

2,5-*Diacetoxycyclohex*-3-*enecarboxylic Acid* (X).—*trans-trans*-1,4-Diacetoxybutadiene [12] (2·0 g.), acrylic acid (freshly distilled; 2·0 g.) and quinol (100 mg.) were kept at 85—90° under nitrogen for 3 hr. Excess of unpolymerised acrylic acid was removed at 0·3 mm. and the residue extracted with warm benzene (2 × 30 ml.; polymer nearly insoluble). Addition of light petroleum to the concentrated benzene extract furnished the crystalline *adduct* (X) (1·55 g.; m. p. 142—143°), after removal of contaminating oil with cold ether. The ether washings afforded a further crop (230 mg.; m. p. 140—143°). The analytical specimen (leaflets from benzene–light petroleum) had m. p. 141—143° (Found: C, 54·6; H, 5·85. $C_{11}H_{14}O_6$ requires C, 54·55; H, 5·85%).

2,5-*Diacetoxy*-3,4-*dihydroxycyclohexanecarboxylic Acid* (XI).—The adduct (X; R = H) (1·0 g.) in dry ether (50 ml.) was added to osmium tetroxide (1·0 g.) in dry ether (10 ml.) and dry pyridine (6 ml.). After 5 days in the dark at 20° the osmate suspension was saturated with hydrogen sulphide; filtration and removal of solvent left a dark oil (160 mg.) which, on treatment with benzene, afforded crystalline diol (30 mg.) and starting material (110 mg.). The hard residual cake of solid was readily broken up on addition of methanol (15 ml.), and the suspension again saturated with hydrogen sulphide. Working up in the usual way yielded the major amount of (dark, gummy) diol (690 mg.). Sublimation 200—210° (bath-temp.)/0·8 mm. then afforded the pure *diol* (XI; R = H) (310 mg.) in prisms, m. p. 225—226° (Found: C, 48·0; H, 5·8. $C_{11}H_{16}O_8$ requires C, 47·8; H, 5·85%).

This acid was converted quantitatively by ethereal diazomethane into the *methyl ester*, plates (from benzene–light petroleum), m. p. 161—163° (Found: C, 49·75; H, 6·1. $C_{12}H_{18}O_8$ requires C, 49·65; H, 6·25%).

Hydrogen chloride was passed for 15 sec. into the methyl ester (480 mg.) dissolved in dry acetone (50 ml.). After 16 hr. the solution was shaken with excess of solid sodium hydrogen carbonate for 10 min. Removal of solid and solvent, chromatography of the residue in benzene over activated alumina (15 g.; grade V) and elution with benzene afforded *methyl* 2,5-*diacetoxy*-3,4-*isopropylidenedioxycyclohexanecarboxylate* (XII; R = Me) (280 mg.) and, by elution with ethyl acetate, unchanged diol (170 mg.). Sublimed (130°/0·1 mm.) for analysis, the product (XII; R = Me) formed prisms, m. p. 146—147° (Found: C, 54·65; H, 6·6. $C_{15}H_{22}O_8$ requires C, 54·55; H, 6·7%).

The derivative (XII; R = Me) was more conveniently and profitably prepared as follows: The adduct (X) (900 mg.) was kept with osmium tetroxide (1·0 g.) in dry ether (20 ml.) for 3 days. Methanol (30 ml.) was added, and the suspension saturated with hydrogen sulphide. Removal of solid and solvent left the diol (1·1 g.) as a dark oil. Conversion into the diacetate (XII; R = Me) without isolation of intermediates afforded the compound (740 mg., 59%) with m. p. 145—147°.

Isopropylidene Derivative (I; R = Me, R′ + R′ = $>$CMe$_2$, R″ = Ac) *of* (±)-*Methyl Shikimate Acetate*.—(*a*) The diacetate (XII; R = Me) (100 mg.) was mixed with magnesium oxide (500 mg.) and kept at 290°/760 mm. for 2 min. The volatile material was then distilled off at 10 mm., the distillate melted and allowed to run back into the magnesium oxide, and the sequence repeated twice.

The colourless oil (65 mg.) so obtained crystallised when seeded with the ester (I; R = Me, R′ + R′ = $>$CMe$_2$, R″ = Ac) prepared from naturally derived shikimic acid (m. p. 75—76°) and had m. p. 68—72° (mixed m. p. 66—70°). The ultraviolet spectrum ($\lambda_{max.}$ 211—212 mμ; ε 9000) and infrared spectrum (film) were virtually identical with those of the natural material, and proved the absence of aromatic products (Found: C, 58·1; H, 6·65. Calc. for $C_{13}H_{18}O_6$: C, 57·75; H, 6·7%).

(*b*) 10 mg. portions of the diacetate (XII; R = Me) sublimed unchanged when heated under the following conditions: (i) 150° at 0·1, 15, or 760 mm.; (ii) 300° and 450° at 0·1 or 760 mm. in nitrogen; (iii) intimately mixed with five times its weight of powdered soft glass and kept at 300°/0·1 mm. in nitrogen.

(*c*) Heating at 560°/0·1 mm. in nitrogen afforded a colourless oil which was judged by its infrared spectrum to be aromatic.

(*d*) Heated at 290°/15 mm., mixed with five times its weight of magnesium oxide and suspended in silicone fluid, the diacetate (XII; R = Me) afforded the desired product (20—30%) which could be separated from contaminating silicone fluid only with difficulty.

Base-induced Elimination of Acetic Acid from the Diacetate (XI; R = Me).—The diacetate (50 mg.) was kept in dry methanol (10 ml.) containing dissolved sodium (40 mg.) at 20° for 3 days. Distilled water (3 ml.) was then added and after 6 hr. the solution was passed through an ion-exchange column of Amberlite I.R.-120 (H). The resulting oil, which failed to crystallise, was methylated and acetylated and the oily product (78 mg.) adsorbed on activated alumina (3 g.; grade V). Benzene eluted a fraction (22 mg.) which, on hydrolysis, afforded (±)-shikimic acid identical with material obtained as below.

(±)-*Shikimic Acid.*—The isopropylidenedioxy-ester (I) (90 mg.) obtained as in (*a*) above was kept in 1 : 4 aqueous acetic acid (5 ml.) for 26 hr., the solvents were removed at 0·1 mm., and the residue was treated with 1 : 4 aqueous-methanolic 0·02N-potassium hydroxide for 16 hr. at 20°. Filtration through an acidic ion-exchange resin [Amberlite I.R.-120 (H); 10 g.] afforded an oil (40 mg.) which crystallised on trituration with methanol–ethyl acetate as needles, m. p. 191—192°; the mixed m. p. with natural (−)-shikimic acid of m. p. 190—191° was 188—191°. It had $\lambda_{\text{max.}}$ 212 mμ (ε 8200) [(−)-shikimic acid has $\lambda_{\text{max.}}$ 213 mμ (ε 8900)]. The infrared spectrum (KCl disc) showed very minor differences in the fingerprint region from that of (−)-shikimic acid.

Attempted Resolution of (±)-*Shikimic Acid.*—(*a*) (±)-Shikimic acid (20 mg.) and (+)-quinidine (14 mg.; 0·8 equiv.) were dissolved in the minimum of methanol. When the solution was seeded with (+)-quinidine (−)-shikimate {(m. p. 215—218°; $[\alpha]_D$ +133° (*c* 0·51)} and kept for 50 hr., crystals {3·7 mg.; m. p. 194—195°; mixed m. p. 170—200°; $[\alpha]_D$ −50° (*c* 0·25); infrared spectrum (KCl disc) virtually identical with that of (±)-shikimic acid} separated which were apparently shikimic acid resolved to the extent of about 20%. $[\alpha]_D$ was not substantially improved by further crystallisation.

(*b*) (±)-Shikimic acid (23 mg.) and (−)-quinine methohydroxide (2 ml. of a standard solution containing 1·01 mol. of the base prepared and estimated by the method of Major and Finkelstein [21]) were taken to dryness and the residue crystallised three times from methanol–ethyl acetate, affording needles (32 mg.), m. p. 205—206°, $[\alpha]_D$ −144° (*c* 0·68). Further crystallisation or change of solvent did not improve this $[\alpha]_D$. The salt prepared from (−)-shikimic acid had m. p. 200—202°, $[\alpha]_D$ −211° (*c* 0·37) and mixed m. p. 195—202°.

Resolution of (±)-*Tri*-O-*acetylshikimic Acid.*—(±)-Shikimic acid (56 mg.) was kept with acetic anhydride (1 ml.) and pyridine (1 ml.) for 16 hr. Removal of solvent afforded an oil (86 mg.) whose infrared spectrum (film) was essentially identical with that of naturally derived material. To this oil (86 mg.) in aqueous methanol (5 ml.) was added one equivalent of (−)-quinine methohydroxide in water (see above). Removal of solvent left a colourless froth (164 mg.) which was dissolved in methanol (3—4 drops), ethyl acetate (5 ml.), and ether (2—3 ml.); an amorphous fraction (33 mg.) (A) separated. Addition of ether (3—4 ml.) to the filtrate gave crystals (38 mg.) (B), forming long plates, m. p. 189—191°, $[\alpha]_D$ −189° (*c* 0·35 in MeOH), from methanol–ethyl acetate; after two further crystallisations, these had m. p. 189—191°, $[\alpha]_D$ −200° (Found: C, 62·45; H, 6·6; N, 4·65. $C_{34}H_{42}O_{10}N_2,CH_3{\cdot}OH$ requires C, 62·75; H, 6·85; N, 4·2%); the m. p. was not depressed on admixture with naturally derived material. The latter, after three crystallisations, had m. p. 190—192°, $[\alpha]_D$ −203° (*c* 0·38).

The mother-liquors from (B) afforded a further quantity (36 mg.) of semi-crystalline solid (C) and a gum (48 mg.) (D). Fractions (A) and (D), after passage through Amberlite I.R.-120 (H), furnished essentially tri-*O*-acetylshikimic acid (infrared spectrum) of $[\alpha]_D$ respectively −60° and +45°.

(−)-*Shikimic Acid.*—The above salt (B) (40 mg., $[\alpha]_D$ −200°) was kept with potassium hydroxide (220 mg.) in 1 : 4 aqueous methanol (10 ml.) for 16 hr. and the solution filtered through Amberlite I.R.-120 (H). Removal of solvent from the filtrate and crystallisation from methanol–ethyl acetate furnished substantially pure (−)-shikimic acid (8 mg.), m. p. 190—191°, $[\alpha]_D$ −161° (*c* 0·57). The mixed m. p. with natural shikimic acid {m. p. 190—191°; $[\alpha]_D$ −157° (*c* 0·94)] was 190—191°. The infrared spectra (KCl discs) of the two substances were superposable.

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[21] Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368.