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SYNTHESIS OF (±) MONTAGNETOL AND (±) ERYTHRIN

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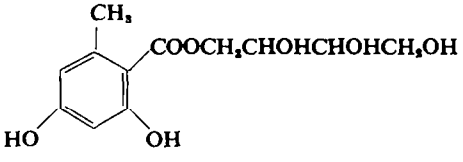
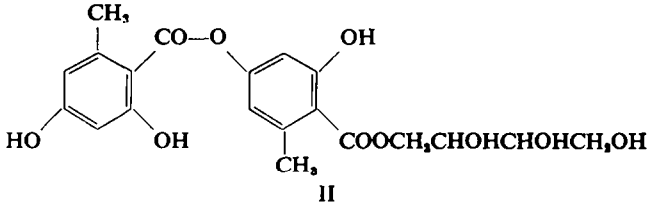
Abstract—Montagnetol and erythrin the main components of *Roccella montagnei* were earlier shown to be erythrityl esters of orsellinic acid and lecanoric acid respectively. The details of the structures have now been established by their syntheses involving the preparation of the esters of the carboxylic acids with *cis*-2-butene-1,4-diol and hydroxylating the ethylenic groups by means of Milas' reagent.

MONTAGNETOL (I) and erythrin (II) are the erythrityl esters of orsellinic acid and lecanoric acid respectively. These occur together in *Roccella montagnei* along with roccellic acid, lecanoric acid, orcinol and erythritol.[1] Erythrin has also been shown to be the chromogen of many lichens belonging to the *Roccella* genus (*e.g. Roccella tinctoria*) and also of certain others like *Lecanora tartarea, Dendographa leucophoea, Aspicilia calcarea, Parmelia olivetorum* and *Evernia furfuracea*.[2]

Montagnetol is the only example of a simple orsellinic acid derivative found in lichens. Its structure was established by Rao and Seshadri on the basis of degradative studies.[3] The structure of erythrin was also established by degradation reactions[4,5] and by the synthesis of its trimethyl ether.[4] These structures of montagnetol and erythrin have now been confirmed by their syntheses involving the building up of the sugar alcohol chain on orsellinic acid and lecanoric acid respectively.



I



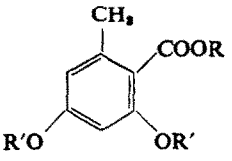
II

Orsellinic acid dibenzyl ether (III), obtained from methyl orsellinate by benzylation and subsequent ester hydrolysis, was used as the starting material for the

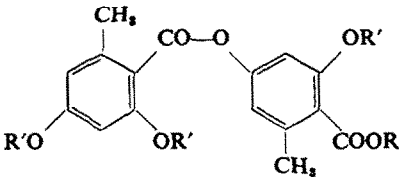
[1] V. S. Rao and T. R. Seshadri, *Proc. Ind. Acad. Sci.* (A)**12**, 466 (1940); *Ibid.* (A)13, 199 (1941).
[2] A. G. Perkin and A. G. Everest, *The Natural Organic Colouring Matters*. Longmans Green, London (1918).
[3] V. S. Rao and T. R. Seshadri, *Proc. Ind. Acad. Sci.* (A)**15**, 18 (1942).
[4] Y. Sakurai, *J. Pharm. Soc. Japan* **61**, 45 (1941).
[5] V. S. Rao and T. R. Seshadri, *Proc. Ind. Acad. Sci.* (A)**16**, 23 (1942).

synthesis of montagnetol. On condensation with *cis*-2-butene-1,4-diol (1:1) in dioxan solution in the presence of N,N′-dicyclohexylcarbodiimide, it afforded the ester (IV) which on *cis*-hydroxylation using Milas' reagent[6] (H_2O_2 in *t*-butanol with OsO_4 as catalyst), was converted into montagnetol dibenzyl ester (V). The protecting benzyl groups were then removed by catalytic hydrogenation over Pd–C. The product obtained, however, could not be crystallized. The presence of montagnetol was detected by paper chromatography using (i) water saturated with phenol and (ii) water–acetone mixture (9:1) as the irrigating solvents. The isolation of pure montagnetol from the crude sample was carried out using thick paper chromatography. The pure product, m.p. 153–154°, was optically inactive and showed the same behaviour as authentic (±) montagnetol on co-chromatography and mixed chromatography; the mixed m.p. was undepressed. The synthetic and authentic samples also had identical in UV and IR spectra. The synthesis conclusively proves that the primary alcoholic group of erythritol is involved in the esterification.

Similarly erythrin has now been synthesized by building up the sugar alcohol chain on lecanoric acid. Tricarbethoxylecanoric acid[7] (VI), prepared by the carbethoxylation of lecanoric acid, was condensed with *cis*-2-butene-1,4-diol, using N,N′-dicyclohexylcarbodiimide. The product (VII), after purification, was hydroxylated to VIII using Milas' reagent[6] and the latter decarbethoxylated. The final product, m.p. 165–166° was optically inactive. It was identical with a natural sample of (+)-erythrin in UV and IR spectra. Further confirmation was obtained by the formation of its hexaacetate, which gave the same UV spectrum as the acetate of natural erythrin.



III, R = H; R′ = C_7H_7
IV, R = $CH_2{\cdot}CH = CH{-}CH_2OH$; R′ = C_7H_7
V, R = $-CH_2CHOHCHOHCH_2OH$; R′ = C_7H_7



VI, R = H; R′ = C_2H_5OCO-
VII, R = $-CH_2{\cdot}CH = CH{\cdot}CH_2OH$; R′ = C_2H_5OCO-
VIII, R = $-CH_2{\cdot}CHOH{\cdot}CHOH{\cdot}CH_2OH$; R′ = C_2H_5OCO-

EXPERIMENTAL

Synthesis of montagnetol (I)

Di-O-benzylorsellinic acid (III). It was prepared by complete benzylation of methyl orsellinate using benzyl chloride and acetone–K_2CO_3 and subsequent hydrolysis of the methyl ester with 5% alc. KOH.

[6] N. A. Milas and S. Susman, *J. Amer. Chem. Soc.* **58**, 1302 (1936).
[7] Y. Asahina and I. Yosioka, *Ber. Dtsch. Chem. Ges.* **70**, 200 (1937).

It crystallized from benzene as tiny colourless needles, m.p. 106°. (Found: C, 75·8; H, 6·2. $C_{32}H_{40}O_4$ requires: C, 75·8; H, 5·7%.)

Condensation of III *with 2-butene-1,4-diol.* A mixture of orsellinic acid dibenzyl ether (2·0 g; 1 mole), 2-butene-1,4-diol (K & K Labs., Inc. New York) (0·5 g; 1 mole), dicyclohexylcarbodiimide (1·2 g) and dioxan (30 ml) was stirred (16 hr) at room temp. The solid dicyclohexylurea (1·3 g) was filtered off and washed with a little dioxan, m. p. 225–227°. The solvent was removed from the filtrate by distillation under reduced press and the residue dissolved in ether. The ether solution was washed with 5% $NaHCO_3$ aq (5 × 10 ml) and water, dried over Na_2SO_4 and the solvent removed. The sticky residue (1·9 g) was used in the next stage of hydroxylation.

The condensation product was treated with 3,5-dinitrobenzoyl chloride and pyridine. The 3,5-dinitrobenzoate crystallized as colourless plates from benzene–light petroleum, m.p. 74–76°. (Found: C, 64·7; H, 4·6. $C_{32}H_{36}O_{10}N_2$ requires: C, 64·3; H, 4·3%.)

Hydroxylation of the condensation product. A mixture of the condensation product (1·5 g), H_2O_2 reagent[6] (6·3% solution in t-butanol; 5·8 ml) and osmium tetroxide solution in t-butanol (0·5 ml) was allowed to stand at room temp for 48 hr. The mixture was distilled to remove t-butanol; the residue was macerated with water and after decanting off the aqueous solution, it was dissolved in ether, the ether extract washed with water and dried over Na_2SO_4. The residue obtained after removal of the solvent, was used for debenzylation.

The hydroxylation product was converted into its 3,5-dinitrobenzoate which crystallized from AcOEt–light petroleum as colourless fine needles, m.p. 105°. (Found: 54·6; H, 3·3. $C_{46}H_{32}O_{22}N_6$ requires: C, 54·1; H, 3·1%.)

Debenzylation of V. Pd–C (1·0 g; 5%) in AcOEt was saturated with H_2 gas with stirring and V (1·0 g) in AcOEt (50 ml) was then added. After the absorption of H_2 had ceased, the reaction mixture was filtered and the residue washed with AcOEt. The solvent was removed from the solution. The dark red residue gave a violet ferric reaction. The presence of montagnetol in the residue was indicated by co-chromatography with authentic montagnetol, using (i) water saturated with phenol and (ii) water-acetone mixture (9:1) as the irrigating solvents. The chromatograms were developed with alc. $FeCl_3$ (R_f = 0·72 and 0·75 respectively); the impurity did not move in these solvent systems. The dark red residue, however, could not be purified by crystallization to yield pure montagnetol.

The isolation of the pure compound by paper chromatography was next carried out, using Whatman 3 M.M. paper and aqueous acetone (9:1) as the irrigating solvent. The zone, in which pure montagnetol was detected was cut and extracted with acetone. The solvent was removed from the acetone extract and the sticky residue crystallized from a mixture of AcOEt and light petroleum (2:1) when montagnetol was obtained as almost colourless cubes, m.p. 153–154°. It was optically inactive and showed the same chromatographic behaviour as authentic (±) montagnetol. UV absorption: λ_{max}^{MeOH} 262, 298 mμ (log ε 3·8, 4·2); λ_{min}^{MeOH} 237, 283 mμ (log ε 3·6, 3·7). For authentic (±) montagnetol, λ_{max}^{MeOH} 262, 298 mμ (log ε 3·9, 4·3); λ_{min}^{MeOH} 237, 282 mμ (log ε 3·7, 3·7). Main IR bands (KBr) for both authentic and synthetic samples: 3448, 1639, 1449, 1307, 1242, 1190, 1163, 1099 cm^{-1}.

Synthesis of erythrin (II)

Condensation between VI *and 2-butene-1,4-diol.* A mixture of VI[7] (2·0 g; 1 mole) in dioxan (50 ml), 2-butene-1,4-diol (0·33 g; 1 mole) and dicyclohexylcarbodiimide (0·76 g; 1 mole) was stirred (16 hr). The crystalline dicyclohexyl urea was filtered off and washed with a small volume of dioxan, m.p. 226–228°. The solvent was distilled off under reduced press and the residue dissolved in ether. The ether solution was washed with 5% $NaHCO_3$ aq (5 × 10 ml) and then with water, dried and the solvent removed. The sticky residue (1·5 g) was used for the next stage of hydroxylation.

The condensation product yielded a 3,5-dinitrobenzoate which crystallized as light brown needles from benzene–light petroleum, m.p. 80–82°. (Found: 54·0; H, 4·5. $C_{36}H_{34}O_{18}N_2$ requires: C, 54·2; H, 4·3%.)

Hydroxylation of VII *and decarbethoxylation.* A mixture of the condensation product (1·25 g), H_2O_2 reagent[6] (7·5 ml) and osmium tetroxide solution in t-butanol (1 ml) was kept at room temp for 48 hr. The solvent was then removed by distillation. The resulting oily residue was macerated with water (3 × 5 ml) and the washings decanted off.

The residue (0·8 g) was suspended in 1N NaOH (5 ml) and kept at room temp for 2 hr, while H_2 gas was being passed through. The alkaline solution was filtered and the residue washed with water (2 × 5 ml). The combined filtrate and washings were then acidified with ice-cold HCl. The

precipitated solid was filtered off, washed with water and dried, m.p. 130–134°. On crystallization from AcOEt–light petroleum, it was obtained as light brown tiny needles (0·08 g), m.p. 165–166°. UV absorption: (a) synthetic sample: λ_{max}^{MeOH} 268, 300 mμ (log ε 4·0, 4·2); (b) natural sample: λ_{max}^{MeOH}, 269, 303 mμ (log ε 4·0, 4·3). Main IR bands (KBr) for both natural and synthetic samples: 3448 1639, 1625, 1504, 1462, 1399, 1250, 1245, 1075, 909, 877 and 833 cm^{-1}.

(±) *Erythrin hexaacetate.* The decarbethoxylated product was acetylated using Ac_2O–pyridine. The acetate crystallized from benzene–light petroleum as colourless needles, m.p. 145°. (Found: C, 56·4; H, 5·4. $C_{32}H_{34}O_{16}$ requires: C, 57·0; H, 5·0%.) UV absorption: λ_{max}^{MeOH} 238 mμ as for natural erythrin hexaacetate.