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SYNTHESIS OF ROYAL JELLY ACID

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ROYAL jelly acid, which was first isolated by Townsend and Lucas[1] and characterized as 10-hydroxydec-2-enoic acid of m.p. 54-56° by Butenandt and Rembold,[2] has recently been found to possess cancer-inhibiting properties under special conditions.[3] When we decided to synthesize this acid its configuration was undetermined and we therefore planed to prepare both stereoisomerides.

We now wish to report briefly the synthsis of trans-10-hydroxy-dec-2-enoic acid of m.p. 64-65°[4] which proved to be identical (mixed melting point and infra-red spectra) with royal jelly acid from natural sources. Specimens were kindly provided by Dr. Rembold of the Max-Planck Institute for Biochemistry, Munich, and by Dr. W. H. Brown of the Ontario Agricultural College, Guelph, Canada, to both of whom we are greatly indebted. Since then data of nuclear magnetic resonance measurements have been published[5]

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1 G.F. Townsend and C.C. Lucas, Biochem.J. 34, 1155 (1940).

2 A. Butenandt and H. Rembold, Z.Physiol.Chem. 308, 284 (1957).

3 G.F. Townsend, J.F. Morgan and B. Hazlett, Nature, Lond. 183, 1270 (1959).

4 U.K. Patent Application No. 25692/59 (27.7.1959).

5 S.A. Barker, A.B. Foster, D.C. Lamb and L.M. Jackman, Nature, Lond. 184, 634 (1959).

which also identify the natural product as the trans-isomer.

We have so far synthesized royal jelly acid by two methods known to be specific for the preparation of trans-α β-unsaturated acids. The first uses the known 10-acetoxy-decanoic acid,[6,7] which we obtained either from undecylenic acid[6] or from castor oil by a modification of a patented procedure.[8] Bromination of the acid chloride, followed by hydrolysis with water, gave crude 10-acetoxy-2-bromodecanoic acid which was successively refluxed with an ethanolic solution of sodium iodide and an aqueous alcoholic solution of sodium hydroxide. Isolation of the acidic material, chromatographic separation on Florex, and repeated crystallizations from ether - light petroleum (b.p. 40 - 60°) of the solid eluted with ether - benzene (10, 20 and finally 50% ether) yielded trans-10-hydroxydec-2-enoic acid as colourless prisms, m.p. 64 - 65°, infra-red max (paraffin paste) at 2.97 (free OH), 5.89 (conjugated C=O), 6.05 (conjugated C=C) and 10.17 μ (trans CH=CH), light absorption max 211 mμ; ε = 12.000 (Found: C, 64.4; H, 9.6 $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

8-Acetoxyoctanal, which is apparently not recorded in the literature, was the key intermediate for our second synthesis of royal jelly acid. We prepared this aldehyde either from 8-acetoxyoctanoic acid (previously obtained in very poor yield from suberic acid[9] but much more readily available from 6-chlorohexanol[10] by malonic ester synthesis and subsequent

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6 A. Grün and T. Wirth, Ber. 55, 2206 (1922).

7 P. Chuit, F. Boelsing, J. Hausser and G. Malet, Helv. Chim. Acta. 9, 1074 (1926).

8 U.K. Patent No. 675,434.

9 P. Chuit, Helv. Chim. Acta 12, 463 (1929).

10 W.R. Coleman and W.G. Bywater, J. Amer. Chem. Soc. 66, 1821 (1944).

acetylation) by reduction of the corresponding acid chloride according to Rosenmund, or from 8-acetoxy-1-bromo-octane[11] via 8-acetoxyoctyl toluene-p-sulphonate by oxidation with dimethyl sulphoxide.[12] Thus 8-acetoxyoctanal was obtained as a colourless oil, b.p. 81°/0.3 mm, infra-red max at 3.67 (aldehydic C-H) and 5.75 μ (C=O) (Found: C, 64.3; H, 9.7. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%). Condensation of the aldehyde with malonic acid in pyridine in the presence of a little piperidine at 50° gave trans-10-acetoxydec-2-enoic acid, b.p. 148 - 150°/0.2 mm, infra-red max at 5.78 (C=O), 5.9 (conjugated C=O), 6.07 (conjugated C=C) and 10.2 μ (trans CH=CH) (Found: C, 62.9; H, 8.9. $C_{12}H_{20}O_4$ required C, 63.1; H, 8.8%). Hydrolysis with ethanolic potassium hydroxide yielded trans-10-hydroxydec-2-enoic acid, which after two crystallizations from ether - light petroleum (b.p. 40 - 60°) had m.p. 64 - 65° and was identical with the previously prepared specimen.

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[11] F.L.M. Pattison, W.C. Howell, A.J. McNamara, J.C. Schneider and J.F. Walker, J. Org. Chem. 21, 739 (1956).

[12] N.Kornblum, W.J.Jones and G.J. Andersen, J. Amer. Chem. Soc. 81, 4113 (1959).