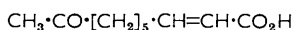


739. A New Synthesis of Queen Substance.

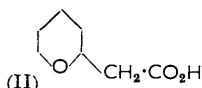
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Interaction of 2-hydroxytetrahydropyran and malonic acid gives *trans*-7-hydroxyhept-2-enoic acid, readily convertible into the 7-bromo-acid. Treatment of the latter with ethyl acetoacetate and subsequent hydrolysis produces queen substance (*trans*-9-oxodec-2-enoic acid).

IN 1954, Butler¹ showed that the queen honeybee secretes a substance which inhibits ovary development in worker bees and also queen-rearing within the colony and named this material "queen substance." The pure compound responsible for this effect was obtained crystalline by two groups of workers^{2,3} and shown by them^{4,5} to be *trans*-9-oxodec-2-enoic acid (I). This was confirmed by a synthesis from each group, one starting from azelaic acid⁴ and the other from cycloheptanone.⁶ We now report a simple new synthesis starting from dihydropyran.



(I)



(II)



(III)

Acid hydrolysis of 2,3-dihydropyran⁷ furnished tetrahydro-2-hydroxypyran (5-hydroxypentanal) which was condensed under Doebner conditions with malonic acid. Two products were isolated and were separated by distillation. The first, which was crystalline, proved to be tetrahydropyran-2-ylacetic acid⁸ (II); the higher-boiling, liquid product had properties in full accordance with the structure *trans*-7-hydroxyhept-2-enoic acid (III; X = OH). A further amount of this acid was obtained by ring cleavage of the tetrahydropyranylacetic acid with zinc chloride in acetic acid⁹ and hydrolysis of the acetate

¹ Butler, "The World of the Honeybee," Collins, London, 1954; *Bee World*, 1959, **40**, 269; *Endeavour*, 1961, **77**, 5; *Experientia*, 1960, **16**, 424.

² Butler, Callow, and Johnston, *Nature*, 1959, **184**, 1871.

³ Barbier, Lederer, Reichstein, and Schindler, *Helv. Chim. Acta*, 1960, **43**, 1682.

⁴ Callow and Johnston, *Bee World*, 1960, **41**, 152.

⁵ Barbier and Lederer, *Compt. rend.*, 1960, **250**, 4467.

⁶ Barbier and Lederer, *Compt. rend.*, 1960, **251**, 1135.

⁷ Woods, *Org. Synth.*, Coll. Vol. III, p. 470.

⁸ Zelinski, *J. Amer. Chem. Soc.*, 1952, **74**, 1504.

⁹ Elam and Hasek, U.S.P. 2,798,080.

thus obtained. Use of dihydropyran itself in the original Doebner condensation gave the same two products, but in lower yield.

Treatment of the hydroxy-acid (III; X = OH) with an excess of phosphorus tribromide gave the crystalline bromo-acid (III; X = Br) though the yield remained low in spite of much variation in reaction conditions; the yield was, however, improved by use of the methyl ester and subsequent hydrolysis. However, the most practical route to the bromo-acid (III; X = Br) involved treatment of either the hydroxy-acid (III; X = OH) or tetrahydropyranylacetic acid with hydrogen bromide. This produced an unstable dibromo-acid, which was presumably 3,7-dibromoheptanoic acid, since it was smoothly converted into *trans*-7-bromohept-2-enoic acid (III; X = Br) by mild treatment with collidine in benzene. Condensation of this bromo-acid with ethyl acetoacetate in the presence of two mol. of sodium ethoxide gave the substituted acetoacetate which was subjected, without purification, to hydrolysis and decarboxylation. The resulting crystalline *trans*-9-oxodec-2-enoic acid proved identical with a sample of queen substance kindly provided by Dr. R. K. Callow.

EXPERIMENTAL

Condensation of Tetrahydro-2-hydroxypyran and Malonic Acid.—Tetrahydro-2-hydroxypyran⁷ (20.5 g.) and reagent-grade malonic acid (23 g.) were dissolved in dry pyridine (24 g.) containing piperidine (1 ml.). After being kept overnight at room temperature, the mixture was heated on the steam bath until evolution of carbon dioxide had ceased (4 hr.), and then evaporated under reduced pressure. The residue was poured into 2*N*-sulphuric acid (15 ml.), and the product isolated by extraction in ether. Distillation gave tetrahydropyran-2-ylacetic acid (2.5 g., 9%) as the fraction, b. p. 140—150°/5 mm., crystallising from light petroleum (b. p. 40—60°) in needles, m. p. 55° (lit.,⁸ 55—57°) (Found: C, 58.5; H, 8.4. Calc. for C₇H₁₂O₃: C, 58.3; H, 8.4%), ν_{\max} . (Nujol mull) 2650, 1710 cm.⁻¹. The major product, a viscous oil, b. p. 160°/0.1 mm. (12 g., 43%), consisted of 7-hydroxyhept-2-enoic acid. A redistilled sample had b. p. 152°/0.1 mm., n_D^{19} 1.4870, ν_{\max} . (thin film) 3300, 2650, 1700, 1650, 985 cm.⁻¹. The α -naphthylurethane, which formed in quantitative yield, crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 136.5° (Found: C, 69.0; H, 6.3; N, 4.6. C₁₈H₁₉NO₄ requires C, 69.0; H, 6.1; N, 4.5%).

Conversion of Tetrahydropyran-2-ylacetic Acid into 7-Hydroxyhept-2-enoic Acid.—Tetrahydropyran-2-ylacetic acid (5.5 g.) was treated with zinc chloride in acetic acid, as described by Elam and Hasek,⁹ to give 7-acetoxyhept-2-enoic acid which, without purification, was refluxed with aqueous sodium hydroxide for 2 hr. Acidification and ether extraction gave the hydroxy-acid (1.6 g., 29%), b. p. 152°/0.1 mm., n_D^{21} 1.4850. It was shown to be identical with the material prepared as above by comparison of infrared spectra and by a mixed m. p. of the α -naphthylurethanes.

Reaction of 2,3-Dihydropyran with Malonic Acid.—2,3-Dihydropyran (4.1 g.) was treated with malonic acid (4.6 g.) in pyridine (5 ml.) containing piperidine (0.25 ml.) under the conditions described above. Distillation gave tetrahydropyran-2-ylacetic acid (0.35 g., 6%), m. p. and mixed m. p. 55°, and 7-hydroxyhept-2-enoic acid (1.7 g., 30%) (α -naphthylurethane, m. p. and mixed m. p. 136.5°).

7-Bromohept-2-enoic Acid.—(a) A stirred solution of 7-hydroxyhept-2-enoic acid (7 g.) in pyridine (5 ml.) and dry ether (50 ml.) was treated dropwise with phosphorus tribromide (6.5 g.) at <10°. A sticky mass was precipitated. The mixture was then stirred and refluxed overnight. Cooling, addition of water (15 ml.), isolation of the product with ether, and distillation gave the *bromo-acid* (2.5 g., 23%), b. p. 120°/0.1 mm., needles, m. p. 64° [from light petroleum (b. p. 40—60°)] (Found: C, 40.5; H, 5.7. C₇H₁₁O₂Br requires C, 40.5; H, 5.3%), ν_{\max} . (Nujol mull) 2650, 1700, 1650, 985 cm.⁻¹.

Using chloroform or benzene as solvent, using 1 mol. of pyridine, or omitting the pyridine gave even lower yields of bromo-acid.

(b) Methyl 7-bromohept-2-enoate (see below) (2.2 g.) was left overnight in methanol (20 ml.) with sodium hydroxide (0.4 g.). The mixture was concentrated, water (5 ml.) was added, and the solution washed with ether to remove unchanged ester. After acidification with dilute

sulphuric acid and ether extraction, distillation of the extract gave the bromo-acid (1.3 g., 65%, *i.e.*, 42% based on the hydroxy-acid), b. p. 120°/0.1 mm., m. p. and mixed m. p. 64°.

(c) Tetrahydropyran-2-ylacetic acid (4.5 g.) was refluxed for 2 hr. with an excess of a solution (50% w/v) of hydrogen bromide in glacial acetic acid. The cooled mixture was poured into water (100 ml.) and extracted with ether. The ether extracts were washed with water, dried, and evaporated, to give a dark brown oil (8.8 g.). The product was an acid which showed no hydroxyl or double-bond absorption in the infrared spectrum and contained bromine (sodium fusion). A sample decomposed when distillation was attempted.

The crude oil (8 g.) was refluxed in benzene (30 ml.) with collidine (3.5 g., 1 mol.) for 30 min. 6*N*-Sulphuric acid (10 ml.) was added and the mixture extracted with ether. The ether extracts, after being washed successively with dilute sulphuric acid and brine, were dried and evaporated. Distillation afforded the bromo-acid (3 g., 50%), b. p. 120—130°/0.1 mm., m. p. and mixed m. p. 64°.

Methyl 7-Bromohept-2-enoate.—7-Hydroxyhept-2-enoic acid (10 g.), in ether (100 ml.), was treated with a slight excess of ethereal diazomethane. After 15 min., the solution was decolorised by addition of a few drops of acetic acid, washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated. Distillation gave the hydroxy-ester (9 g.), b. p. 86—90°/0.1 mm.

A solution of the above hydroxy-ester (7.5 g.) in benzene (30 ml.) containing pyridine (0.5 ml.) was treated dropwise with phosphorus tribromide (5 g.) in benzene (10 ml.), the temperature being kept below 15°. The mixture was then heated under reflux for 4 hr. and allowed to cool. After addition of pyridine (5 ml.) and water, the mixture was extracted with ether and the extracts were washed successively with 6*N*-sulphuric acid and brine. Evaporation of the dried ether extracts and distillation of the residue gave the *bromo-ester* (8.9 g., 70%), b. p. 92—102°/0.1 mm., n_D^{25} 1.4800. A redistilled sample had b. p. 78—80°/0.05 mm., n_D^{25} 1.4795 (Found: C, 43.7; H, 6.0; Br, 36.3. $C_8H_{13}O_2Br$ requires C, 43.5; H, 5.9; Br, 36.1%), ν_{max} (thin film) 1710, 1670, 970 cm^{-1} .

9-Oxodec-2-enoic Acid.—7-Bromohept-2-enoic acid (1.5 g.) in absolute ethanol (5 ml.) was added dropwise to a stirred solution prepared from sodium (0.4 g.), absolute ethanol (45 ml.), and ethyl acetoacetate (2 g.). The solution was refluxed overnight and then concentrated. After addition of water and acidification, ether extraction gave a yellow oil which was dissolved in 5% aqueous sodium hydroxide (10 ml.) and left at room temperature for 8 hr. 50% Sulphuric acid (2 ml.) was then added and the mixture kept overnight. The product, taken up in ether, was extracted with saturated aqueous sodium hydrogen carbonate. Acidification and ether extraction gave the keto-acid (0.6 g., 46%), m. p. 40—50°, raised to 54.5—55° by crystallisation from light petroleum (b. p. 40—60°) (Found: C, 64.8; H, 8.5. Calc. for $C_{10}H_{16}O_3$: C, 65.2; H, 8.8%). The infrared spectrum was identical with that of an authentic sample of queen substance and a mixed m. p. showed no depression.

The *semicarbazone* crystallised from aqueous ethanol in needles, m. p. 163.5—164.5° (Found: C, 54.6; H, 8.0. $C_{11}H_{19}N_3O_3$ requires C, 54.8; H, 7.9%).

The authors thank Dr. R. K. Callow of the National Institute for Medical Research for a sample of natural queen substance and Mr. J. M. L. Cameron, B.Sc., and his assistants for the micro-analyses. This work was carried out under the tenure of a Gas Council Scholarship (by J. K.) and of an I.C.I. Fellowship (by N. J. McC.).