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A SIMPLE SYNTHESIS OF "QUEEN SUBSTANCE"*

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Abstract—A convenient synthesis of *trans*-9-oxodec-2-enoic acid is described.

IN December 1959 Butler, Callow and Johnston[1] published data which indicated that "queen substance"—a physiologically highly active material secreted in the mandibular glands of the queen honeybees, which inhibits the development of ovaries in the worker bees and prevents the construction of queen cells[2,3]—was structurally closely related to *trans*-10-hydroxydec-2-enoic acid (royal jelly acid) (I).[4,5] Interpretation of the reproduced infra-red spectrum[1] led us to the conclusion that the substance was either the aldehydo-acid 10-oxodec-2-enoic acid (II) or the isomeric keto-acid (III), of which, on biogenetic grounds, the structure II seemed somewhat the more probable.

$$HO(CH_2)_7{\cdot}CH{=}CH{\cdot}COOH \qquad OCH{\cdot}(CH_2)_7{\cdot}CH{=}CH{\cdot}COOH \qquad OCH{\cdot}(CH_2)_6\ldots.$$

I II

$$CH_3CO{\cdot}(CH_2)_5{\cdot}CH{=}CH{\cdot}COOH$$

III

Since we had recently synthesized royal jelly acid,[5] we examined several schemes for the preparation of both compounds (II) and (III).

While this work was in progress Callow and Johnston[6] showed that "queen substance" was, in fact, identical with the keto-acid (III), which they synthesised from azelaic acid in nine steps. At about the same time Barbier and Lederer[7] reached the same conclusion as a result of their investigations of the natural product.

The present communication describes a much simpler synthesis of *trans*-9-oxodec-2-enoic acid (III) from the known 7-oxo-octanoic acid (IVa),[8] which is readily accessible from cyclohexanone and acetic anhydride by way of 2-acetylcyclohexanone.[8,9] The acid (IVa) was converted in excellent yield into the corresponding acid chloride (IVb) by means of oxalyl chloride; thionyl chloride proved a less satisfactory reagent for this purpose. Reduction of 7-oxo-octanoyl chloride (IVb) according to Rosenmund gave 7-oxo-octanal (V) which, after purification, was condensed with malonic acid under the conditions of the Doebner reaction. Crystallization of the resulting product from ether–light petroleum (b.p. 40–60°) furnished the keto-acid (III) as transparent,

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* U.K. Patent Application No. 33,447/60 (September, 1960).

[1] C. G. Butler, R. K. Callow and N. C. Johnston, *Nature, Lond.* **184**, 1871 (1959).

[2] C. G. Butler, *Bee World* **40**, 269 (1959).

[3] M. Barbier and J. Pain, *C. R. Acad. Sci., Paris* **250**, 3740 (1960).

[4] A. Butenandt and H. Rembold, *Z. Physiol. Chem.* **308**, 284 (1957).

[5] G. I. Fray, R. H. Jaeger and Sir Robert Robinson, *Tetrahedron Letters* No. 4, 15 (1960).

[6] R. K. Callow and N. C. Johnston, *Bee World* **41**, 152 (1960).

[7] M. Barbier and E. Lederer, *C.R. Acad. Sci., Paris* **250**, 4467 (1960).

[8] R. C. Hauser and J. T. Adams, *J. Amer. Chem. Soc.* **66**, 345 (1944).

[9] H. Meerwein and D. Vossen, *J. Prakt. Chem.* **141**, 149 (1934).

elongated plates, m.p. 53–54°, raised by re-crystallization from the same solvent mixture to 54·5–55·5° (constant). Callow and Johnston[6] quote m.p. 45–52° for their synthetic product and m.p. 52–53·5° for the purified material from natural sources.

$CH_3CO{\cdot}(CH_2)_5COR$ — IVa, R=OH; IVb, R=Cl

$CH_3CO{\cdot}(CH_2)_5CHO$ — V

The acid (III) prepared in the above manner gave a positive iodoform test and its infra-red spectrum was consistent with the structure of "queen substance"; it formed a yellow 2,4-dinitrophenylhydrazone, m.p. 127–128°. The assignment of the *trans*-configuration follows from the mode of synthesis.[10]

After this work was completed we learnt that Barbier *et al.*[11] had obtained the keto-acid (III), m.p. 51–54° by an elegant synthesis, starting from cycloheptanone.

EXPERIMENTAL

Trans-*9-Oxodec-2-enoic acid* (III). Oxalyl chloride (22 g) was added dropwise to a solution of 7-oxo-octanoic acid[8] (9·4 g) in dry benzene (20 cc) at 0° under nitrogen. After the addition was complete the mixture was allowed to react at room temperature for 45 min and finally at 60–70° for 1 hr. Excess of reagent and solvent were removed under reduced pressure and the residue was fractionated; the acid chloride (IVb) distilled as a colourless liquid, b.p. 90–92°/0·25 mm (9·15 g = 87% yield). Its infra-red spectrum had strong bands at 5·51 (COCl) and 5·81 μ (C=O). An experiment carried out under similar conditions, using thionyl chloride as the reagent, gave the acid chloride in only 48% yield, leaving a large amount of charred material as residue after distillation. The above acid chloride (9·1 g), dry xylene (120 cc) and palladium on barium sulphate (1·2 g of 5%) were heated in an oil bath at 150–160° while a vigorous stream of hydrogen was passed through the stirred mixture. Evolution of hydrogen chloride virtually ceased after 45 min; the reaction mixture was rapidly chilled, a little Celite added, and the solids removed by filtration. After removal of the solvent under reduced pressure and fractionation of the residue, 7-oxo-octanal (V) was obtained as a colourless, fragrant liquid, b.p. 62–64°/0·2 mm (4·1 g). The infra-red spectrum showed peaks at 3·65 (aldehydic C—H) and 5·79 μ (comprising aldehydic and ketonic C=O). The keto-aldehyde gave persistently low values for carbon content, doubtless due to absorption of oxygen from the air.

Solutions of 7-oxo-octanal (4·1 g) and of malonic acid (3·3 g) in dry pyridine (13 cc each) were mixed at 0° and piperidine (12 drops) was added. The mixture was kept in the dark at 50° for 48 hr chilled and slowly added to ice-cold 50% sulphuric acid (60 cc). The product was extracted with ether, the extract washed twice with dilute hydrochloric acid and then with saline, and dried. After removal of the solvent the crude residue solidified; crystallisation from ether–light petroleum (b.p. 40–60°) gave *trans*-9-oxodec-2-enoic acid as large, transparent colourless plates, m.p. 53–54° (2·51 g). Recrystallisation of a sample from the same solvent mixture raised the m.p. to 54·5–55·5°, unchanged on further crystallization. The infra-red spectrum (Nujol mull) had bands at 5·83 (C=O), 5·90 (conjugated C=O), and 6·07 μ (conjugated C=C). (Found: C, 65·3; H, 8·9. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·7%).

The *2,4-dinitrophenylhydrazone* of the keto-acid (III) was prepared with Brady's reagent and crystallized from ethanol as yellow prisms, m.p. 127–128° (Found: C, 53·1; H, 5·9; N, 15·2. $C_{16}H_{20}O_6N_4$ requires C, 52·8; H, 5·5; N, 15·4%).

[10] K. V. Auwers *Ann.* **432**, 46 (1923).

[11] M. Barbier, E. Lederer and T. Nomura, *C. R. Acad. Sci., Paris* **251**, 1133 (1960).