Tetrahedron, 1961, Vol. 15, pp. 18 to 25. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF *TRANS*-10-HYDROXYDEC-2-ENOIC ACID* AND RELATED COMPOUNDS

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(*Received* 12 *April* 1961)

Abstract—Syntheses of the two stereoisomeric 10-hydroxydec-2-enoic acids are described. The *trans*-isomer is identical with the main fatty acid isolated from royal jelly of honeybees.

Some compounds closely related to this *trans*-acid have also been prepared.

A convenient process for the preparation of 10-acetoxy-decanoic acid from castor oil has been developed.

THE lipid portion of royal jelly of honeybees has as chief constituent a C_{10}-fatty acid, which was first isolated by Townsend and Lucas[1] and later characterized as 10-hydroxydec-2-enoic acid by Butenandt and Rembold.[2] A recent observation[3] that this acid can under special conditions completely suppress the development of transplantable leukaemia and ascitic tumours in mice prompted us to synthesize it and analogous bifunctional compounds for comparative biological studies.

At that stage the configuration of the olefinic linkage in this unsaturated hydroxy-acid was still undetermined; it was apparently not possible to draw any definite conclusions from the infra-red spectrum.[4] We therefore decided to synthesize both stereoisomerides of 10-hydroxydec-2-enoic acid. Brief accounts of these syntheses have been published elsewhere[5,6] and they have been patented.[7,8]

As has already been recorded,[6,7] synthetic *trans*-10-hydroxydec-2-enoic acid (I, R · H), m.p. 64–65° proved to be identical with the acid from natural sources, for which m.p. 54–56° had been quoted.[2] We are most grateful to Dr. H. Rembold of the Max-Planck Institut für Biochemie, München and to Dr. W. H. Brown of the Ontario Agricultural College, Guelph, Canada, for providing samples of the natural acid, which enabled us to identify the compound by the mixed melting point and a comparison of the infra-red spectra. Shortly after our patent application concerning the *trans*-acid[7] had been filed, nuclear magnetic resonance data were published[9] which confirmed that the natural product was the *trans*-isomer.

We prepared royal jelly acid (I, R · H) by two methods frequently used for synthesizing α, β-unsaturated *trans*-acids. In our case this involved (a) elimination of hydrogen iodide from 10-acetoxy-2-iododecanoic acid (II) or its methyl ester (III) by means of

* We propose the term royal jelly acid for this compound.

[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] S. A. Barker, A. B. Foster and D. C. Lamb, *Nature, Lond.* **183**, 996 (1959).
[5] G. I. Fray, R. H. Jaeger and Sir Robert Robinson, *Tetrahedron Letters* No. 4, 15 (1960).
[6] G. I. Fray, E. D. Morgan and Sir Robert Robinson, *Tetrahedron Letters* No. 13, 34 (1960).
[7] U. K. Patent Application No. 25692/59 (27.7.1959).
[8] U. K. Patent Application No. 8576/60 (1960).
[9] S. A. Barker, A. B. Foster and D. C. Lamb, *Nature, Lond.* **184**, 634 (1959).

alkali, and (b) condensation of 8-acetoxyoctanal (IV) with malonic acid under the conditions of the Doebner reaction, followed by hydrolysis of the acetyl group. Since our earlier publication[5] we have considerably improved these two processes and we are confining ourselves in the present communication to a description of the reaction conditions which gave us the best results.

$HO\cdot(CH_2)_7\cdot CH^{t}CH\cdot CO_2R$ (I)

$CH_3COO\cdot(CH_2)_7\cdot CHO$ (IV)

$CH_3COO\cdot(CH_2)_8\cdot CHX\,COR$

II (X = I; R = OH)
III (X = I; R = OMe)
V (X = Br; R = Cl)
VI (X = Br; R = OH)
VII (X = Br; R = OMe or OBu^t)

10-Acetoxydecanoic acid can now be very conveniently prepared from castor oil by our modification[10] of a patented process.[11] This acid was converted by means of thionyl chloride into the acid chloride, which was brominated without previous isolation, and the resulting product was hydrolysed with water to the crude bromo-acid (VI). After reaction of this with sodium iodide in methyl ethyl ketone[12] and treatment of the resulting iodo-acid (II) with alcoholic potassium hydroxide *trans*-10-hydroxydec-2-enoic acid (I, R = H), m.p. 64–65° was isolated by one crystallization from ether–light petroleum (b.p. 40–60°).

Alternately, the crude brominated acid chloride (V) was converted into the corresponding bromo-esters (VII) by reaction with the appropriate alcohol in pyridine; the presence of pyridine is essential to prevent transesterification and the resulting formation of polyesters. Attempts to dehydrobrominate the ester (VII; R = OBu^t) with diethylaniline[13] were unsuccessful, whereas conversion of the ester (VII; R = OMe) into the iodo-ester (III) with sodium iodide in acetone, followed by treatment with methanolic potassium hydroxide, was satisfactory.

The preferred method for preparing 8-acetoxyoctanal (IV), which was required as an intermediate for the second route to royal jelly acid (I; R = H), consisted in converting 8-bromo-octanoic acid[14] into 8-acetoxyoctanoic acid; from this the aldehyde (IV) was obtained by Rosenmund reduction of the acid chloride.

We also prepared the aldehyde (IV)—though in very poor yield—from 8-acetoxy-1-bromo-octane[15] via the tosylate (VIII; Ts = toluene-*p*-sulphonyl) which was oxidized by means of dimethyl sulphoxide in the presence of sodium hydrogen carbonate.[16]

$CH_3COO\cdot(CH_2)_8\cdot OTs$
VIII

Doebner condensation of 8-acetoxyoctanal (IV) with malonic acid, followed by hydrolysis of the resulting *trans*-10-acetoxydec-2-enoic acid yielded very pure royal jelly acid (I, R = H). The methyl ester (I, R = Me) was prepared from the parent acid with diazomethane.

An attempt to apply the Wittig reaction to the synthesis of the acid (I, R H)

[10] U. K. Patent Application No. 30163/60 (1960).
[11] U. K. Patent No. 675434 (1952).
[12] R. S. Sweet and F. I. Estes, *J. Org. Chem.* **21**, 1426 (1956).
[13] G. D. Hunter and G. Popják, *Biochem. J.* **50**, 163 (1951).
[14] F. Salmon-Legagneur and C. Neveu, *Bull. Soc. Chim. Fr.* 1345 (1956).
[15] F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider and J. F. Walker, *J. Org. Chem.* **21**, 739 (1956).
[16] N. Kornblum, W. J. Jones and G. J. Anderson, *J. Amer. Chem. Soc.* **81**, 4113 (1959).

from acetoxyoctanal (IV), using methoxycarbonylmethylenetriphenylphosphorane,[17] produced the desired substance only in low yield.

The chosen route to *cis*-10-hydroxydec-2-enoic acid (IX)[6,8] was by way of the acetylenic acid (X), since the partial hydrogenation of such acids in the presence of Lindlar's catalyst[18] is known to give the corresponding *cis*-ethylenic compounds with a high degree of stereospecificity.

$HO\cdot(CH_2)_7\cdot CH=CH\cdot CO_2H$ (IX)

$HO\cdot(CH_2)_7\cdot C\equiv C\cdot CO_2H$ (X)

$Py\cdot O\cdot(CH_2)_7\cdot X$ (XI)

$Py\cdot O\cdot(CH_2)_7\cdot C\equiv CH$ (XII)

XI-XIII (Py = 2-Tetrahydropyranyl)

$[Py\cdot O\cdot(CH_2)_7\cdot C\equiv C]_2Mg$ (XIII)

7-Chloroheptanol[19] was converted into the corresponding tetrahydropyranyl ether (XI, X = Cl) from which the crude iodo-compound (XI, X = I) was obtained by halogen exchange in the known manner. Reaction of the iodide with sodium acetylide in dimethylformamide according to a method recommended for the preparation of long-chain alk-1-ynes[20] yielded tetrahydropyranyloxynon-1-yne (XII). Since it has been demonstrated that magnesium acetylides can be very readily carboxylated,[21] the acetylenic compound (XII) was converted by means of diethyl magnesium into the magnesium derivative (XIII), which was treated with solid carbon dioxide. The resulting crude acid was immediately hydrolysed to 10-hydroxydec-2-ynoic acid (X), m.p. 72–73°; reduction with Lindlar's catalyst[18] gave *cis*-10-hydroxydec-2-enoic acid (IX), m.p. 73·5–74·5° in virtually quantitative yield.

Our next objective was the synthesis of some compounds structurally related to royal jelly acid, in order to examine whether such analogues also possessed cancer-inhibiting properties. In this connection the C_{12}-homologue (XIV, R = H) of royal jelly acid appeared to be particularly interesting since it also bears some relationship to traumatic acid (*trans*-dodec-2-en-1,12-dioic acid),[22] which is known to affect the cell growth of plants.

$RO\cdot(CH_2)_9\cdot CH=CH\cdot CO_2H$ (XIV)

trans-12-Hydroxydodec-2-enoic acid (XIV, R = H) was obtained by the Doebner reaction from malonic acid and 10-acetoxydecanal; this aldehyde was prepared from 10-acetoxydecanoic acid[10] by Rosenmund reduction of the derived acid chloride. Hydrolysis of the acetoxy-acid (XIV, R = CH_3CO) then furnished the C_{12}-hydroxy-acid (XIV, R = H).

The decision to synthesize the compound XV was influenced by the consideration that this substance may be regarded as an analogue of I (R = Me) in which an oxygen

[17] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helv. Chim. Acta* **40**, 1242 (1957).
[18] H. Lindlar, *Helv. Chim. Acta* **35**, 446 (1952).
[19] W. R. Coleman and W. G. Bywater, *J. Amer. Chem. Soc.* **66**, 1821 (1944).
[20] E. F. Jenny and K. D. Meier, *Angew. Chem.* **71**, 245 (1959).
[21] J. H. Wotiz, C. A. Hollingsworth and R. E. Dessy, *J. Amer. Chem. Soc.* **78**, 1221 (1956).
[22] J. English Jr., J. Bonner and A. J. Haagen-Smit, *J. Amer. Chem. Soc.* **63**, 941 (1941).

atom replaces the C_8-methylene group; furthermore, the starting materials required for this synthesis were readily available.

$$HO{\cdot}(CH_2)_3{\cdot}O{\cdot}(CH_2)_4{\cdot}CH{=}CH{\cdot}CO_2Me$$
XV

Condensation of 5-hydroxypentanal[23] with malonic acid by Doebner's method gave a mixture consisting of tetrahydropyranylacetic acid[24] (XVI, R = H) and the desired *trans*-7-hydroxyhept-2-enoic acid (XVII, R = H), which could not be separated by distillation owing to the formation of polyesters. The crude mixture was therefore esterified and the two isomeric esters (XVI, R = Me) and (XVII, R = Me) isolated by fractionation; the latter was characterized as the solid 3,5-dinitrophenylurethan.

XVI

$$HO{\cdot}(CH_2)_4{\cdot}CH \quad CH{\cdot}CO_2R$$
XVII

Alkaline hydrolysis of the hydroxy-ester (XVII, R = Me) did not furnish the corresponding acid (XVII, R = H), but caused complete re-arrangement to tetrahydropyranylacetic acid[24] (XVI, R = H). The hydroxyethylation of the ester (XVII, R = Me) was achieved by converting it first into the tosylate (XVIII, Ts = toluene-*p*-sulphonyl), and treating this with the monosodio-derivative of ethylene glycol. Transesterification evidently took place during this process; the crude reaction product was therefore hydrolysed and re-esterified with methanol, yielding methyl *trans*-7-(2'-hydroxyethoxy)-hept-2-enoate (XV, R = Me), which formed a crystalline 3,5-dinitrophenylurethan.

$$TsO{\cdot}(CH_2)_4{\cdot}CH \quad CH{\cdot}CO_2Me$$
XVIII

The acidic product isolated after hydrolysis of the ester (XV, R = Me) failed to crystallize and could not be distilled, since this would have given rise to polyesters. We have, however, been informed[25] that methyl esters are now used in preference to the parent acids in the biological tests for which the compounds described in this paper have been prepared.

EXPERIMENTAL

Light petroleum without further definition means the fraction of b.p. 40–60°. Ethereal extracts were dried over magnesium sulphate. Infra-red spectra of solids were determined for Nujol mulls. Ultra-violet absorption data refer to ethanolic solutions.

Preparation of 10-acetoxydecanoic acid from castor oil

A mixture of sodium hydroxide (115 g), water (40 cc), tri-cresol (45 g) and castor oil (150 g) was heated under reflux at a bath temp of 180–195°, with vigorous stirring. The violent frothing occurring in the earlier stages of the reaction was kept under control by stirring at high speed. After 3 hr the volatile products were allowed to distil. The residue was cautiously dissolved in water (1·5 l.), acidified to Congo red with 50% sulphuric acid, and the mixture heated to boiling. The oily layer was separated while hot in a pre-heated separating funnel, diluted with ether and the solution was dried. After removal of the ether, the residue (ca. 175 g) was refluxed with acetic anhydride (350 cc) for 5–6 hr, the reaction mixture poured onto ice and left overnight. The product was collected in

[23] G. F. Woods, *Org. Synth.* Coll. Vol. III, 470 (1955).
[24] R. P. Zelinski, N. G. Peterson and H. R. Wallner, *J. Amer. Chem. Soc.* 74, 1504 (1952).
[25] Professor G. F. Townsend, private communication.

ether, the ethereal extract thoroughly washed with water, and dried. After removal of the solvent, the residue was carefully fractionated. First a fraction of b.p. 136-160°/0·2 mm was collected; re-fractionation of this gave a fraction, b.p. 140-146°/0·2 mm and final fractionation yielded pure 10-acetoxydecanoic acid (45 g), b.p. 140-142°/0·2 mm. A sample had m.p. 36° (as quoted in the lit.[24]) after crystallization from light petroleum (b.p. below 30°).

By adopting the following procedure it was found possible considerably to reduce the volume to be fractionated without serious loss of the required material. Before acetylation, the oily layer of acidic products, isolated from the hot, aqueous mixture and dried as before, was dissolved in hot light petroleum (b.p. 60-80°; 300 cc), and the solution allowed to cool. The supernatant liquid was decanted from the precipitated material, which was then acetylated as described above to yield 10-acetoxydecanoic acid (41 g) from 150 g of castor oil.

(i) trans-10-*Hydroxydec*-2-*enoic acid* (I, R = H) *from* 10-*acetoxydecanoic acid*

(a) *Preparation* via 10-*acetoxy*-2-*bromodecanoic acid* (VI). 10-Acetoxydecanoic acid (23·6 g) was refluxed with purified thionyl chloride (30 cc) on the steam bath for 1½ hr. Bromine was then added slowly over a period of 2 hr to the refluxing solution and refluxing continued for a further 3 hr. The excess of the reagents was removed under reduced press and the residue poured into water (600cc). The mixture was warmed with shaking for 15 min (internal temp 40-50°) and finally kept at room temp overnight. The material was collected in ether, washed until the washings were neutral to litmus, and the extract rigorously dried. The crude bromo-acid (32 g) was refluxed with sodium iodide (33 g) and methyl ethyl ketone (330 cc) on the steam bath for 2 hr. After cooling, sodium bromide (11·5 g; 100%) was filtered off, the solid washed with dry acetone and the filtrate concentrated under reduced press. The residue was diluted with water, and acidified to Congo red with dilute sulphuric acid at 0°. The mixture was shaken with 10% aqueous sodium hydrogen sulphite, and the product collected with ether, washed and dried. The crude iodo-acid (36 g) was diluted with a little methanol and added in a thin stream to a hot solution of potassium hydroxide (30 g) in methanol (120 cc) under nitrogen. After refluxing for 3 hr, the mixture was concentrated *in vacuo*, and sufficient water was added to dissolve the precipitated salt. Some undissolved material was removed by means of ether, the aqueous portion acidified at 0° with 25% sulphuric acid, and the oily product collected with ether. The ethereal extract, after being washed with saline and dried, was decolourized with activated charcoal, filtered and concentrated to a small volume; light petroleum was added and, after several days in the refrigerator, trans-10-*hydroxydec*-2-*enoic acid* (4·98 g) was obtained as colourless prisms, m.p. 64·5-65°; a further amount (0·6 g), m.p. 64°, crystallized from the concentrated mother liquor (Found: C, 64·4; H, 9·6. $C_{10}H_{18}O_3$ requires: C, 64·5; H, 9·7%). Ultra-violet absorption: max 211 mμ (ε 12000). The infra-red spectrum had bands at 2·92 (free OH), 5·89 (conjugated C=O) and 6·05 (conjugated C=C) μ; the band at 10·17 μ cannot be quoted as characteristic for the *trans*-ethylenic linkage since both 10-hydroxydecanoic acid[4] and *cis*-10-hydroxydec-2-enoic acid absorb in this region. The acid proved to be identical with 10-hydroxydec-2-enoic acid from natural sources (mixed m.p. and infra-red spectra).

(b) *Preparation* via *methyl* 10-*acetoxy*-2-*bromodecanoate* (VII, R = OMe). 10-Acetoxydecanoic acid (49 g) was converted as before into the crude bromo-acid chloride, which was poured slowly into an ice-cold mixture of dry methanol (50 cc) and dry pyridine (25 cc) and left for 4 hr. The product was isolated by adding ether and washing successively with dil sulphuric acid, water, and dil sodium hydroxide. The ethereal solution was dried, the solvent evaporated and the residue fractionated to give *methyl* 10-*acetoxy*-2-*bromodecanoate* (56·6 g), b.p. 130–134°/0·2 mm (Found: C, 48·4; H, 7·3. $C_{13}H_{23}O_4Br$ requires: C, 48·3; H, 7·2%). The bromo-ester (19 g) was refluxed with sodium iodide (19 g) in acetone (150 cc) for 1 hr, the mixture was then concentrated, and ether and water added to the remainder; the ether layer was washed with sodium thiosulphate solution, dried and evaporated. The crude iodo-ester was refluxed with a solution of potassium hydroxide (40 g) in methanol (140 cc) for 2½ hr, diluted with water, acidified and extracted with ether. The extract was washed with saturated aqueous sodium chloride, dried and evaporated. Crystallization of the oily residue from ether light petroleum in the refrigerator yielded *trans*-10-hydroxydec-2-enoic acid (4·75 g), m.p. 62-64°. Chromatography of the mother liquor gave more material (0·5 g) of the same m.p.

Isobutyl 10-*acetoxy*-2-*bromodecanoate* (VII, R = OBu^i). This was prepared from 10-acetoxydecanoic acid (23 g) in the same manner as the corresponding methyl ester, using isobutanol (20 cc)

[24] P. Chuit, *Helv. Chim. Acta* **9**, 1074 (1926).

and pyridine (12 cc); fractionation yielded the *ester* (29·5 g), b.p. 140–142°/0·1 mm (Found: C, 52·3; H, 8·3. $C_{16}H_{29}O_4Br$ requires: C, 52·6; H, 8·0%). Refluxing this bromo-ester with diethylaniline[15] and hydrolysing the reaction product failed to produce *trans*-10-hydroxydec-2-enoic acid.

8-*Acetoxyoctanal* (IV). 8-Bromo-octanoic acid[14] (33 g) was refluxed with silver acetate (27 g) and glacial acetic acid (270 cc) for 3 hr. The resulting 8-acetoxyoctanoic acid[27] (28 g) was heated on the steam bath with purified thionyl chloride (15 cc) and dry benzene (50 cc) for 1 hr; excess reagent and solvent were removed under reduced press and the residue distilled, to give the acid chloride as a colourless liquid (27 g), b.p. 94–96°/0·2 mm. The acid chloride (26 g), dry xylene (200 cc) and 5% palladized barium sulphate (3·4 g) were heated in an oil bath at 150–160° while a vigorous stream of hydrogen was passed through the stirred mixture. After 45 min the evolution of hydrogen chloride slowed down appreciably, and the reaction was stopped after a further 15 min. The mixture was chilled, some Celite added to it, and the solids removed by filtration. After concentration of the filtrate under reduced press on the steam bath, the residue was fractionated; 8-*acetoxyoctanal* was obtained as a colourless, fragrant liquid (16 g), b.p. 80–82°/0·3 mm (Found: C, 64·3; H, 9·7. $C_{10}H_{18}O_3$ requires: C, 64·5; H, 9·7%). Its infra-red spectrum had bands at 3·67 (aldehydic C–H) and 5·75 μ (C=O).

The 2,4-*dinitrophenylhydrazone* was prepared in pyridine according to Braude's method,[28] and crystallized from benzene–light petroleum (b.p. 60–80°) as fine, yellow needles, m.p. 75° (Found: C, 52·7; H, 6·0; N, 15·5. $C_{16}H_{22}O_6N_4$ requires: C, 52·5; H, 6·0; N, 15·3%).

A small quantity of the above aldehyde was also obtained when 8-acetoxy-1-toluene-*p*-sulphonyloxyoctane (VIII; 24 g)—prepared from 8-acetoxy-1-bromo-octane[13] (27 g) by reaction with silver toluene-*p*-sulphonate (39 g) in acetonitrile (250 cc)—was treated with dimethyl sulphoxide (450 cc) and sodium hydrogen carbonate (60 g) according to the procedure of Kornblum *et al.*[16] The aldehyde (2·4 g) was isolated by means of its bisulphite addition compound.

(ii) trans-10-*Hydroxydec*-2-*enoic acid* (I; R = H) *from* 8-*acetoxyoctanal*

(a) *By the Doebner reaction.* 8-Acetoxyoctanal (8·7 g) and malonic acid (5·2 g), each dissolved in pyridine (20 cc), were mixed at 0° and piperidine (15 drops) was added. The solution was kept at 50° for 48 hr, with exclusion of moisture and light. The reaction mixture was then chilled in ice, acidified with ice-cold 50% sulphuric acid (80 cc), and the product collected in ether. The ethereal layer was shaken with dilute hydrochloric acid, dried and evaporated. Fractionation of the residue gave trans-10-*acetoxydec*-2-*enoic acid* as a colourless oil (7·8 g), b.p. 148–151°/0·2 mm (Found: C, 62·9; H, 8·9. $C_{12}H_{20}O_4$ requires: C, 63·1; H, 8·8%); its infra-red spectrum had bands at 5·78 (C=O), 5·9 (conjugated C=O) and 6·07 μ (conjugated C=C). The acetoxy-acid (7·5 g) was refluxed under nitrogen for 3 hr, with potassium hydroxide (5 g), water (10 cc) and ethanol (50 cc). Most of the alcohol was removed under reduced press, the residue diluted with a little water, and the alkaline solution extracted with ether to remove some impurity. The aqueous layer was acidified at 0° with 25% sulphuric acid, saturated with ammonium sulphate, and extracted with ether. The extract was washed with a little water, dried and evaporated, leaving a residue (5·6 g), which solidified on trituration with light petroleum and crystallized from ether–light petroleum as rosettes of colourless prisms (4 g), m.p. 63°; a second crystallization from the same solvent mixture raised the m.p. to 64–65°. This material was identical with *trans*-10-hydroxydec-2-enoic acid prepared from 10-acetoxydecanoic acid.

(b) *By the Wittig reaction.* Reaction of a solution of 8-acetoxyoctanal (2·3 g) in benzene (80 cc) with methoxycarbonylmethylenetriphenylphosphorane (4·1 g) under the conditions described by Isler *et al.*[17] yielded *methyl* trans-10-*acetoxydec*-2-*enoate* (2·0 g), b.p. 133–135°/0·5 mm (Found: C, 64·5; H, 9·3. $C_{13}H_{22}O_4$ requires: C, 64·4; H, 9·1%). Hydrolysis of this ester (2·0 g) with methanolic potassium hydroxide gave an oil (1·4 g), which failed to crystallize. After chromatographic separation on Florex, the *trans*-acid (0·19 g), m.p. 64·5–65°, identical with previously prepared specimens, was obtained.

Methyl trans-10-*hydroxydec*-2-*enoate* (I, R = Me). A solution of the acid (I, R = H; 5 g) in ether (50 cc) was treated with an ethereal solution of diazomethane. After removal of the solvent the residue was distilled to give the *ester* (5 g) as a colourless liquid, b.p. 115–118°/0·15 mm, n_D^{22} 1·4660 (Found: C, 67·9; H, 10·5. $C_{13}H_{24}O_3$ requires: C, 68·4; H, 10·5%).

[27] P. Chuit, *Helv. Chim. Acta* **12**, 465 (1929).
[28] E. A. Braude, *J. Chem. Soc.* 3131 (1953).

Synthesis of cis-10-*hydroxydec-2-enoic acid* (IX)

7-*Chloro*-1-2′-*tetrahydropyranyloxyheptane* (XI; X = Cl). Two drops of conc hydrochloric acid were added to 7-chloroheptanol[19] (38 g) in 2,3-dihydropyran (25 g) at 0°. Distillation from a few pellets of potassium hydroxide gave 7-*chloro*-1-2′-*tetrahydropyranyloxyheptane* (53 g), b.p. 92–95°/0·2 mm, n_D^{25} 1·4605 (Found: Cl, 14·9. $C_{12}H_{23}O_2Cl$ requires: Cl, 15·1%).

9-2′-*Tetrahydropyranyloxynon*-1-*yne* (XII). The above ether (13·5 g) was refluxed with sodium iodide (18 g) in acetone (150 cc) for 5 hr. The precipitated sodium chloride was removed and the filtrate refluxed with a further quantity of sodium iodide (2 g) for 7 hr. The reaction mixture was filtered, and the filtrate was diluted with ether, washed with sodium thiosulphate solution and water, and dried. After evaporation of the solvent, the crude iodide (XI; X = I; 18 g) was dissolved in dimethylformamide (150 cc) and slowly added to sodium acetylide (from 5·3 g of sodium) in liquid ammonia (500 cc). The ammonia was allowed to evaporate, and the remaining solution was stirred at 70° under nitrogen for 4 hr, cooled in ice and extracted with ether. The extract was washed successively with dil hydrochloric acid, aqueous sodium hydroxide and water, and was then dried and freed from the solvent; fractionation afforded 9-2′-*tetrahydropyranyloxynon*-1-*yne* (8·25 g), b.p. 90–91°/0·3 mm, n_D^{23} 1·4618 (Found: C, 75·1; H, 10·7. $C_{14}H_{24}O_2$ requires: C, 75·0; H, 10·8%). The infra-red spectrum exhibited bands at 3·05 (C≡CH) and 4·75 μ (C≡C).

10-*Hydroxydec*-2-*ynoic acid* (X). Ethylmagnesium bromide, prepared from ethyl bromide (5·25 g) and magnesium (0·8 g) in ether (60 cc) was refluxed for 5 hr with dioxan (2·9 g, purified by treatment with ethylmagnesium bromide in ether, followed by distillation). Tetrahydropyranyloxynon-1-yne (6·7 g) in ether (20 cc) was added, and the mixture refluxed, with stirring, for 1 hr. The product was poured onto solid carbon dioxide, left for 1 hr, and then shaken with saturated ammonium chloride solution to which a few drops of dil hydrochloric acid had been added. The ethereal solution was extracted with aqueous sodium carbonate, and the extracts acidified. Collection of the product with ether yielded crude 10-2′-tetrahydropyranyloxydec-2-ynoic acid (4·6 g), which was refluxed with methanol (30 cc) and water (30 cc) containing a little toluene-*p*-sulphonic acid. Removal of the solvent and crystallization from ether–light petroleum (b.p. 60–80°) furnished 10-*hydroxydec*-2-*ynoic* acid (2·1 g), m.p. 72–73° (Found: C, 65·4; H, 8·7. $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·8%). The infra-red spectrum had bands at 3·06 (free OH), 4·45 (C≡C) and 6·02 μ (C=O).

cis-10-*Hydroxydec*-2-*enoic acid* (IX). The above acetylenic acid (1·52 g) was hydrogenated in ethyl acetate (50 cc) in the presence of Lindlar's catalyst[18] (0·4 g) and quinoline (1 drop) until one equivalent of hydrogen had been absorbed. After removal of the catalyst by filtration and evaporation of the solvent, the residue crystallized from ether–light petroleum (b.p. 60–80°), yielding cis-10-*hydroxydec*-2-*enoic acid* (1·35 g) as colourless prisms, m.p. 73·5–74·5° (Found: C, 64·4; H, 9·6. $C_{10}H_{18}O_3$ requires: C, 64·5; H, 9·7%). The ultra-violet absorption showed a maximum at 210 mμ (ε 12,450). The infra-red spectrum had bands at 2·90 (free OH), 5·92 (conjugated C=O), 6·15 (conjugated C=C) and 12·3 μ (*cis* CH=CH).

Synthesis of compounds related to royal jelly acid

10-*Acetoxydecanal*. 10-Acetoxydecanoic acid (10·1 g) was converted into the acid chloride (10·7 g), b.p. 108°/0·15 mm, which was reduced with hydrogen in the presence of 5% palladized barium sulphate, as described for the preparation of 8-acetoxyoctanal; fractionation yielded 10-*acetoxydecanal* (6·7 g), b.p. 110°/0·4 mm (Found: C, 66·8; H, 10·2. $C_{12}H_{22}O_3$ requires: C, 67·3; H, 10·3%). The infra-red spectrum had bands at 3·70 (aldehydic C—H) and 5·75 μ (C=O).

trans-12-*Acetoxydodec*-2-*enoic acid* (XIV, R = CH_3CO). A solution of malonic acid (3·5 g) in dry pyridine (20 cc) was added at 0° to 10-acetoxydecanal (6·3 g), followed by piperidine (0·6 cc). The mixture was kept at room temp overnight and then warmed under nitrogen at 50–55° for 1 hr and at 90° for 3 hr. The reaction mixture was worked up as described for the preparation of *trans*-10-hydroxydec-2-enoic acid by the Doebner reaction. trans-12-*Acetoxydodec*-2-*enoic acid* separated from light petroleum (b.p. 60–80°) as yellowish prisms (4·2 g), m.p. 42·5–43° (Found: C, 65·4; H, 9·0. $C_{14}H_{24}O_4$ requires: C, 65·6; H, 9·4%). Its infra-red spectrum had bands at 5·76 (C=O), 5·90 (conjugated C=O) and 6·06 μ (conjugated C=C).

trans-12-*Hydroxydodec*-2-*enoic acid* (XIV, R = H). The above acetoxyacid (3·2 g) was refluxed with a solution of potassium hydroxide (2 g) in water (5 cc) and ethanol (20 cc) for 3 hr under nitrogen. The solution was concentrated *in vacuo*, water was added and the acid precipitated at 0° with 25% sulphuric acid. The solid was washed with water, dissolved in ether and the ethereal solution shaken

with conc brine, and dried. trans-12-*Hydroxydodec*-2-*enoic acid* (2·5 g) crystallized from ether, m.p. 69–69·5°; a second crystallization from ether light petroleum raised the m.p. to 70–71° (Found: C, 67·7; H, 10·3. $C_{12}H_{22}O_3$ requires: C, 67·4; H, 10·3%). The infra-red spectrum showed bands at 2·96 (free OH), 5·92 (conjugated C=O) and 6·07 μ (conjugated C=C).

Methyl trans-7-*hydroxyhept*-2-*enoate* (XVII, R = Me). 5-Hydroxypentanal[23] (50 g) was added to a cold solution of malonic acid (104 g) in pyridine (160 cc) containing piperidine (5 cc); the mixture was kept at room temp for 5 days, and then finally heated on the steam bath for 5 hr. The solvent was removed under reduced press, the oily residue (81 g) mixed with methanol (2l) and conc sulphuric acid (25 cc), and the mixture left at room temp. for 9 days. The resulting solution was concentrated under reduced press. and added to a mixture of ether and ice. The ethereal solution was washed with aqueous sodium hydrogen carbonate and water, dried and evaporated; fractionation gave methyl tetrahydropyran-2-ylacetate (XVI, R = Me; 14·6 g), b.p. 106–110°/26 mm, followed by *methyl* trans-7-*hydroxyhept*-2-*enoate* (32 g), b.p. 110–113°/0·4 mm, n_D^{20} 1·4675 (Found: C, 60·7; H, 9·0. $C_8H_{14}O_3$ requires: C, 60·7; H, 8·9%). The infra-red spectrum had bands at 2·95 (free OH), 5·82 (conjugated C=O) and 6·05 μ (conjugated C=C). The 3,5-*dinitrophenylurethan* crystallized from methanol, m.p. 124–125·5° (Found: C, 48·5; H, 4·9; N, 11·7. $C_{15}H_{17}N_3O_8$ requires: C, 49·0; H, 4·7; N, 11·4%).

Alkaline hydrolysis of methyl *trans*-7-hydroxyhept-2-enoate (2·1 g) afforded tetrahydropyran-2-ylacetic acid (1·8 g), m.p. 56–58°,[24] after crystallization from ether–light petroleum, as the sole product of the reaction.

Methyl trans-7-(2′-*hydroxyethoxy*)-*hept*-2-*enoate* (XV). Pyridine (16 cc) was added to a stirred mixture of methyl *trans*-7-hydroxyhept-2-enoate (7·9 g) and toluene-*p*-sulphonyl chloride (10·5 g) cooled in ice–salt, at such a rate that the temperature did not exceed 0°. After the addition (1 hr), stirring was continued for 3 hr, while the temp was allowed to rise gradually to 15°. A mixture of conc hydrochloric acid (50 cc) and crushed ice (100 g) was added, and the product was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The resulting crude toluene-*p*-sulphonate (13·9 g) was added to a solution of sodium (1·06 g) in ethylene glycol (18 cc), and the mixture stirred under nitrogen at 60–65° (bath) for 4 hr, then at 80–90° (bath) for 45 min, and was finally left overnight at room temp. Water (25 cc) was added and the solution extracted continuously with ether for 12 hr. Evaporation of the ether gave an oil (6·2 g), which was heated on the steam bath for 4 hr with a solution of sodium hydroxide (2·5 g) in water (4 cc). After acidification and collection with ether, the product (3·2 g) was refluxed with methanol (80 cc) and conc sulphuric acid (0·7 cc) for 12 hr. Working up in the usual way yielded, after fractional distillation, *methyl* trans-7-(2′-*hydroxyethoxy*)-*hept*-2-*enoate* (1·2 g), b.p. 104–106°/0·08 mm, n_D^{20} 1·4623 (Found: C, 59·6; H, 9·0. $C_{10}H_{18}O_4$ requires: C, 59·4; H, 9·0%). The infra-red spectrum had bands at 2·92 (free OH), 5·80 (conjugated C=O), 6·04 (conjugated C=C) and 8·91 μ (ether C—O). The 3,5-*dinitrophenylurethan* crystallized from methanol, m.p. 110–111·5° (Found: C, 49·8; H, 5·1; N, 10·5. $C_{17}H_{21}N_3O_8$ requires: C, 49·6; H, 5·1; N, 10·2%).