SYNTHESES OF FATTY ACIDS AND PYRROLIZIDINE ALKALOIDS.

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THESIS

presented to the University of Glasgow

for the degree of Ph.D.

1962.

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The contents of this thesis are my own special work carried out at the University of Glasgow during the years 1959-1962.

I wish to express my thanks to Professor R.A. Raphael, F.R.S., and Dr. N.J. McCorkindale for their constant encouragement and advice during the past three years.

I acknowledge, with gratitude, the award of a Gas Council Research Scholarship during the years 1959-1962.

I also wish to thank Mr. J.M.L. Cameron, B.Sc. and his very able assistants for speedy and accurate microanalyses.

C O N T E N T S

Part One.

SYNTHESIS OF (±) cis-9-HYDROXYOCTADEC-12-ENOIC ACID.

INTRODUCTION

An examination of the seed oil of Strophanthus Sarmentosus by Gunstone [1,2] showed it to contain an appreciable amount (6%) of a new laevorotatory acid. Later work [3] showed that this acid was also present in the seed oils of Strophanthus hispidus (13%) and Strophanthus courmontii (10%).

The acid was soluble in acetone -50°C, and the methyl ester distilled at a higher temperature than the C_{18} unsaturated esters. Iodine values, although subsequently shown to be anomalous, suggested that the acid was unsaturated. The pure acid was solid at room temperature and was insoluble in light petroleum. The physical properties were those to be expected of an unsaturated hydroxy-acid.

Catalytic hydrogenation indicated that the acid contained one ethylenic linkage and that the product of reduction (A2) was not identical with the well-known 12-hydroxystearic acid. The methyl ester of the reduced acid (A3) was oxidised to the corresponding keto ester (A4) and the derived mixture of geometrically isomeric oximes (A5, A6) was subjected to a Beckmann rearrangement and subsequent acid hydrolysis. Of the four hydrolysis products, the acidic components were isolated and shown to be azelaic (A7) and decanoic (A8) acids respectively. These observations indicated that the hydroxyl group had originally been attached to $C_{(9)}$.

The position of the double bond was found in the following manner. The naturalacid (A1) was oxidised with potassium permanganate in acetone and the resultant degradation products identified as hexanoic acid (A9) and the lactonic acid (A10). The formation of this lactone (A10) indicated that the

No synthetic work on cis-9-hydroxyoctadec-12-enoic (A1) acid had been reported before the initial investigation of Lewis[7]. Repetition of Lewis' work and continuance of his projected synthesis has led to the total synthesis of (±) cis-9-hydroxyoctadec-12-enoic[8] (A1). This work has confirmed the structure of the natural acid proposed by Gunstone[2].

DISCUSSION

The main objective in the synthesis of iso-ricinoleic acid (A1) was the construction of a C_{18} straight chain carboxylic acid which contained a potential cis double bond between $C_{(12)}$ and $C_{(13)}$, and a potential hydroxyl group at $C_{(9)}$. Since an acetylenic bond readily furnishes a cis double bond on catalytic reduction and a keto group gives a hydroxyl function on chemical reduction, 9-oxo octadec-12-ynoic acid (A29) was chosen as the key intermediate. It was envisaged that reduction of this compound with sodium borohydride followed by catalytic hydrogenation over Lindlar [9] catalyst would give the desired (±) cis-9-hydroxyoctadec-12-enoic acid (A1).

The free hydroxyl group in propargyl alcohol was protected by the addition reaction with 2:3-dihydropyran [10], to give tetrahydropyranyloxyprop-1-yne (A17). The sodio derivative of this compound in liquid ammonia was condensed with n-pentyl bromide (A16) and the crude product hydrolysed with dilute mineral acid to remove the protecting group [11]. The product, oct-2-yn-1-ol (A18), was readily converted to the corresponding bromide (A19) by treatment with phosphorus tribromide in the presence of pyridine[12].

This alkynyl bromide (A19) was condensed with diethyl sodio-malonate [13] to give mainly the mono substituted malonic ester (A20) although a trace of the corresponding di-substituted compound was also formed. Alkaline hydrolysis of the mono-substituted malonic ester gave the corresponding malonic acid which on decarboxylation at 160° gave dec-4-ynoic acid (A21).

Hunig, Lucke and Benzing [14,15] have shown that aliphatic acyl chlorides readily condense with enanimes of cydohexanone;

mild acid hydrolysis of the product yields the corresponding 2-acylcyclohexanone. This 1:3-diketone on alkaline hydrolysis gives a 7-keto carboxylic acid differing in chain length by six carbon atoms from the original acyl chloride. This procedure thus comprises a convenient method of extending the chain length of a carboxylic acid by six carbon atoms.

Lewis [7] attempted to convert dec-4-ynoyl chloride (A22) to 9-oxooctadec-12-ynoic-acid (A29) by condensing it with the morpholine enamine of cyclooctanone and hydrolysing the product. Although he obtained the acylcyclooctanone, this compound on basic hydrolysis yielded decynoic acid and cyclooctanone and not the desired C_{18} keto acid (A29). Since the chain extension by eight carbon atoms could not be achieved by this one step procedure it was carried out in two stages. The first stage involved chain extension by six carbon atoms using the enanime of cyclohexanone and the second, a further increase of two carbon atoms, via a malonate condensation.

Dec-4-ynoyl chloride (A22), readily prepared from the corresponding acid (A21) by treatment with oxalyl chloride in dry benzene, was condensed with the morpholine enamine of cyclohexanone in the presence of triethylamine; acid hydrolysis of the product [15] gave dec-4-ynoyl cyclohexanone (A23) which on alkaline hydrolysis and subsequent acidification provided 7-oxohexadec-10-ynoic acid (A24). This molecule now required to be extended by two carbon atoms to give the key compound 9-oxooctadec-12-ynoic acid (A29).

Prior to reduction with lithium aluminium hydride the oxo function in the keto acid (A24) was protected by conversion to ethylene ketal; the conditions used for this protection, ethylene glycol in refluxing benzene with a trace of toluene

p-sulphonic acid in a Dean and Stark apparatus, were such that the carboxylic acid grouping was also esterified. The resultant ketal ester (A25) was reduced to the corresponding ketal alcohol with lithium aluminium hydride; removal of the ketal protecting group with dilute mineral acid yielded 7-oxohexadec-10-yn-1-ol (A26). This alcohol was readily converted to the bromide by treatment with phosphorus tribromide in the presence of pyridine[12].

7-Oxohexadec-10-ynyl bromide was then condensed with diethyl sodiomalonate in absolute ethanol[13]. The resultant malonic ester (A27) was obtained in only 46% yield. In an attempt to better this, the condensation was carried out using sodium hydride as base and tetrahydrofuran as solvent,[16] but this technique failed to increase the yield. The resultant mono-substituted malonic ester (A27) was hydrolysed to the corresponding malonic acid (A28) which underwent thermal decarboxylation at 160° to give 9-oxooctadec-12-ynoic acid (A29).

To complete the synthesis of iso-ricinoleic acid (A1) all that now remained was to reduce the keto group at $C_{(9)}$ with borohydride and then catalytically reduce the product over Lindlar catalyst. It seemed that these reductions would present no difficulty since Crombie and Jacklin[17] had carried out cognate reactions on the isomer, 12-oxooctadec-9-ynoic acid in their total synthesis of ricinoleic acid.

Reduction of the keto acid (A29) with sodium borohydride gave the hydroxyacetylenic acid (A30) as an oil which very slowly solidified. Purification by low temperature crystallisation was followed by selective catalytic reduction. Use of the Lindlar catalyst[9] with interruption of the reduction when 1 mole of hydrogen had been absorbed ensured that the

hydroxyacetylenic acid (A30) was converted to ($\pm$) cis-9-hydroxyoctadec-12-enoic acid (A1).

This synthetic racemate had physical properties identical with those of the natural (-) isomer. The infrared spectra were identical and the melting points comparable, as were the respective cracking patterns in the mass spectrometer. Since the waxy nature and low melting points of synthetic and natural material did not allow satisfactory mixed melting point determinations to be carried out, further proof of identity was sought.

Natural and synthetic iso-ricinoleic acid (A1) were oxidised separately at 0^{o} with chromium trioxide and sulphuric acid in acetone. The product was the optically inactive cis-9-oxooctadec-12-enoic acid (A31). The samples obtained from natural and from synthetic iso-ricinoleic acid were identical in all their physical properties: melting point, infrared spectrum and mass spectrometric cracking pattern. The crystalline nature of this compound (A31) allowed mixed melting point determinations to be undertaken: no depression was observed on admixture.

In order to provide a more exact comparison the sample of the keto-acid (A31) derived from the laevorotatory natural iso-ricinoleic acid was reduced with sodium borohydride and the resultant racemic acid (A1) was shown to be identical with synthetic material.

This synthesis has confirmed Gunstone's[2] suggestion that the acid derived from the seed oil of Strophanthus sarmentosus was (-)cis-9-hydroxyoctadec-12-enoic acid (A1).

EXPERIMENTAL

Tetrahydropyranyloxyprop-1-yne[10] (A17)

Concentrated hydrochloric acid (0.5ml) was added to a mixture of redistilled dihydropyran (84g: 1M) and propargyl alcohol (56g: 1M). The mixture rapidly became warm and was cooled in an ice bath. When the reaction had subsided the contents of the flask were shaken and allowed to stand at room temperature for two hours. The product was shaken with potassium hydroxide pellets which were filtered off when the mixture was dry. The pellets were washed with ether. The ether was removed from the filtrate and the residue was distilled to give the desired product (120g: 87%) b.p.75-77°/19m.m. n_D^{19} 1.4570. (lit.[10] 78°/20m.m. n_D^{19} 1.4520).

Oct-2-yn-1-ol. (A18)

Tetrahydropyranyloxyprop-1-yne (117g: 0.825M) in absolute ether (100ml) was added during one hour to a stirred suspension of sodamide in liquid ammonia, prepared from sodium[18] (24g: 1.04M). After two hours n-pentyl bromide (154g: 1M) in anhydrous ether (100ml) was added dropwise, with stirring. The mixture was stirred for a further 4 hours and the ammonia then allowed to evaporate overnight. Water (100ml) was added cautiously and the mixture thoroughly extracted with ether. The extracts were dried over anhydrous magnesium sulphate and the solvent removed.

The residue was dissolved in methanol (200ml) and stirred, at room temperature, with 25% aqueous sulphuric acid (40ml) for 8 hours. The mixture was poured into water (1l), the solution extracted with ether and the ether extracts washed with saturated sodium hydrogen carbonate solution and then brine. Drying and removal of solvent gave

a dark brown oil which was distilled to give oct-2-yn-1-ol. (80g: 63%) b.p. 100°/18m.m. n_D^{20} 1.4561. (lit[12] 76-82°/2m.m. n_D^{20} 1.4550).

In the distillation a low boiling fraction was obtained (b.p.62°/15m.m. 2:4 dinitrophenylhydrazone m.p.106°) (lit[11] 62-66°/10m.m. 2:4 dinitrophenylhydrozone m.p. 107-109°) this was probably tetrahydro-2-hydroxypyran.

1-Bromooct-2-yne[12] (A19)

Phosphorus tribromide (113g: 0.42M) was added slowly to a stirred solution of oct-2-yn-1-ol (132g:1.04M) and dry pyridine (20ml) in anhydrous ether (200ml) at 0°C. The mixture was gently refluxed for 3 hours and water (300ml) carefully added to the cooled solution. The ether extracts were combined, washed with sulphuric acid (2N), saturated sodium hydrogen carbonate solution and brine. After drying over anhydrous magnesium sulphate the solvent was removed and the residual oil distilled. b.p.58-62°/0.2m.m. n_D^{22} 1.4832 (148g: 75%). (lit[12] b.p. 69.5-70.5°/2m.m. n_D^{20} 1.4839).

Diethyl oct-2-ynylmalonate (A20)

To sodium (23g:1M) in absolute ethanol (I.Il) was rapidly added diethyl malonate (197g: 1.2M) with stirring. After 1 hour 1-bromooct-2-yne (143g: 0.77M) was added dropwise, and the mixture refluxed for 6 hours. After concentration of the ethanol solution, water (500ml) was added and the mixture extracted with ether. Solvent removal gave a dark brown oil which was fractionated through a 15 cm. Vigreux column. Two fractions were obtained.
(a) Diethyloct-2-ynyl malonate (145g:71%) b.p.12o°-124°/o.1m.m. $n_D^{17.3}$ 1.4488. (quoted[7] 61%; 124-128°/0.3m.m, n_D^{25} 1.4463)

(b) Diethyl di-(oct-2-ynyl) malonate (25g:8%) b.p.156-158°/ 0.2m.m; n_D^{22} 1.4629 (quoted[7] 11%; 154-160°/0.3m.m; n_D^{25} 1.4620)

Oct-2-ynylmalonic acid

Diethyloct-2-ynyl malonate (145g:0.54M) was refluxed, for 3 hours, with potassium hydroxide (91g: 1.8M) in ethanol (700ml). The solution was concentrated and water (450ml) added. Neutral products were removed with ether. Acidification of the aqueous solution with 6N hydrochloric acid followed by ether extraction gave a dark brown oil which solidified. The product crystallised from light petroleum as white plates (93g: 80%) m.p. 110-111°. (quoted[7] 91%; m.p. 109-110°).

Dec-4-ynoic acid. (A21)

Oct-2-ynylmalonic acid (93g) was heated in an oil bath at 160° until carbon dioxide was no longer evolved (about 3 hours). On cooling the light brown oil solidified and crystallised from light petroleum as white plates (59g:79%) m.p. 36.5°C. (lit[7] 96%: m.p.36.5-37°).

Infrared spectrum (Nujol mull), ν_{max} 2500-2700, 1710 cm^{-1}.

Dec-4-ynoyl chloride (A22)

Oxalyl chloride (52g: 0.41M) was added dropwise to a stirred solution of dec-4-ynoyl acid (58g: 0.34M) in dry benzene (120ml). The mixture was left at room temperature overnight and then the benzene and excess oxalyl chloride removed at the water pump. Distillation of the residue gave a colourless oil (57g: 90%) b.p. 76-78°/0.5m.m. n_D^{26} 1.4592. ν_{max} (thin film), 1800 cm^{-1}.(quoted[7] 72%;120-124/17m.m; n_D^{21} 1.4602).

1-Morpholinocyclohex-1-ene[14]

Cyclohexanone (39.2g: 0.4M), morpholine (34.8g:0.4M) and toluene-p-sulphonic acid (0.3g) in dry benzene (100ml) were refluxed in a Dean and Stark apparatus for 8 hours. The cold solution was washed with saturated sodium hydrogen carbonate solution and dried. Removal of the solvent gave an oil which was distilled through a 15cm. Vigreux column to give the desired enamine (57g: 86%) b.p.140°/26m.m. n_D^{26} 1.5118. (lit[14] 117-120°/10m.m.)

2-Dec-4[1]-ynoylcyclohexanone (A23)

Dec-4-ynoyl chloride (55g: 0.295M) in dry chloroform (70ml) was added slowly to a solution of 1-morpholinocyclohex-1-ene (55g: 0.325M) and triethylamine (36.2g: 0.35m) in chloroform (100ml) at 40°. The solution was maintained at 40° for one hour and then stirred at room temperature overnight, 20% sulphuric acid (200ml) was added and the mixture refluxed for 6 hours. The chloroform layer was separated and washed with water until the washings were at pH6. The combined aqueous layer and washings were brought to pH6 and extracted with chloroform. The combined extracts were dried and the solvent removed. Distillation of the residue gave 2-dec-4[1]-ynoylcyclohexanone (40g: 56%) b.p. 130°/10^{-3}m.m. n_D^{25} 1.5032. (quoted[7] 64%; b.p. 138-140°/2.10^{-3}m.m. n_D^{21} 1.5052) ν_{max} (thin film) 2700-2300, 1600 cm^{-1}.

7-Oxohexadec-10-ynoic acid (A24)

2-Dec-4-ynoylcyclohexanone (40g: 0.16M) was refluxed with 10% aqueous potassium hydroxide (170ml) for 3 hours and set aside overnight. Acidification with 3N-sulphuric acid and ether extraction gave the acid which crystallised from aqueous ethanol as plates (30g:75%) m.p. 56-57° (quoted[7] 87% 57-58°). ν_{max} (Nujol mull) 3300-2500,1705, 1700cm^{-1}.

7-Oxohexadec-10-yn-1-ol (A26)

7-Oxohexadec-10-ynoic acid (28g:0.105M), ethylene glycol (12g; 0.200M) and toluene-p-sulphonic acid (0.3g) were refluxed in dry benzene (400ml), with constant removal of water, for 36 hours. The cooled mixture was washed with saturated sodium hydrogen carbonate solution, dried and evaporated to give crude ketal ester (33g). Infrared spectrum (thin film) ν_{max} 3500, 1745, 1070cm^{-1}.

This ketal ester (33g) in dry ether (60ml) was slowly added dropwise to a stirred suspension of lithium aluminium hydride (7.4g: 0.20M) in anhydrous ether (100ml) and the mixture refluxed for 12 hours. After destruction of the excess hydride with ethyl acetate, water (100ml) was added and the mixture extracted with ether. Evaporation gave a colourless oil (38g). Infrared spectrum (thin film) ν_{max} 3500, 1070cm^{-1}.

This crude ketal in ether (75ml) was shaken with 6N-sulphuric acid (80ml) for 6 hours. The ether extracts were washed with saturated sodium hydrogen carbonate and dried over anhydrous magnesium sulphate. Evaporation gave the alcohol which crystallised from methanol as white plates (17.3g: 65%) m.p. 41-42^{o} (quoted[7] 63%; 41.5-42^{o}) ν_{max} (Nujol mull) 3350, 1705 cm^{-1}.

1-Bromo-7-oxohexadec-10-yne.

Phosphorus tribromide (7.5g: 0.028M) was added dropwise to a cooled solution of 7-oxohexadec-10-yn-1-ol (17.3g: 0.069M) and pyridine (5ml) in ether (100ml). After a 6 hour reflux, water (40ml) was carefully added and the mixture extracted with ether. The ether extracts were successively washed with 25% sulphuric acid, saturated

aqueous sodium hydrogen carbonate, and brine. Drying and evaporation gave crude 1-bromo-7-oxohexadec-10-yne (18.3g) ν_{max} (thin film) 1705 cm^{-1}.

Diethyl 7-oxohexadec-10-ynylmalonate

(a) Crude 1-bromo-7-oxohexadec-10-yne (3.2g: 0.01M) in absolute ethanol (10ml) was added dropwise with stirring to a solution prepared from sodium (0.46g:0.02M), ethanol (15ml) and diethyl malonate (4.0g: 0.025M). After 5 hours reflux the solution was concentrated to half its volume and water (15ml) added. Ether extraction gave the desired substituted malonic ester (1.86g: 46%) b.p. 138-140°/10^{-3}m.m. (quoted[7] 46%: 138-146°/10^{-3}m.m.) ν_{max} (thin film)1748, 1720 cm^{-1}.

(b) Crude 1-bromo-7-oxohexadec-10-yne (3.2g: 0.01M) in dry tetrahydrofuran (10ml) was added dropwise,with stirring, to a solution prepared from sodium hydride (0.5g: 0.02M), tetrahydrofuran (15ml) and diethyl malonate (4.0g: 0.025M). After 5 hours' reflux the solution was concentrated and water (15ml) was added. Ether extraction gave the required malonic ester (1.76g: 40%) b.p. 136-140°/10^{-3}m.m.

7-Oxohexadec-10-ynylmalonic acid (A28)

The substituted malonic ester (8.0g: 0.02M) was refluxed for 2 hours with potassium hydroxide (2.3g: 0.04M) in aqueous ethanol (60ml). After concentration, water (30ml) was added to the mixture and the whole extracted with ether to remove neutral products. After acidification ether extraction gave a solid which crystallised from petrol/ethyl acetate as plates (4.5g: 66%) m.p. 108-109°.
(Found: C, 67.0; H 8.7, $C_{19}H_{30}O_5$ requires C 67.4; H,8.9%)
ν_{max} (Nujol mull) 2700-2500, 1705 cm^{-1}.

9-Oxooctadec-12-ynoic acid (A29)

7-Oxohexadec-10-ynylmalonic acid (2.5g) was heated at 160° (oil bath) until evolution of carbon dioxide had ceased. The resultant brown oil solidified on cooling. This solid was dissolved in ether and filtered through a short silica column. The acid crystallised from light petroleum ether (b.p. 40-60°) as plates (1.1g: 53%). Four further crystallisations gave white plates m.p. 66-67° (Found: C,73.6, H,10.2; $C_{18}H_{30}O_3$ required C, 73.4, H.10.3%) ν_{max} (Mujol mull) 2700-2500, 1710, 1705 cm^{-1}.

(±) 9-Hydroxyoctadec-12-ynoic acid (A30)

9-Oxooctadec-12-ynoic acid (200mg: 0.67×10^{-3}M) in ethanol (3ml) was treated with sodium borohydride (80mg: 2×10^{-3}M) in water (2ml) and kept at 0° for 24 hours. 4% aqueous sodium hydroxide solution (1ml) was added and the mixture heated on the steam bath for 1 hour. Acidification and ether extraction gave an oil which solidified after two weeks. Several recrystallisations from light petroleum (b.p.40°-60°) at -70° gave pale yellow solid (100mg: 50%) m.p. 38°-42°. ν_{max} (Nujol mull) 3300, 1710 cm^{-1}.

(±) cis-9-Hydroxyoctadec-12-enoic acid (A1)

Semi-crude 9-hydroxyoctadec-12-ynoic acid (40mg), from the above experiment, in ethanol (10ml) was hydrogenated over Lindlar[9] catalyst (30mg) until 1 mole of hydrogen (2.9ml) had been absorbed. After removal of catalyst and evaporation, crystallisation of the residue from light petroleum (b.p.40-60°) at -70° gave the desired product as a wax (35mg; 87%) m.p.28-32° (lit[2] (-) enantiomorph m.p. 30-34°).

Infrared spectrum (thin film) ν_{max} 3400, 2700-2500, 1710 cm^{-1}. The infrared and mass spectra of the synthetic and natural acids were identical.

cis-9-Oxooctadec-12-enoic acid (A31)

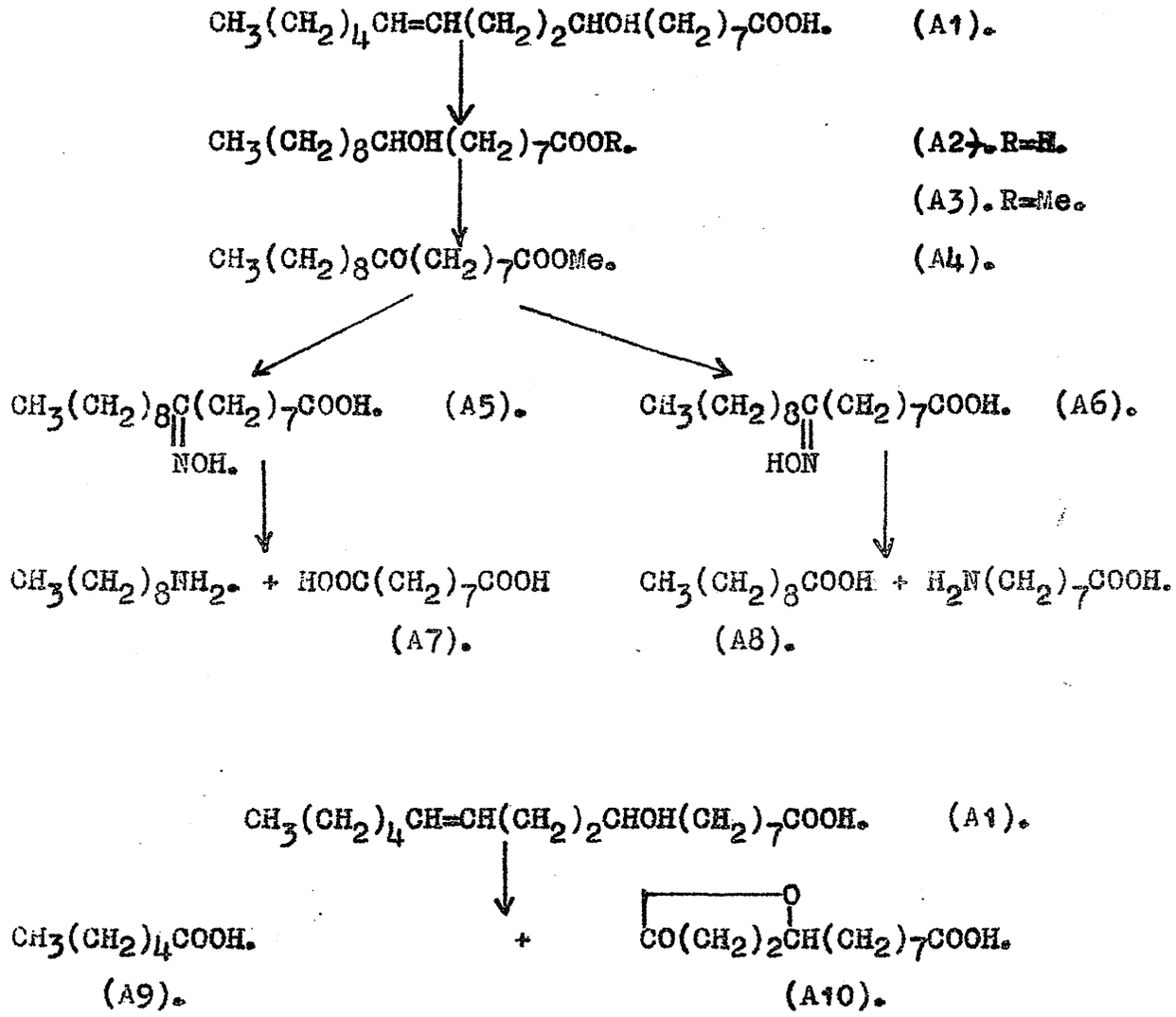
(a) Natural (-) cis-9-hydroxyoctadec-12-enoic acid (0.5g: 1.6×10^{-3}M) in acetone (5ml) was cooled to 0^{o} and a solution of chromium trioxide (0.12g: 1.2×10^{-3}M) in concentrated sulphuric acid (0.4g) and water (1ml) was added dropwise. After 6 hours water was added and the mixture extracted with ether. Evaporation and crystallisation from light petroleum (b.p. 40-60°) at -70° gave the keto-acid as plates (0.35g: 70%) m.p. 44-45°.
(Found: C.72.5; H.10.8; $C_{18}H_{32}O_3$ requires, C,72.9; H,10.9%) ν_{max} (Nujol mull) 1710, 1705, 2500-2700 cm^{-1}.

(b) Oxidation of synthetic (±) cis 9-hydroxyoctadec-12-enoic acid (20mg) under conditions identical with those described above in (a) gave keto-acid (14mg) m.p. 40-42°. This acid was shown by mixed melting point and by the identity of the respective infrared and mass spectra to be identical with the sample of the acid prepared in (a) from natural iso-ricinoleic acid.

cis-9-Hydroxyoctadec-12-enoic acid (A1)

cis 9-Oxo-octadec-12-enoic acid (40mg) obtained by oxidation of natural (-) cis-9-hydroxyoctadec-12-enoic acid was dissolved in ethanol (3ml) and treated with sodium borohydride (16mg: 0.4×10^{-3}M) in water (1ml). The solution was kept at 0° for 24 hours and then 4% aqueous sodium hydroxide (0.5ml) was added and the whole heated on a steam bath for 1 hour. Acidification and ether extraction gave

(±) cis-9-hydroxyoctadec-12-enoic acid (25mg: 63%) m.p.24-28° which was identical with the (±) hydroxy-acid obtained from the synthesis.


CH3(CH2)4CH=CH(CH2)2CHOH(CH2)7COOH. (A1).
CH3(CH2)8CHOH(CH2)7COOR. (A2). R=H. (A3). R=Me.
CH3(CH2)8CO(CH2)7COOMe. (A4).
CH3(CH2)8C(CH2)7COOH. (A5).
NOH.
CH3(CH2)8C(CH2)7COOH. (A6).
HON
CH3(CH2)8NH2. + HOOC(CH2)7COOH (A7).
CH3(CH2)8COOH + H2N(CH2)7COOH. (A8).
CH3(CH2)4CH=CH(CH2)2CHOH(CH2)7COOH. (A1).
CH3(CH2)4COOH. (A9).
+
CO(CH2)2CH(CH2)7COOH. (A10).

$CH_3(CH_2)_5CH{=}CHCH{=}CH(CH_2)_7COOH$.
(A12).

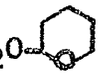
$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH$.
(A11).

$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$.
(A13).

$CH_3(CH_2)_4CH{=}CH(CH_2)_2CHOH(CH_2)_7COOH$.
(A1).

$CH_3(CH_2)_4CH{=}CH(CH_2)_2CH{=}CH(CH_2)_6COOH$.
(A14).

$CH_3(CH_2)_4CH\overset{O}{-}CHCH_2CH{=}CH(CH_2)_7COOH$.
(A15).

$CH_3(CH_2)_4Br$. (A16). $HC{\equiv}CCH_2O$  (A17).

$CH_3(CH_2)_4C{\equiv}CCH_2OH$. (A18).

↓

$CH_3(CH_2)_4C{\equiv}CCH_2Br$. (A19).

↓

$CH_3(CH_2)_4C{\equiv}CCH_2CH(COOEt)_2$. (A20).

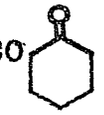
↓

$CH_3(CH_2)_4C{\equiv}CCH_2CH_2COOH$. (A21).

↓

$CH_3(CH_2)_4C{\equiv}CCH_2CH_2COCl$. (A22).

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO$  (A23).

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO(CH_2)_5COOH$ (A24).

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2C(CH_2)_5COOCH_2CH_2OH$  (A25).

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO(CH_2)_5CH_2OH$. (A26).

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO(CH_2)_5CH_2Br$.

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO(CH_2)_5CH_2CH(COOEt)_2$. (A27)

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO(CH_2)_5CH_2CH(COOH)_2$. (A28).

P.T.O.

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CO(CH_2)_7COOH.$ (A29).

↓

$CH_3(CH_2)_4C{\equiv}C(CH_2)_2CHOH(CH_2)_7COOH.$ (A30).

↓

$CH_3(CH_2)_4CH{=}^{c}CH(CH_2)_2CHOH(CH_2)_7COOH.$ (A1).

⋮

↓

$CH_3(CH_2)_4CH{=}^{c}CH(CH_2)_2CO(CH_2)_7COOH.$ (A31).

PART TWO

SYNTHESIS OF QUEEN SUBSTANCE

Let mares and cows, by calculating,
Improve themselves with loveless mating,
Let groundings breed in modern fashion,
I'll stick to the air and grand old passion,
I may be small and I'm just a bee,
But I won't have Science improving me.

Song of the Queen Bee.

INTRODUCTION

A normal colony of honeybees (Apis mellifera) is composed of three main types of adult members. These members are:-

1. The Queen Bee

The queen honeybee is a female who, under normal circumstances, is responsible for the laying of eggs from which all members of the colony arise. With evolution, she has become so highly specialised as an egg-producing mechanism that she differs in a great many respects from the normal female members of the colony, i.e. the worker bees. Indeed, so specialised is she that she is totally dependent on the worker bees to provide her with a nest, and food and to raise her offspring.

At the height of summer, when a colony is most active, there is usually only one mated queen in the hive.

2. The Worker Bees.

The worker bees, which constitute by far the largest part of any single colony, are sterile females. As their name implies they are responsible for the upkeep of the whole community, their work ranging from collecting pollen and nectar, to raising the larvae within the hive. Since a queen bee can only originate from a fertilised egg, worker bees are incapable of laying eggs from which a new queen may be raised; they can, however, lay unfertilised eggs and these invariably produce drones, the male of the species. It is only under abnormal conditions that workers will lay such eggs, e.g. loss of the queen from the hive. Normally all eggs are laid by the queen herself.

Thriving communities usually contain about fifty thousand workers.

3. The Drones

The drone honeybee is a fertile male whose sole apparent role is to take part in the reproductive cycle of the species. He does no work within the hive nor does he collect pollen or nectar.

Whereas most colonies contain large numbers of worker bees they only contain a few hundreds of drones.

Mated queen honeybees are capable of laying both fertilised and unfertilised eggs. The latter always produce drones whereas the former invariably produce female honeybees. In principle then, every fertilised egg can give rise to a queen or to a worker. The most recent theory[19] to account for the dual productive power of a female egg is based on the differential feeding of the larva which emerges from the egg. It has been observed that all larvae are provided with the same food (brood food), and in the same quantities, during the first three days of their existance, but that after this time the potential queens are fed brood food in larger quantities than are potential workers. It may also be that the quality of the food differs, certain further constituents to the normal diet being necessary to promote complete differentiation. Furthermore, the cell from which a queen will eventually emerge is always very much larger than normal. This, of course, allows the larva in such a cell to have the necessary, much larger, store of foodstuff.

From these facts, then, it is apparent that the worker bees, provided they have access to a female larva which is not more than three days old can, by a process of differential feeding and queen cell construction, raise a new queen. However, the whole social organisation within the hive is

FIGURE 11 – *Marked queen (with a green spot) with 'court'. The worker near her tail is probably collecting queen substance, the one near her head is feeding her. (Natural size.)*

The collection of queen substance. The second worker from the left is licking the queen substance from the body of her queen.

Worker bees interchanging food which probably contains queen substance (From

dependent on there being only one, or, at the most two queens, in a hive at the same time. Hence, random raising of new queens by the workers would lead to chaos within the hive and complete destruction of "colony morale." Fortunately, a mechanism is operative within a colony which inhibits queen rearing by the worker bees.

Butler,[20] and de Groot and Voogd[21] observed that, provided a healthy queen was present in a hive, the worker bees did not attempt to raise a new queen and that under these conditions their ovaries remained small and undeveloped with no differentiation in the ovarioles. It was also shown that the ethanolic extract of the queen's body had the same inhibitory effect as the queen herself. Further work by Butler[22-28] and his co-workers has led to an almost complete understanding of the inhibitory mechanism of queen rearing.

Provided worker bees were in direct physical contact either with the queen bee herself or with other members of the community who were, their ovaries remained undeveloped and no attempts were made to raise new queens. Butler[20] proposed that the queen herself was producing a compound which had this inhibitory effect on the workers. This compound he called "queen substance." He showed that "queen substance" is produced in the mandibular glands of the queen and is distributed over the body of the queen when she grooms herself. Workers in bodily contact with their queen lick this material from her body and can pass it on to other members of the community, who are not in direct contact with the queen, in regurgitated food (see prints). Thus all members of the colony are kept reasonably well supplied with "queen substance". Provided that the workers are not deprived of this material they will not attempt to raise a new queen.

Such compounds which are produced by one individual of a species and which affect the development processes in another individual have been called pheromones[29] and compounds showing similar physiological properties have been found in silkworms,[30] gypsy moths,[31] water bugs,[32] ants,[29] termites[29] locusts,[33] and prawns[34]. It is postulated that the pheromones are not the active species concerned in the physiological effect, but that they supply a"trigger-mechanism" for the active species.[29]

Although "queen substance" inhibits queen raising in a healthy colony it does not prejudice further propagation of the species. When a colony becomes overcrowded, supplies of "queen substance" are cut down due to increased demand, and so, being deprived of the inhibitory factor, some sections of the community set about raising a new queen from a female larva which is not more than three days old. Having raised the queen the workers then follow her, i.e. "swarming" occurs, and so propagate the species. In the event of a queen failing to yield sufficient "queen substance" for her colony, through illness, old age or death, then once again a new queen is raised and eventually "supercedes" the old one.

Hence "queen substance" operates a mechanism whereby colonial organisation is kept intact without prejudicing further propagation of the species.

Ethanolic extraction of queen bees gave a compound which inhibited queen rearing.[23] From this extract by a process of solvent extraction, partition and chromatography, Butler, Callow and Johnston[35] and Barbier, Lederer, Reichstein and Schindler[36] isolated a crystalline carboxylic acid. The characteristic infrared and ultraviolet spectra

of this compound indicated that "queen substance" was an $\alpha:\beta$ - unsaturated carboxylic acid which contained a further unconjugated carbonyl function. The 2:4 dinitrophenylhydrazone showed maximum absorption in the ultraviolet spectrum at 362mu, confirming the presence of a saturated ketonic grouping. The positive iodoform test which was obtained confirmed the presence of a methyl ketone in the molecule.

When potentiometric measurements gave a molecular weight of the order of 190 it was suggested[35] that "queen substance" was closely related to trans-10-hydroxydec-2-enoic acid[37] (B23) (Royal Jelly acid) which is the predominant acidic component of brood food.

Subsequent work by Butler, Callow and Johnston[38,39] and by Barbier and Lederer[40] has led to the complete elucidation of the structure.

Complete Clemmensen[38] reduction of "queen substance" gave decanoic acid (B2), Catalytic reduction[38] over Adam's catalyst yielded a ketonic acid which was identical with 9-oxodecanoic acid (B3). Huang-Minlong reduction[40] of the natural product afforded dec-2-enoic acid (B10). Finally, complete reduction[40] of the acid with lithium aluminium hydride gave the diol (B9) which was reportedly identified by synthesis, although no details were given.

These observations indicated that "queen substance" was 9-oxodec-2-enoic acid (B1) and the infrared spectrum suggested that it was probably the trans isomer of this compound.

Subsequently the keto acid (B3) obtained from the catalytic hydrogenation of queen substance has been more thoroughly investigated.[39] Conversion of the keto acid (B3) to the mixed oximes (B4, B6) was followed by a

Beckmann rearrangement and acid hydrolysis. Paper chromatography of the products, identified methylamine (B6) acetic acid (B7) and ω-aminooctanoic acid (B8), thus confirming that the keto-acid was indeed 9-oxodecanoic acid (B3). This conclusively fixed the position of the carbonyl group in queen substance (B1).

That "queen substance" was, indeed, trans 9-oxodec-2-enoic acid (B1) was confirmed by the following synthesis[38,39] details of which were not available until completion of the present work.

Azelaic acid (B11) was converted to methyl hydrogen azeleate (B12); the acid chloride of this ester (B13) was brominated and then esterified with isopropanol to give isopropyl methyl α-bromoazeleate (B15). Dehydrobromination with powdered calcium carbonate[39] or with collidine[38] afforded the unsaturated ester (B16) which was selectively hydrolysed to give isopropyl 8-carboxyoct-2-enoate (B17). The corresponding acid chloride (B18) was treated with cadmium dimethyl and the resultant keto-ester (B19) hydrolysed. The product, trans-9-oxo-dec-2-enoic acid was identical in all respects with natural queen substance and in a concentration of 0.13 ug per bee inhibited the construction of queen cells.

Recently, Butler[41] has shown that although synthetic queen substance is biologically active, it is not active to the same extent as the extract from a queen bee's body. This increased activity in natural material he attributes to the presence of a scent in the natural material which attracts the worker bees to the source. Both the methyl ester of queen substance and cis 9-oxodec-2-enoic acid[42] have been shown to be biologically active. However the C_9 homologue 8-oxonon-2-enoic acid[43] is inactive.

Several C_{10} straight chain carboxylic acids have been isolated from honeybee sources. Royal Jelly, the brood food of the honeybee, has been thoroughly investigated as a source of carboxylic acids. The first acid to be identified in Royal Jelly was trans-10-hydroxydec-2-enoic acid[32] (B23); closer investigation showed the presence of trans-dec-2-enedioc acid[44] (B24), sebacic acid[44] (B25) and ω-hydroxy-decanoic acid[45] (B26). Brown and Felaner[46] have isolated 9-hydroxydec-2-enoic acid (B22) from Royal Jelly and this substance may well constitute the biogenetic link between Royal Jelly and queen substance. It seems reasonable to suppose that all of these compounds belong to a biosynthetic plan which is peculiar to honeybees. A tentative scheme accommodating all the facts is shown on the accompanying chart.

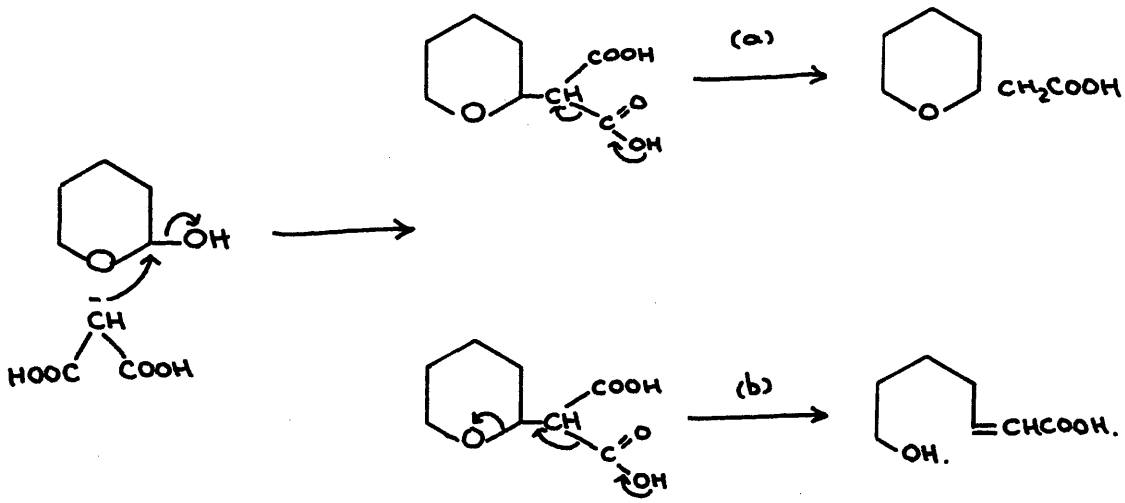
The 9:10-epoxydec-2-enoic acid (B21) may be regarded as the key substance, built up by the repeated condensation of acetate units. It would be feasible for this acid to undergo enzymatic transformation with opening of the epoxide ring to give either 9-hydroxydec-2-enoic acid (B22) or 10-hydroxydec-2-enoic acid (B23). Oxidation of the hydroxy acid (B22) will then give queen substance (B1); it would appear that such a process can only take place in the mandibular glands of the queen bee. Royal jelly acid (B23) can by a series of enzymatic oxidations and reductions give rise to the co-occurring acids (B24, B25, B26). The postulated key biogenetic precursor 9:10-epoxydec-2-enoic acid (B21) has not been isolated but in this context epoxy acids in nature are not unknown[5].

DISCUSSION

Under acidic conditions 2:3 dihydropyran (B27) reacts with water to give 2-hydroxytetrahydropyran[47] (B28), the cyclic hemiacetal tautomer of 5-hydroxypentanal. Colonge and Corbet[48,49] have shown that, in aqueous base 2-hydroxytetrahydropyran (B28) condensed with compounds which contain an active methylene group to give tetrahydropyranyl derivatives substituted in the 2-position: e.g. condensation with acetone gives 2^1 - tetrahydropyranyl acetone in 63% yield. In all cases quoted by these authors no cyclic compounds were isolated.

2-Hydroxytetrahydropyran (B28) was condensed with malonic acid in dry pyridine with an added trace of piperidine. Spontaneous decarboxylation took place and from the reaction mixture two products were isolated by fractional distillation. The lower boiling component, which solidified at room temperature, was shown to be 2-tetrahydropyranylacetic acid (B33). The other component, a viscous oil, had an infrared spectrum which suggested that it was a hydroxy-α:β-unsaturated acid; this acid was characterised via the corresponding crystalline α-napythylurethane and the structure (B29) was confirmed by subsequent conversion of the acid to the crystalline trans 7-bromohept-2-enoic acid (B35). Further verification was obtained in the following way. 2-tetrahydropyranylacetic acid (B33) was refluxed in acetic acid containing anhydrous zinc chloride[50]. The resultant 7-acetoxyhept-2-enoic acid (B32) was hydrolysed to give 7-hydroxyhept-2-enoic acid (B29) which was identical in all respects with the compound derived from the condensation of 2-hydroxytetrahydropyran (B28) with malonic acid.

A possible mechanism for the condensation is shown overleaf.



I.

Condensation of 2-hydroxytetrahydropyran with malonic acid gives the intermediate (I), decarboxylation of which by route (a) without concomitant ring scission, yields 2-tetrahydropyranylacetic acid (B33), whereas decarboxylation with ring scission as in route (b) gives 7-hydroxyhept-2-enoic acid (B29).

Under identical conditions 2:3 dihydropyran condensed with malonic acid to give the same products as did 2-hydroxytetrahydropyran, although in somewhat smaller yield. This represents a completely novel reaction of 2:3-dihydropyran: the usual reaction of this compound with carboxylic acids yields tetrahydropyranyl esters[51].

This reaction can be rationalised in terms of piperidine addition across the double bond of 2:3-dihydropyran (B27) to give 2-piperidinotetrahydropyran which is then attacked by a malonic acid anion to give the intermediate (I)

This can then give rise to the same products as were derived from 2-hydroxytetrahydropyran (B28).

By using an excess of malonic acid (10-50%) in the condensation an overall yield of 52% was obtained. This yield was composed of approximately 10% 2-tetrahydropyranyl-acetic acid (B33) and 40% trans-7-hydroxyhept-2-enoic acid (B29). The corresponding overall yield from 2:3-dihydropyran was 30%.

Attempted conversion of 2-tetrahydropyranylacetic acid into 7-hydroxyhept-2-enoic acid using toluene-p-sulphonic acid or sodium ethoxide failed. However, conversion was affected by treatment with zinc chloride in acetic acid[50].

7-Hydroxyhept-2-enoic acid (B29) was converted into 7-bromohept-2-enoic acid (B35) in 25% yield by treatment with phosphorus tribromide in the presence of pyridine. Further attempts to increase the yield of this bromination by varying the concentration of pyridine and the nature of the solvent failed. The poor yield was probably due to intermolecular esterification of the hydroxy acid (B29) to give a polymer. This seems reasonable in light of the fact that the corresponding methyl ester (B30) brominated very smoothly. Chlorination and Tosylation also failed to give higher yields.

Esterification prior to bromination was attempted. In an excess of methanol containing 5% concentrated sulphuric acid, 7-hydroxyhept-2-enoic acid gave a 2:1 mixture of methyl 7-hydroxyhept-2-enoate (B30) and methyl 2-tetrahydropyranylacetate. The latter was identified by synthesis from 2-tetrahydropyranylacetic acid and diazomethane. Esterification of 7-hydroxyhept-2-enoic acid with diazomethane gave an 84% yield of trans-methyl

7-hydroxyhept-2-enoate (B30). This ester was readily converted into methyl 7-bromohept-2-enoate in 70% yield by treatment with phosphorus tribromide in the presence of pyridine. Mild alkaline hydrolysis of the bromo ester (B31) with one equivalent of base afforded the corresponding bromo acid (B35) in 65% yield.

When 2-tetrahydropyranylacetic acid (B33) was treated either with anhydrous gaseous hydrogen bromide at 120°, or with an excess of a 50% solution of hydrogen bromide in glacial acetic acid, a saturated bromine-containing acid was formed. Distillation of this acid gave a product which showed weak double bond absorption in the infrared spectrum. This suggested that the original product was losing hydrogen bromide on distillation and was probably 3:7-dibromoheptanoic acid (B32). Similar treatment of 7-hydroxyhept-2-enoic acid (B29) gave an identical product. When this product was treated with collidine in benzene, 7-bromohept-2-enoic acid was obtained in 50% yield.

It was found convenient to treat the crude mixture of the acids (B29) and (B33), obtained from the condensation of 2-hydroxytetrahydropyran with malonic acid, successively with hydrogen bromide in glacial acetic acid and collidine in benzene. From the reaction mixture 7-bromohept-2-enoic acid (B35) was isolated in an overall yield of 35%.

Condensation of 7-bromohept-2-enoic acid (B35) with one mole of ethyl acetoacetate in the presence of two moles of sodium ethoxide gave a substituted acetoacetate (B36) which was not purified. Mild hydrolysis with 5% sodium hydroxide gave the corresponding acid (B37) which decarboxylated in acidic solution to yield crystalline trans-9-oxodec-2-enoic acid (B1) in an overall yield (from 7-bromohept-2-enoic acid) of 46%.

The product gave a correct analysis for $C_{10}H_{16}O_3$ and was further characterised by its semicarbazone, and 2:4-dinitrophenylhydrazone. The infrared spectrum was identical with that of natural "queen substance" and a mixed melting point determination with a natural sample showed no depression.

Attempted condensation of methyl 7-bromohept-2-enoate with ethyl acetoacetate under identical conditions gave an acidic product which did not solidify. This product showed very weak double bond absorption in the infrared spectrum. Sublimation of the crude product gave a small amount of a crystalline solid which was shown to be 2-tetrahydropyranyl-acetic acid (B33).

Since the main product appeared to be saturated it is possible that the alkylation of ethyl sodio-acetoacetate had not taken place and that a Michael addition of ethyl acetoacetate across the double bond of methyl 7-bromohept-2-enoate had occurred preferentially. In the case of 7-bromohept-2-enoic acid, the presence of a carboxyl anion may well have prevented the occurrence of this unfavourable condensation.

Since the completion of this work two different independent syntheses of "queen substance" have been reported.

Barbier, Lederer and Nomura,[43,53] converted cycloheptanone (B38) into 1-methylcycloheptanol (B39) by a Grignard reaction. The product (B39) was dehydrated to give methylcyclohept-1-ene (B40); ozonolysis and reductive cleavage of the ozonide yielded 7-oxooctanal (B41) which was condensed with malonic acid in a Doebner reaction. The product, trans-9-oxodec-2-enoic acid (B1), was identical with natural material. The same workers have also published[42] a synthesis of <u>cis</u>-9-oxodec-2-enoic acid.

Jaeger and Robinson[54] hydrolysed 2-acetylcyclohexanone (B42) to 7-ketooctanoic acid (B43). The acid chloride of this acid (B44) was hydrogenated in xylene over palladium on barium sulphate to give 7-oxooctanal (B44). Doebner condensation of this aldehyde with malonic acid gave trans-9-oxodec-2-enoic acid (B1).

EXPERIMENTAL

All melting points were determined on a Kofler Block and infrared spectra on a Perkin Elmer Infracord spectrophotometer.

2-Hydroxytetrahydropyran[47] (B28)

2:3 Dihydropyran (50g) was added to a vigorously stirred mixture of concentrated hydrochloric acid (12ml) and water (150ml). After the mixture became homogeneous stirring was continued for a further 30 minutes. The reaction mixture was then carefully treated with 20% aqueous sodium hydroxide until it was just alkaline to phenolphthalein. The mixture was continuously extracted with ether overnight and the ether extract dried. Removal of solvent gave a pale yellow oil which was distilled under reduced pressure. The product (44g: 73%) distilled at $81^{o}/15$m.m; n_D^{21} 1.4512 (Lit.[47] $62-66^{o}/10$m.m. n_D^{25} 1.4513).

Condensation of 2-hydroxytetrahydropyran and malonic acid.

2-Hydroxytetrahydropyran (20.5g: 0.2M) and reagent grade malonic acid (23g: 0.22M) were dissolved in dry pyridine (24g; 0.3M) containing piperidine (Iml). After standing overnight at room temperature, the mixture was heated on the steam bath until evolution of carbon dioxide ceased (4 hr) and then most of the pyridine was evaporated off. The residue was poured into sulphuric acid (15ml;2N), saturated with salt, and extracted with ether. The extracts were dried and solvent removal gave a clear, pale yellow oil. Fractional distillation through a 15 cm. Vigreux column gave two fractions:-

(i) 2-Tetrahydropyranyl acetic acid (2.5g: 9%) b.p.140^{o}-150^{o}/5m.m. crystallising from light petroleum (b.p.40^{o}-60^{o}) in colourless needles m.p. 55^{o} (lit.[56] 55^{o} -57^{o}).
(Found: C.58.5; H.8.4. Calc. for $C_7H_{12}O_3$: C, 58.3; H.8.4%)

ν_{max} (Nujol mull): 2650, 1710, 1090, 1050 cm^{-1}.

(ii) 7-Hydroxyhept-2-enoic acid (12g: 43%) b.p. 160°/0.1m.m. A redistilled sample had b.p. 152°/0.1m.m. n_D^{19} 1.4780. 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 colourless needles, m.p. 136.5°.
(Found: C.69.0; H.6.3; N.4.6. Calc. for $C_{18}H_{19}NO_4$: C.69.0; H.6.1; N.4.5%).

Condensation of 2:3-dihydropyran with malonic acid

2:3 Dihydropyran (4.1g: 0.04M) was treated with malonic acid (4.6g: 0.044M) in pyridine (5ml) containing piperidine (0.25ml) under the same conditions as in the reaction of 2-hydroxytetrahydropyran described above. Distillation gave 2-tetrahydropyranylacetic acid (0.35g: 6%) : m.p. and mixed m.p. 55° and 7-hydroxyhept-2-enoic acid (1.7g: 30%). (α-Naphthylurethane, m.p. and mixed m.p. 136.5°).

When this experiment was repeated using one molar equivalent of piperidine, malonic acid was recovered in 75% yield, no product being isolated.

No reaction took place when there was no piperidine present in the reaction mixture.

Conversion of 2-tetrahydropyranylacetic acid (B33) into 7-hydroxyhept-2-enoic acid (B29)

(a) 2-Tetrahydropyranylacetic acid (5.5g) was refluxed for 3 hours with zinc chloride (100mg) in acetic acid (20ml). Most of the acetic acid was removed under reduced pressure and 20% aqueous sodium hydroxide added until the solution was alkaline. Filtration, acidification with concentrated hydrochloric acid and ether extraction gave a colourless oil (2.8g).

ν_{max} (thin film) 1730, 1700, 1650, 1250 cm^{-1}.

The crude product was hydrolysed with aqueous sodium hydroxide for 2 hours on the steam bath. Acidification followed by ether extraction gave a viscous oil (1.6g) which was distilled. b.p. 152^{o}/0.1m.m. n_{D}^{21} 1.4850. This was shown to be identical with the 7-hydroxyhept-2-enoic acid prepared above by comparison of infrared spectra and by a mixed m.p. of the α-naphthylurethanes.

(b) When 2-tetrahydropyranylacetic acid was distilled from a small proportion (5%) of p-toluenesulphonic acid, starting material was recovered unchanged.

(c) After treatment with sodium ethoxide in refluxing ethanol in catalytic and molar proportions 2-tetrahydropyranylacetic acid was recovered unchanged.

7-Bromohept-2-enoic acid (B35)

(a) To a cooled solution of 7-hydroxyhept-2-enoic acid (7g: 0.049M) in pyridine (5ml) and dry ether (50ml), phosporus tribromide (6.5g: 0.025M) was added slowly with stirring at a rate such that the temperature did not exceed 10^{o}. A sticky semi-solid mass separated out. The mixture was refluxed overnight with stirring and on cooling, water (15ml) was added. The ether layer was separated and the aqueous phase extracted with ether. The combined extracts were washed with dilute acid, dried, and the solvent removed under reduced pressure. Distillation of the residue gave a colourless oil b.p. 120^{o}/0.1m.m. (2.5g: 23%) which crystallised from light petroleum (b.p. 40^{o}-60^{o}) in colourless needles, m.p. 64^{o}.
(Found: C.40.5; H.5.7. $C_7 H_{11} O_2 Br$. requires: C 40.5; H.5.3%)
ν_{max} (Nujol mull): 2650, 1700, 1650, 985 cm^{-1}.

The above procedure was repeated using benzene and chloroform as solvents but in neither case was the yield greater than 20%.

The use of pyridine in molar quantities also failed to improve the yield. In the absence of pyridine the yield was again less than 20%.

(b) 2-Tetrahydropyranylacetic acid (4.5g) was refluxed for 2 hours with an excess of hydrogen bromide in glacial acetic acid (50% w/v). The cooled mixture was poured into water (100ml). A heavy oil separated out and this was extracted from the aqueous mixture with ether. The combined ether extracts were thoroughly washed with water and dried. Removal of solvent gave a dark brown oil (8.8g). The product was an acid which showed no hydroxyl or double bond absorption in the infrared, and contained bromine (sodium fusion). ν_{max} (thin film) 1710, 2650 cm^{-1}.

A sample of the product on distillation gave a colourless oil b.p. 130°/0.1m.m. but the infrared spectrum was not identical with that of the crude material. ν_{max} (thin film) 2650, 1705, 1650, 980 cm^{-1}.

The crude oil (8g) was refluxed in benzene (30ml) with collidine (3.5g: 1 equiv.) for 30 minutes. Sulphuric acid (6N, 10ml) was added to dissolve the collidine hydrobromide and the whole extracted with ether. The ether extracts after washing with dilute sulphuric acid and brine were dried and evaporated. Distillation of the dark brown oil (6g) gavetthe bromo-acid (3g: 50%) b.p. 120-130°/0.1m.m. m.p. and mixed m.p. 64°.

(c) A mixture of 7-hydroxyhept-2-enoic acid and 2-tetrahydropyranyl acetic acid (10g) (obtained from the condensation of 2-hydroxytetrahydropyran and malonic acid without fractionation)

was refluxed with an excess of hydrogen bromide in glacial acetic acid (50% $^{w}/_{v}$) for 3 hours. The treatment with collidine, as described in part (b) above, gave a dark brown oil (9g) which on distillation gave 7-bromohept-2-enoic acid (5g: 35%) b.p. 120-130°/0.1m.m., m.p. and mixed m.p. 64°.

7-Chlorohept-2-enoic acid.

Redistilled thionyl chloride (6g: 0.041M) was added dropwise with stirring to a cooled solution of 7-hydroxyhept-2-enoic acid (5g: 0.035M) in ether (50ml) containing pyridine (0.5ml). After heating on a steam bath for 2 hours, pyridine (5ml) and water (10ml) was added and the mixture extracted with ether. Drying and removal of solvent gave a dark brown oil (4.8g) which was distilled to give a colourless liquid (1.5g: 25%) b.p. 112-116°/0.1m.m., n_D^{18} 1.4859.
ν_{max} (thin film) 2750, 1700, 1650, 980 cm^{-1}.

7-Tosylhept-2-enoic acid.

Tosyl chloride (700mg) was added in portions to an ice cold solution of 7-hydroxyhept-2-enoic acid (500mg) in pyridine (5ml). After standing at 0° for 24 hours the mixture was poured into water and extracted with ether. The ether extract was thoroughly washed with dilute acid and water, dried over magnesium sulphate and evaporated. The resultant pale yellow oil (600mg) failed to crystallise.

Methyl 7-Hydroxyhept-2-enoate (B30)

(a) 7-Hydroxyhept-2-enoate (10g) was refluxed for 2 hours with methanol (100ml) containing concentrated sulphuric acid (5ml). Most of the solvent was removed under reduced pressure and water was added. Ether extraction was followed by washing the extracts with bicarbonate solution, brine and

drying. Removal of solvent gave a colourless oil (8g). Fractional distillation gave two products:-

(i) b.p. 68-71°/2m.m. n_D^{20} 1.4450 (2.5g: 23%)

(ii)b.p. 88-90°/0.1m.m. n_D^{26} 1.4608 (5g: 46%)

Methyl 2-tetrahydropyranylacetate was prepared from 2-tetrahydropyranylacetic acid and was identical with the lower boiling fraction.

ν_{max} (thin film): 1720, 1030, 1080 cm^{-1}.

The higher boiling fraction was assumed to be methyl 7-hydroxy hept-2-enoate.

ν_{max} (thin film) 3400, 1710, 1670, 970 cm^{-1}.

(b) 7-Hydroxyhept-2-enoic acid (10g) was dissolved in anhydrous ether (100ml) and titrated with an ethereal solution containing diazomethane (~3g) until immediate evolution of nitrogen ceased and a faint yellow colouration appeared. After standing for 15 minutes a few drops of acetic acid were added to destroy excess reagent. The ethereal solution was washed with bicarbonate dried and evaporated. Distillation gave methyl 7-hydroxyhept-2-enoate (9g: 84%) b.p. 86-90°/0.1m.m. n_D^{20} 1.4630.

ν_{max} (thin film) 3400, 1710,1670, 970 cm^{-1}.

Methyl 7-bromohept-2-enoate (B31)

To an ice cold solution of methyl 7-hydroxyhept-2-enoate (7.5g) in dry benzene (30ml) containing pyridine (0.5ml), phosphorus tribomide (5g) in benzene (10ml) was added at such a rate that the temperature did not exceed 15°. The mixture was then heated under reflux for 4 hours. On cooling, pyridine (5ml) and water (10ml) were added. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed with

sulphuric acid (6N), brine, dried and evaporated. The colourless oil was distilled (8.9g: 84%) b.p.92-102°/0.1m.m. A redistilled sample had b.p. 78°-80°/0.05m.m. n_D^{25} 1.4795. (Found: C.43.7; H.6.0; Br.36.3. $C_8 H_{13} O_2 Br$ requires C.43.5; H.5.9; Br 36.1%)

ν_{max} (thin film) 2650, 1710, 1670, 970 cm^{-1}.

7-Bromohept-2-enoic acid (B35)

Methyl 7-bromohept-2-enoate (2.2g: .01M) was allowed to stand at room temperature in methanol (20ml) containing sodium hydroxide (0.4g: .01M). Most of the solvent was removed and water (5ml) added. Neutral material was removed with ether. Acidification with dilute sulphuric acid and ether extraction gave 7-bromohept-2-enoic acid (1.3g: 65%) b.p. 120-130°/0.1m.m. m.p. and mixed m.p.64°.

9-Oxodec-2-enoic acid (B1)

7-Bromohept-2-enoic acid (1.5g: 0.007M) in absolute ethanol (5ml) was added dropwise with stirring to a solution prepared from sodium (0.4g: 0.017M), absolute ethanol (45ml) and ethylacetoacetate (2g: 0.016M). The pale yellow solution was refluxed overnight and then concentrated. After acidification, ether extraction gave a yellow oil (1.3g) which was then dissolved in 5% aqueous sodium hydroxide solution (10ml) and allowed to stand overnight at room temperature. Sulphuric acid (50%: 2ml) was then added and the mixture kept overnight. The product taken up in ether was extracted with saturated aqueous sodium bicarbonate. Acidification and ether extraction gave the keto-acid as a pale yellow oil (0.6g: 46%) which rapidly solidified m.p. 40-50°, raised to 54.5-55° by recrystallisation 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%)
ν_{max} (Nujol mull) 2715, 1710, 1685, 1640, 994 cm^{-1}.
was identical with that of an authentic sample of queen substance and a mixed m.p. showed no depression.

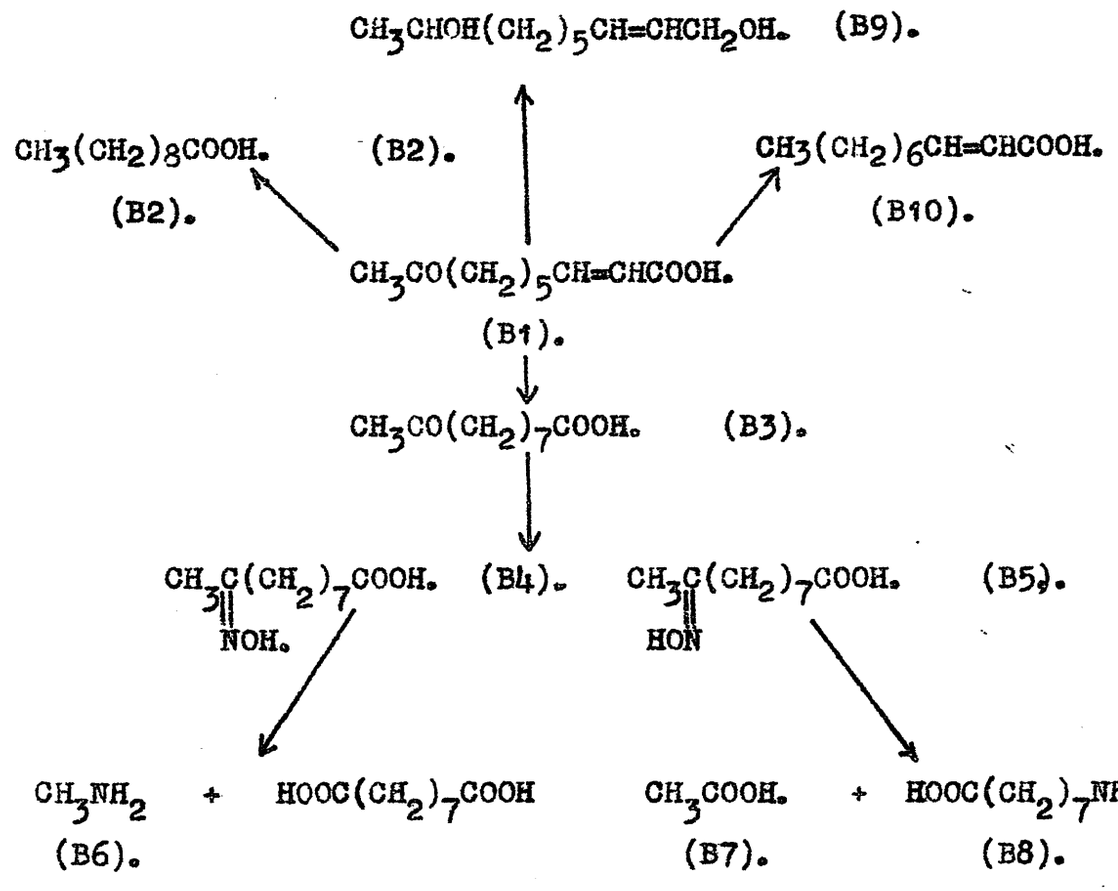
The semicarbazone recrystallised from aqueous ethanol in colourless needles m.p. 163.5-164.5° (Found: C.54.6; H. 8.0; Calc. for $C_{11}H_{19}N_3O_3$: C.54.8; H 7.9%). The 2:4 dinitrophenylhydrazone m.p. 105-119°.

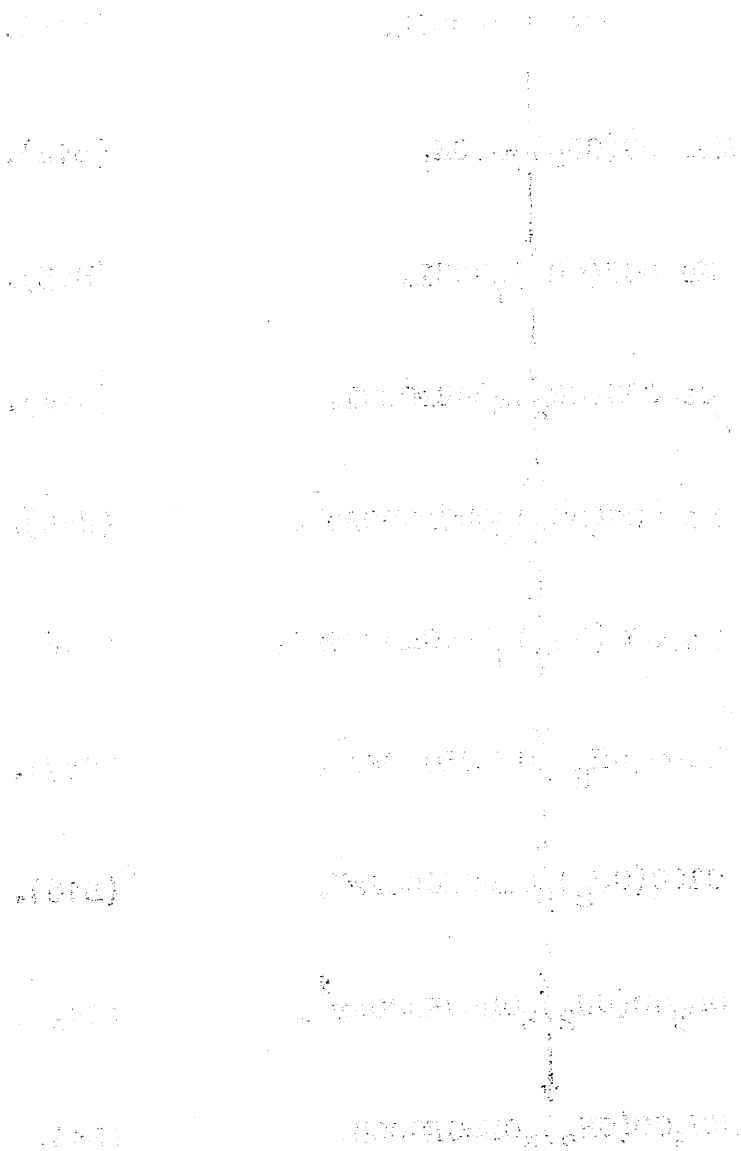
Condensation of methyl 7-bromohept-2-enoate with acetoacetic ester.

Methyl 7-bromohept-2-enoate (3g) in absolute ethanol (5ml) was added dropwise to a stirred solution prepared from sodium (0.46g: 1.4 equivs.), acetoacetic ester (2.38g; 1.3 equivs.) and ethanol (30ml). After stirring for one hour the mixture was refluxed overnight and then concentrated. Addition of dilute acid was followed by ether extraction. The resultant pale yellow oil was stirred with sodium hydroxide (2g: 2.6 equivs.) in water (20ml). After 8 hours sulphuric acid (6ml; 50%) was added and the whole left overnight. The product, taken up in ether, was extracted with saturated aqueous sodium bicarbonate. Acidification and ether extraction gave a dark brown oil (1.9g) which did not solidify.
ν_{max} (thin film) 2750, 1710 cm^{-1}.

Sublimation at $70°/10^{-3}$ m.m. of a portion gave a white solid m.p.54-56°. This melting point was undepressed on mixing with 2-tetrahydropyranylacetic acid. An unidentified colourless oil was also obtained. This oil showed very weak double bond absorption in the infrared spectrum.

IB


CH3CHOH(CH2)5CH=CHCH2OH. (B9).
CH3(CH2)8COOH. (B2).
(B2).
CH3(CH2)6CH=CHCOOH.
(B10).
CH3CO(CH2)5CH=CHCOOH.
(B1).
CH3CO(CH2)7COOH. (B3).
CH3C(CH2)7COOH. (B4).
NOH.
CH3C(CH2)7COOH. (B5).
HON
CH3NH2 + HOOC(CH2)7COOH
(B6).
CH3COOH. + HOOC(CH2)7NH2.
(B7). (B8).



$HOOC(CH_2)_7COOH$. (B11).

↓

$Me.OOC(CH_2)_7COOH$. (B12).

↓

$Me.OOC(CH_2)_7COCl$. (B13).

↓

$Me.OOC(CH_2)_6CHBrCOCl$. (B14).

↓

$Me.OOC(CH_2)_6CHBrCOOPr^i$. (B15).

↓

$Me.OOC(CH_2)_5CH{=}CHCOOPr^i$. (B16).

↓

$HOOC(CH_2)_5CH{=}CHCOOPr^i$. (B17).

↓

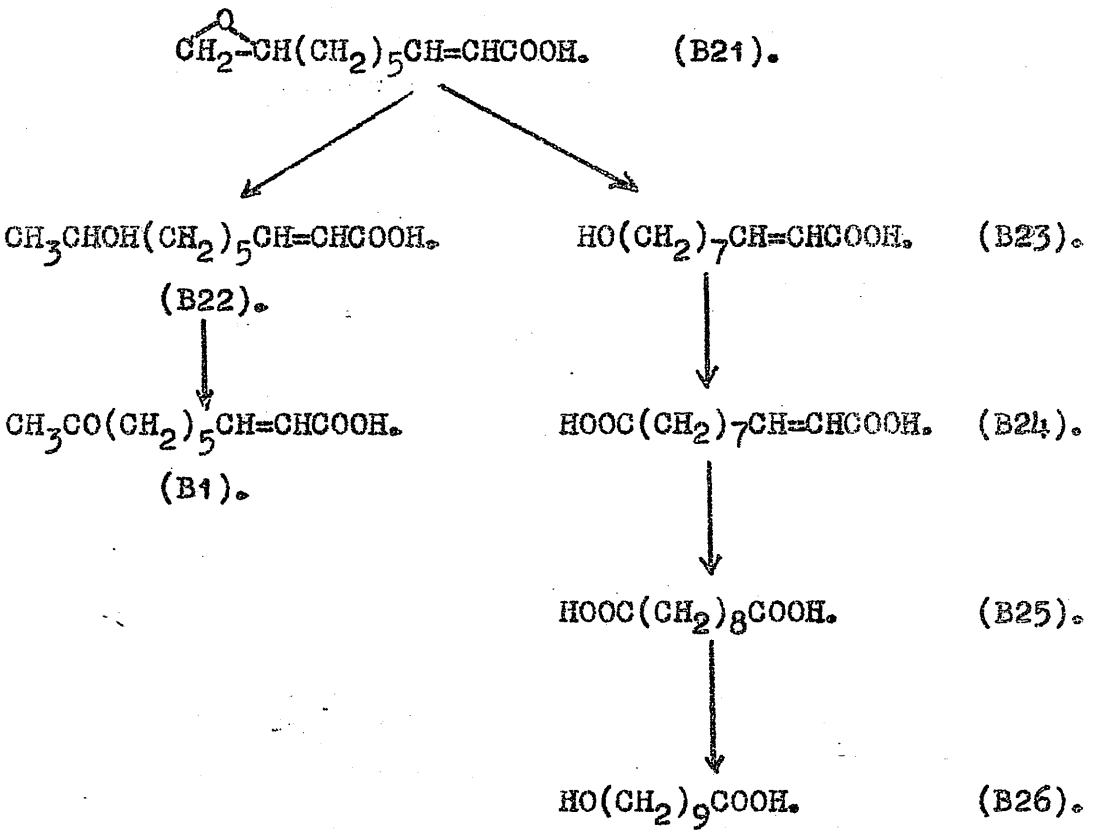
$ClOC(CH_2)_5CH{=}CHCOOPr^i$. (B18).

↓

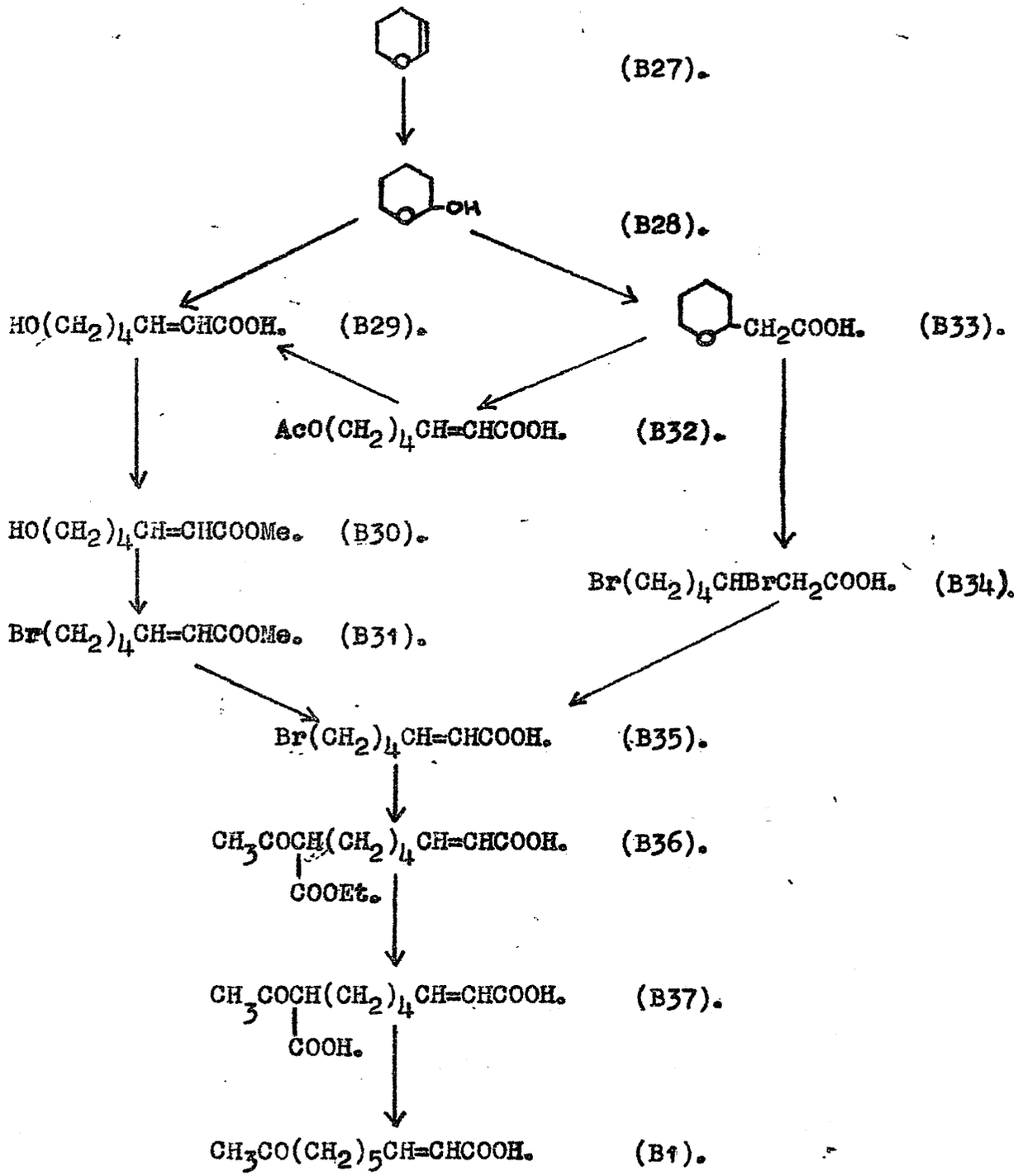
$CH_3CO(CH_2)_5CH{=}CHCOOPr^i$. (B19).

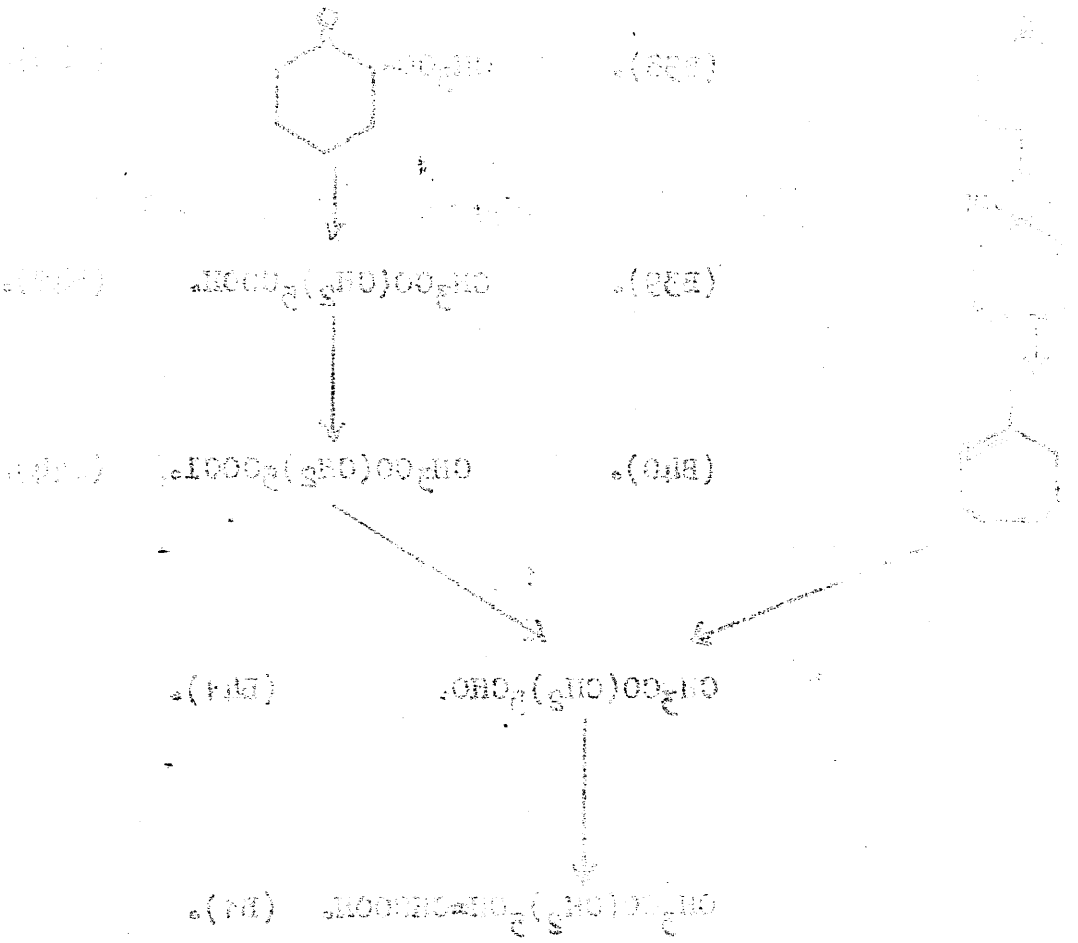
↓

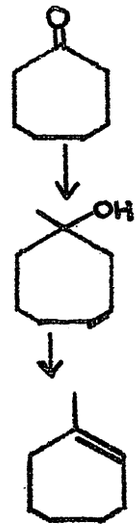
$CH_3CO(CH_2)_5CH{=}CHCOOH$. (B1).


CH_2-$CH(CH_2)_5CH$=$CHCOOH$. (B21).
$CH_3CHOH(CH_2)_5CH$=$CHCOOH$. (B22).
$HO(CH_2)_7CH$=$CHCOOH$. (B23).
$CH_3CO(CH_2)_5CH$=$CHCOOH$. (B1).
$HOOC(CH_2)_7CH$=$CHCOOH$. (B24).
$HOOC(CH_2)_8COOH$. (B25).
$HO(CH_2)_9COOH$. (B26).

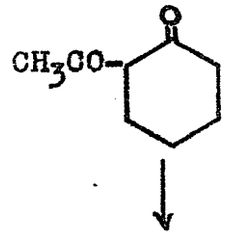
4B


(B27).
OH
(B28).
HO(CH2)4CH=CHCOOH. (B29).
CH2COOH. (B33).
AcO(CH2)4CH=CHCOOH. (B32).
HO(CH2)4CH=CHCOOMe. (B30).
Br(CH2)4CHBrCH2COOH. (B34).
Br(CH2)4CH=CHCOOMe. (B31).
Br(CH2)4CH=CHCOOH. (B35).
CH3COCH(CH2)4CH=CHCOOH. (B36).
COOEt.
CH3COCH(CH2)4CH=CHCOOH. (B37).
COOH.
CH3CO(CH2)5CH=CHCOOH. (B1).





(B38).



(B42).

(B39). $CH_3CO(CH_2)_5COOH$. (B42).

(B40). $CH_3CO(CH_2)_5COCl$. (B44).

$CH_3CO(CH_2)_5CHO$. (B41).

$CH_3CO(CH_2)_5CH=CHCOOH$. (B1).

SYNTHESIS OF CIS-10-HYDROXYDEC-2-ENOIC ACID.

During the first three days of their existence all larvae of a honeybee colony are fed, as part of their diet, a highly nutritious protein-rich food which is produced by the worker nurse bees in their pharyngeal salivary glands.[57] This, the brood food, has been called "Royal Jelly" and all adult worker bees between the ages of 5 and 10 days are capable of producing this material in their mandibular glands[19]. After the third day only the female larvae which are destined to be queen bees are provided with further quantities of Royal Jelly; those larvae which will give rise to worker bees are no longer supplied with this material and their diet throughout the rest of their life consists mainly of pollen and honey. The supply of Royal Jelly to the queen is maintained and continues throughout the span of her life.

It thus seemed reasonable to postulate that some active constituent in this material was responsible for the differentiation of the female honeybees[57]. This proposed physiological activity has led to a thorough investigation of the components of Royal Jelly in an attempt to find the active constituent.

The best source of the natural material has been the contents of the large cells in which the worker bees had set about raising a queen bee from a larva. Townsend and Lucas[57] collected Royal Jelly, dried it over phosphorus pentoxide and extracted dried material with ether. None of the lipid-insoluble components[29,58,45] showed any noteworthy physiological activity in the female differentiation process. However, it was shown that the lipid soluble fraction, which was shown to be almost completely acidic in nature, had a definite effect on the sexual behaviour of the

fruit fly[59,60]. This allied physiological effect was taken to indicate that the active constituent of Royal Jelly might be in the ether-soluble fraction.

The physical nature and chemical composition of Royal Jelly varies considerably, but it has been shown that the ether soluble fraction constitutes about 5-15% of the dried natural material. Townsend and Lucas[57] isolated a carboxylic acid m.p. 45-56° from the lipids in high yield. The acid was optically inactive, had a molecular weight of approximately 180 and was probably $C_{10}H_{18}O_3$. They wrongly postulated that the acid was saturated.

The chemical structure of this acid (Royal Jelly Acid) was determined by Butenandt and Rembold[37]. The pure acid had a melting point of 54-56° and the previous molecular formula of $C_{10}H_{18}O_3$ was confirmed. In conjunction with the ultraviolet absorption spectrum, the infrared spectrum suggested that the carboxylic acid contained a hydroxyl group (3600 cm^{-1}) and a conjugated double bond (1650 cm^{-1}). The stereochemistry about the double bond was not known at this stage due to complications in the infrared spectrum in the region 800-1000 cm^{-1} which were attributed to the hydroxyl group.

Catalytic hydrogenation[37] of Royal Jelly acid resulted in the uptake of one mole of hydrogen and the formation of 10-hydroxydecanoic acid (C2), a known compound. Further identification was provided by lithium aluminium hydride reduction to decamethylene diol (C3) which was oxidised with chromium trioxide to decanedioic acid (C4).

These results sgggested that Royal Jelly acid was 10-hydroxydec-2-enoic acid (C1,B23). A subsequent investigation[61] has confirmed this structure, and a study

of the nuclear magnetic resonance spectrum[62] of the methyl ester has elucidated the configuration of the double bond. The τ values and the coupling constant which were found for the olefinic protons were those to be expected of a trans disubstituted olefin.

Hence, Royal Jelly acid was shown to be trans-10-hydroxydec-2-enoic acid (C1, B23) and identical with a crystalline acid isolated directly from the mandibular glands of worker bees by Callow, Johnston and Simpson[63].

Several closely related carboxylic acids have been isolated from Royal Jelly in much smaller amounts than 10-hydroxy-dec-2-enoic acid (C1, B23). These acids include dec-2-enedioic acid[44] (B24), decanedioic acid[44] (B25), 10-hydroxydecanoic acid[45] (B26), and 9-hydroxydec-2-enoic acid[46] (B22). It seems likely that along with trans-9-oxodec-2-enoic acid (B1), these C_{10} acids are part of a common biosynthetic plan. (Part 2 p. 25). Although tracer studies using labelled acetate and stearate have been begun[64] no results have yet been published, nor are any results available which establish that 10-hydroxydec-2-enoic acid (C1, B23) is indeed the component of Royal Jelly which causes differentiation in the female larvae. Nevertheless, it is tempting to speculate that 9-hydroxydec-2-enoic acid (B22) and 10-hydroxydec-2-enoic acid (B23, C1) which may have the common biogenetic precursor (B21) (See part 2 p.25) play an important role in the honeybee life cycle. It is plausible that, having been passed on to the larvae, in Royal Jelly, the 10-hydroxy isomer (B23, C1) causes the necessary "trigger reaction" for sexual differentiation of the larvae. The 9-hydroxy isomer (B22), on the other hand, maybe oxidised in the mandibular glands of the queen and passed back to the

workers in the form of queen substance, (B1, Part 2, p.24). The queen substance, in turn, triggers off the process whereby further queen rearing is controlled and in so doing regulates the distribution of further supplies of Royal Jelly (containing the 10-hydroxy isomer) to the larvae.

This postulated mechanism would provide a cyclic regenerative system involving the queen and the workers.

Recent interest in Royal Jelly acid has been further stimulated by the findings[65] that Royal Jelly inhibited the development of transplantable mouse leukaemia and the formation of tumours in mice, and that trans 10-hydroxydec-2-enoic acid (C1) was 100 times more active than Royal Jelly itself.

Prior to the beginning of the work reported in this thesis no synthesis of trans-10-hydroxydec-2-enoic acid (C1) had been reported.

DISCUSSION

The base-catalysed Faworsky rearrangement of α-halogenated ketones[66,69] to carboxylic derivatives is capable of wide structural variations (for full discussion see p.53). One of the least studied examples involves the rearrangement of an $\alpha:\alpha$- dihalogeno-ketone to an $\alpha:\beta$- unsaturated acid, e.g.

$$CH_3.CO.CHBr_2 \xrightarrow{OH^-} CH_2 = CH.COOH.$$

This type of rearrangement has attracted little interest since Faworsky's original work.[66]

The ease of obtaining such dihalogeno-ketones by addition of the respective hypohalous acids to terminal acetylenes[66,67,68] suggested the use of this rearrangement to synthesise trans-10-hydroxydec-2-enoic acid. The key compound in this projected route was 10-hydroxydec-1-yne (C10, R=H) or its acetoxy derivative (C.10; R=Ac); it was envisaged that addition of hypobromous acid to give the dibromoketone (C17) followed by a Faworsky rearrangement would afford a rapid and direct approach to "Royal Jelly acid."

Four syntheses of these key intermediates (C10) were investigated.

1. Attempts to convert the commercially available 1:8-dimethoxyoctane (C5) into 1:8dichlorooctane (C7) by treatment with gaseous hydrogen chloride, and with concentrated hydrochloric acid in the presence of zinc chloride, failed. When the alternative reagent, acetyl chloride in the presence of stannic chloride[71], was used, a negative result was also obtained. The eventual conversion of the ether (C5) into the alkyl halide (C7) was achieved in two stages.

Although aqueous hydrogen bromide solution did not completely demethoxylate the ether (C5), a glacial acetic acid solution of the same reagent achieved the desired result. The product contained no methoxyl groups (infrared:- 1100 cm^{-1}) and in addition to containing bromine it also contained acetoxyl group (s); the mixture was presumably one of 1:8-dibromooctane, 1:8-diacetoxyoctane, and 1-acetoxy-8-bromooctane. Basic hydrolysis of this mixture, or of pure 1:8-dibromooctane, with potassium hydroxide in aqueous ethanol gave a product which still contained bromine. In order to avoid the production of such a mixture on hydrolysis the crude product, obtained from the treatment of the ether with hydrogen bromide in acetic acid, was refluxed with potassium acetate in acetic acid. The hydrolysis of the resultant 1:8-diacetoxy-octane proceeded very smoothly and the yield of 1:8-dihydroxyoctane (C6) from the ether was 70%.

The diol (C6) was readily converted into 1:8-dichlorooctane (C7) by treatment with thionyl chloride in the presence of a catalytic amount of pyridine[72].

Replacement of a single chlorine atom by iodine in a symmetrical dichloro-compound can be achieved by refluxing with 1 equivalent of sodium iodide in acetone.[72,73,74]. By this method, 1:8-dichlorooctane (C7) gave a product of which the physical properties were identical with those quoted[74] for 1-chloro-8-iodooctane (C8), but analytical figures suggested that the compound was impure. Vapour phase chromatography showed that the product was contaminated with a less volatile compound which was probably 1:8-diiodooctane. Fractional distillation did not remove the contaminant.

The crude 1-chloro-8-iodo-octane (C8) was condensed with sodium acetylide in liquid ammonia to give 10-chlorodec-1-yne (C9) which still contained iodine in trace amounts.

Conversion of the chloro group to an acetoxyl function by refluxing with potassium acetate in acetic acid gave 10-acetoxydec-1-yne (C10, R=Ac). Although satisfactory analyses were not obtained for this compound, it was shown to be homogeneous by vapour phase chromatography.

The poor yield in the iodination stage (~30%) and the difficulty in purifying the product prompted the search for a better approach to the required intermediate (C10).

2. The readily available undec-10-enoic acid (C11) was brominated and dehydrobrominated to give undec-10-ynoic acid[75] (C12). The methyl ester of this acid (C13) was subjected to the Barbier-Wieland degradation process as described by Black and Weedon[76] to give 1:1-diphenylundec-1-ene-10-yne (C14) and then by oxidation, dec-9-ynoic acid (C15). The best yield obtained in the oxidation of the enyne (C14) to dec-9-ynoic acid (C14) was 40% although 58% has been quoted in the literature.

This acid (C15) was reduced with lithium aluminium hydride in good yield to give 10-hydroxydec-1-yne (C10, R=H) which was characterised by conversion to the corresponding α-naphthylurethane and also to the derived mercury acetylide. The acetate of the alcohol (C10, R=Ac) was shown by infrared spectroscopy and by gas phase chromatography to be identical with the product obtained by method 1.

The chief objection to this route for preparing the intermediate (C10) was the low yield obtained in the oxidation of 1:1-diphenylundec-1-ene-10-yne (C14) to dec-9-ynoic acid (C15).

3. In the hope of converting undec-10-ynoic acid (C12) into 10-acetoxydec-1-yne (C10, R=Ac) by a two stage process which

would not involve an oxidation, treatment of the acid (C12) with methyl lithium[77] was attempted. No reaction took place; this was probably due to the formation of highly insoluble lithium salts. However, when the corresponding acid chloride was reacted with cadmium dimethyl[78] a heat-labile compound was obtained. This compound formed a crystalline semicarbazone and had an infrared spectrum which was consistent with that expected of 11-oxododec-1-yne (C16). An attempted Baeyer-Villiger reaction on this ketone using trifluoroperacetic acid[79] failed to give any of the desired 10-acetoxydec-1-yne (C10, R=Ac).

This route to the intermediate was not pursued any further since during the course of the work the synthesis as reported below, proved to be the most practicable.

4. 1:1-Diphenylundec-1-ene-10-yne was prepared from methyl undec-10-ynoate (C13) by treatment of the latter with phenyl magnesium bromide and dehydration of the resultant alcohol.[76] Although triple bonds are known to undergo ozonolysis[80] they do so much more slowly than double bonds. It seemed reasonable to suppose, therefore, that careful ozonolysis of 1:1-diphenylundec-1-ene-10-yne (C14) would result in the triple bond remaining intact while the double bond was ozonised.

Ozonolysis of the enyne (C14) at -40^{o}, followed by decomposition of the ozonide in the presence of sodium borohydride[81,82] gave a mixture of diphenylcarbinol and 10-hydroxydec-1-yne (C10, R=H) which could be separated by distillation. The yield of the desired product was 50%. This method was the most convenient route to the intermediate.

When the ozonolysis was prolonged or carried out at room temperature the product contained no characteristic

ethynyl absorption in the infrared spectrum and it was assumed that, under these conditions, the triple bond had been ozonised.

Using N-bromoacetamide in the presence of sodium acetate and aqueous acetic acid. Salamon and Reichstein[68] successfully added two moles of hypobromous acid across a triple bond in a steroid molecule. McCrae[70] employed N-bromosuccinimide in place of N-bromoacetamide and obtained equally good results with aliphatic acetylenic compounds. We have shown that under the same conditions N;N-dibromo-dimethylhydantoin ("Bromodan") is also effective.

Either of these last two reagents gave with 10-hydroxydec-1-yne or 10-acetoxydec-1-yne a heavy oil which decomposed on distillation. The oil formed a bis-2:4 dinitrophenylhydrazone which analysed correctly for the expected structure (C17a; R=H or Ac); the infrared spectrum showed no trace of the ethynyl group but did show absorption at 1710cm^{-1}, characteristic of a ketone.

The dibromoketones (C17; R=H and R=Ac) were added to a solution of three equivalents of potassium hydroxide in ethanol. From the infrared spectrum of the product it was obvious that the acid contained some unsaturated material. The oily product did not crystallise but chromatography or high vacuum sublimation afforded a crystalline, unsaturated, hydroxy acid in 20% yield. This was not the anticipated trans 10-hydroxydec-2-enoic acid[83] but its cis-isomer as was subsequently shown by comparison with an authentic sample[84].

When the rearrangement of the dibromoketone (C17) was carried out using sodium in methanol, hydrolysis of the resulting ester also gave cis-10-hydroxydec-2-enoic acid.

The acidic products from the Faworsky reaction were estenfied with diazomethane.

Thin layer chromatography of these esters on Kieselguhr showed that at least three components were present, but due to the fact that a mixture of authentic cis and trans methyl 10-hydroxydec-2-enoate was not separated on such a plate, it was impossible to deduce if any trans-10-hydroxydec-2-enoic acid had been formed in the rearrangement.

Authentic cis and trans methyl 10-hydroxydec-2-enoate had identical retention times on gas chromatograms and it was impossible to detect any trans isomer in the reaction mixture by this technique.

A gas chromatogram of the esterified reaction product showed that in the sample obtained by the action of potassium hydroxide in ethanol on the dibromoketone (C17) there were two main components. The first of these corresponded in retention time to both cis and trans methyl 10-hydroxydec-2-enoate; the second had a longer retention time. It was found that the relative proportion of this second component was larger in the sample derived from the dibromoketone by the action of sodium in methanol.

The comparatively low yield of $\alpha:\beta$-unsaturated acid and the formation of a major by-product in the Faworsky rearrangement of the $\alpha:\alpha$-dibromoketones (C17, R=H and R=Ac)

prompted a detailed investigation of this reaction using a more readily available dibromoketone. The findings of this investigation are reported later, (p.57), and suggested that this by-product was formed by the addition of methanol to the double bond of the unsaturated acid.

Attempts to convert cis 10-hydroxydec-2-enoic acid to the trans isomer by treatment with base and with iodine in benzene, failed. Chromatography of cis methyl 10-hydroxydec-2-enoate on alumina also failed. (cf.p.59).

Brown and Freure[44] claim to have partially converted the trans isomer to the cis isomer by irradation.

During the course of this work the first syntheses of trans 10-hydroxydec-2-enoic acid were reported[83,85,86].

In one synthesis 10-hydroxydecanoic acid was obtained from castor oil by heating with strong alkali. The hydroxyacid was acetylated to give 10-acetoxydecanoic acid (C19) of which the acid chloride (C20) was brominated (C21). Successive hydrolysis with water and treatment with sodium iodide in ethanol gave the iodo-acid (C22). Aqueous ethanolic sodium hydroxide converted this compound to trans 10-hydroxydec-2-enoic acid (C1) which was shown to be identical with natural Royal Jelly acid.

The same authors also reported an alternative synthesis, in which 1-chloro-6-hydroxyoctane (C23) was converted by a malonic ester synthesis to 8-hydroxyoctanoic acid (C24). The acetate of the corresponding acid chloride (C25) was reduced over palladized barium sulphate to give 8-acetoxyoctanal (C26). A Doebner condensation of this aldehyde with malonic acid yielded 10-acetoxydec-2-enoic acid (C27) which on hydrolysis gave trans 10-hydroxydec-2-enoic acid (C1).

Similar approaches to Royal Jelly acid have been subsequently reported by Fijii, Koga, Osawa and Chuman.[87]

Muren[88] treated cyclo-octanone with trifluoro-peracetic acid to obtain the lactone (C28). This lactone was opened and condensed with the sodium salt of acetonitrile to give 10-hydroxy-3-keto decanonitrile (C29) which on methanolysis yielded methyl 10-hydroxy-3 keto decanoate (C30). Catalytic reduction over a ruthenium catalyst followed by hydrolysis gave 3:10 dihydroxydecanoic acid (C31) which was readily dehydrated to trans 10-hydroxydec-2-enoic acid (C1).

A synthesis of cis 10-hydroxydec-2-enoic acid has also been reported.[84,85]

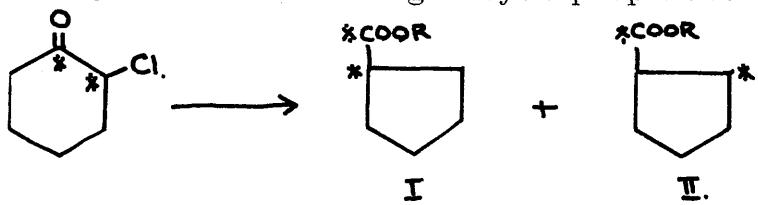
7-Chloroheptanol (C53) was converted into the corresponding tetrahydropyranyl ether and then halogen exchange gave the iodine analogue (C55). Condensation with sodium acetylide gave tetrahydropyranyloxy-non-1-yne (C56), the magnesium derivative of which was carboxylated with carbon dioxide to yield 10-hydroxydec-2-ynoic acid (C58). Hydrogenation over Lindlar catalyst gave cis 10-hydroxydec-2-enoic acid (C59).

THE FAWORSKY REACTION

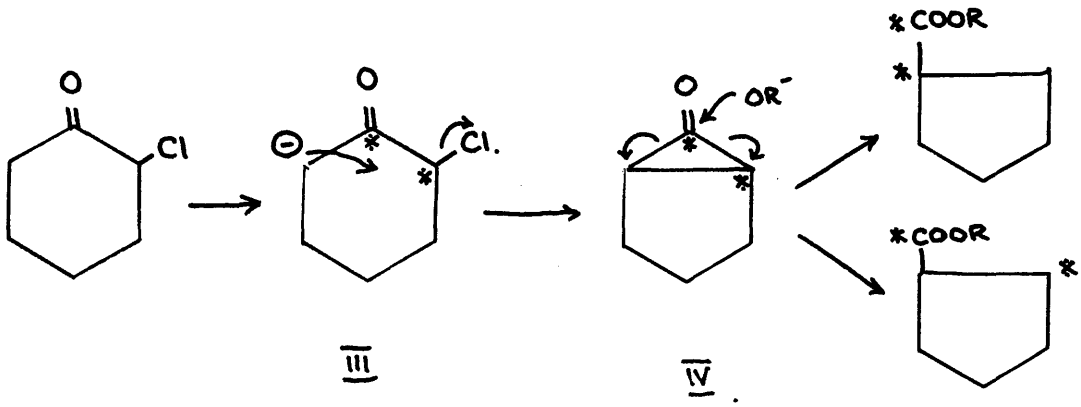
The unexpected stereoselectivity in the conversion of the $\alpha;\alpha$-dibromoketone (C17) to a cis-$\alpha;\beta$-unsaturated carboxylic derivative prompted a more detailed investigation with simpler compounds of the mechanism of this little studied example of the Faworsky rearrangement.

The nature of the intermediate involved in such rearrangements seems now to be well established.

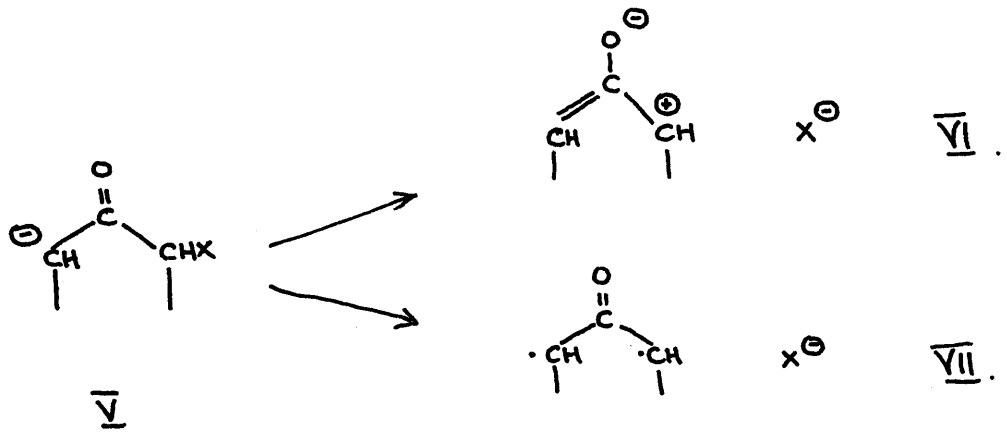
Following a study of the Faworsky rearrangement of 2-chlorocyclohexanone, which was labelled with C^{14} in the $C_{(1)}$ and $C_{(2)}$ positions, Loftfield,[92] in order to account for the products with the isotope distributions I and II postulated a mechanism involving a cyclopropanone intermediate.



He postulated that the initial step was abstraction of a proton from the α' carbon atom of the α-haloketone; the resultant enolate ion (III) then underwent either concerted or consecutive intramolecular ejection of the halide ion to form a cyclopropanone intermediate (IV), cleavage of which gave the products with the expected labelling.



Although they accept the concept of a cyclopropanone intermediate, Aston and Neukirk,[93] and Burr and Dewar[94], question the mode of formation of such an intermediate as proposed by Loftfield.[92] They suggest that the enolate anion (V) gives rise either to a zwitterion[93] (VI) or to a no-bond canonical form of a cyclopropanone[94] (VII). Such intermediates can then readily collapse to form the expected cyclopropanone.

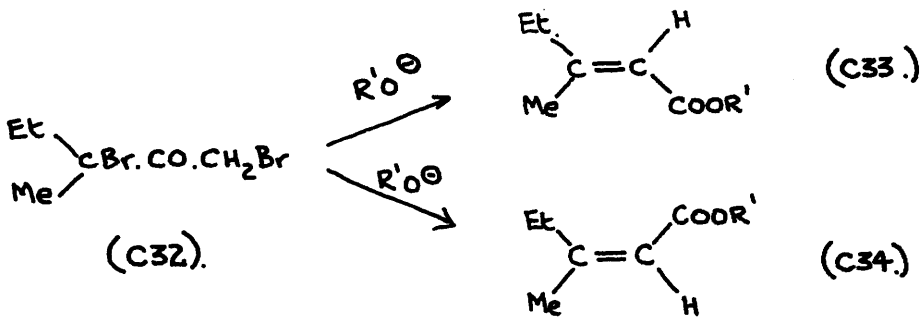


The concerted mechanism for the cyclopropanone formation as proposed by Loftfield[92] necessitates stereochemical inversion about the carbon atom bearing the halogen atom, whereas the modified theory of Burr and Dewar[93,94] would require racemisation about the same centre provided that there was no "shielding"[95] by the departing halogen ion.

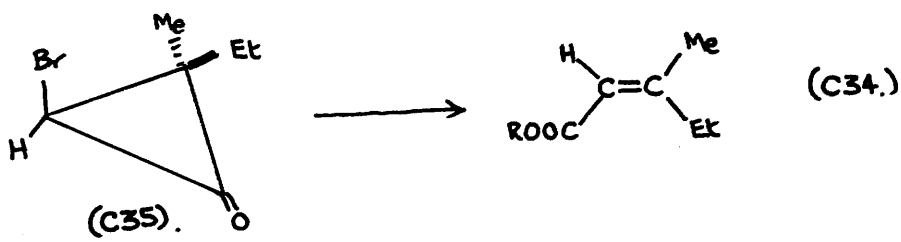
Some cases of stereospecific rearrangements have been claimed[96] but the most recent investigation[97] suggests that stereospecificity is highly dependent on experimental conditions on the structure of the haloketone. Hence the

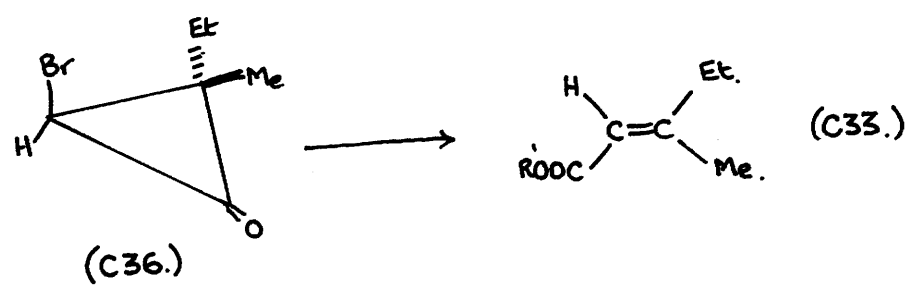
intimate nature of the reaction mechanism is still in doubt even although the general concept of a cyclopropanone intermediate has been accepted.

When Wagner and Moore[98] treated the $\alpha:\alpha'$ dibromoketone (C32) with base, a mixture of two esters was obtained and these were shown to be cis and trans isomers (C33, C34).



Following the publication of Loftfield's theory, Romo and Romo da Vivar[99] rationalised the production of cis and trans isomers in such reactions in terms of the coufiguration of the cyclopropanone intermediate. They suggested that, depending on which of the protons in the position α to the carbonyl group was abstracted, the cyclopropanone could have either of the configurations (C35) and (C36)





Solvolysis of such intermediates would give cis and trans isomers respectively. The observed yields[98] of the isomers were approximately the same ($\sim$ 25%).

DISCUSSION

In the presence of sodium acetate in aqueous acetic acid[68], N-bromosuccinimide[70] reacted with hex-1-yne (C37) to give 1:1-dibromo-2-oxohexane (C38) in 70% yield. This α:α-dibromoketone readily gave a bis-2:4-dinitrophenylhydrazone, a bis-semicarbazone and a dioxime. The ultraviolet spectrum of the bis-2:4-dinitrophenylhydrazone was typical of that recorded for the known α-diketones[100].

This ready conversion in high yield of an acetylene via the α:α-dibromoketone to crystalline derivatives of the corresponding α-diketones represents a very rapid and convenient method of characterising acetylenes. The procedure was extended with complete success, to acetylenes other than hydrocarbons containing such functional groups as hydroxyl, acetoxyl and carboxyl.

Under similar conditions using N;N-dibromodimethylhydantoin ("Bromodan") as the source of hypobromous acid similar results were obtained. When attempts were made to prepare the corresponding α:α-dichloroketone using either, N-chlorosuccinimide or N:N-dichlorodimethylhydantoin ("Hydan") no appreciable amount of the desired 1:1-dichloro-2-oxohexane was obtained. This finding was consistent with the work of Wittorf[67] which showed that hypobromous acid reacts much more readily with ethynyl compounds than does hypochlorous acid.

Bromoketones which contain no hydrogen in the α position cannot undergo the Faworsky rearrangement if the Loftfield theory[92] is correct. This was verified by showing that phenylacetylene (C42) reacted with hypobromous acid to give 1:1-dibromoacetophenone (C43) which, with sodium in ethanol, produced no carboxylic ester but gave the normal ethanolysis product, i.e., diethyl acetal of

phenylglyoxal (C44). Acid hydrolysis of this acetal gave the known, crystalline, phenylglyoxal (C45).

Reaction of 1:1-dibromo-2-oxohexane (C38) with potassium hydroxide in ethanol at reflux temperature for three hours gave, in 58% yield, an acidic product which appeared to contain unsaturated material. Although the physical properties of the crude reaction product were similar to those of trans-hex-2-enoic acid, vapour phase chromatography of the corresponding methyl esters showed that the major constituent had a much longer retention time than methyl trans-hex-2-enoate.

When the reaction was carried out under similar conditions using sodium in absolute methanol the infrared spectrum of the resultant methyl ester showed only weak absorption at 1650 cm^{-1} (conjugated double bond), and once again vapour phase chromatography indicated that the major product was not methyl hex-2-enoate. This major product was isolated by chromatography and distillation and was shown to be identical with methyl 3-methoxyhexanoate (C39) which had been prepared by the addition of methanol to methyl trans-hex-2-enoate[102] (C41). Hence, it appeared that solvent had added across the double bond of the hex-2-enoate during the course of the Faworsky rearrangement.

A similar situation was encounterd by Wagner[103] who found that prolonged treatment of 1:2-dibromo-2-methyl-3-oxobutane (C46), with base at elevated temperatures gave the saturated methoxyester (C48) as well as the unsaturated ester (C47). When the reaction was carried out at room temperature during a much shorter reaction-time, the unsaturated ester predominated.

At room temperature, with a reaction-time of about one hour, reaction of 1:1-dibromo-2-oxohexane (C38) with two equivalents of sodium in methanol gave methyl cis-hex-2-enoate (C40) in 60% yield. No trace of the corresponding trans-ester was detected. The cis structure of the ester was assigned on the basis of the infrared spectrum, which contained characteristic absorption at 1650 and 820 cm^{-1}, [104] and by correct elemental analysis. Further confirmation was derived accidentally when it was found that the cis-ester underwent quantitative stereomutation to the trans isomer by simple absorption on alumina; this simple method of cis-trans conversion does not appear to have been noted before.

In addition to the desired ester, a bromine-containing mixture was obtained. The exact composition of this was not determined although the infrared spectrum showed methoxyl absorption but no carbonyl absorption.

Under similar conditions oct-1-yne (C49) gave 1:1-dibromo-2-oxo-octane (C50) which was converted to methyl cis-oct-2-enoate (C51) in 65% yield. This product was also converted on alumina to the corresponding trans-isomer (C52).

The results obtained from hex-1-yne and oct-1-yne were thus in keeping with the previous observation that 10-hydroxydec-1-yne on successive treatment with hypobromous acid and base gave cis-10-hydroxydec-2-enoic acid (see p. 49).

The instances of the Faworsky rearrangement of acyclic dihaloketones which have so far been reported[66,92] have been non-stereospecific and have given mixtures of olefinic cis and trans isomers. The now established, completely stereospecific rearrangement of α,α-dibromoketones can be rationalised in the following terms.

Since the Faworsky rearrangement of α,α-dibromoketones is stereospecific, giving only the cis-unsaturated ester, the cleavage of the cyclopropanone intermediate with concomitant expulsion of a bromine atom must be a concerted process. Such a process operating in the cis-cyclopropanone (IX) will give, exclusively, the cis-unsaturated ester (VIII): figure (IXa) shows more clearly how expulsion of the bromine atom by bond (i) gives the cis-unsaturated ester (VIII). In a corresponding manner, the trans-cyclopropanone intermediate (XIa) would give the trans-unsaturated ester (X).

To minimise both electrostatic repulsion between the carbonyl group and the bromine atoms, and steric interactions, the preferred conformation of an α,α'-dibromoketone is that shown (XII). In this conformation $H_{(a)}$ and $Br_{(a)}$ are in a trans-antiparallel position, and $H_{(b)}$ and $Br_{(b)}$ are coplanar, thus facilitating removal of hydrogen bromide as $H_{(a)}$ $Br_{(a)}$ or as $H_{(b)}$ $Br_{(b)}$. Since the overall rearrangement is stereospecific such a removal will take place by a concerted mechanism. Irrespective of which elimination occurs the cis-cyclopropanone intermediate (IX) will be formed, (see figure XIIa), giving rise in the end to the cis-unsaturated ester (VIII).

No explanation was given by Hogg[90] regarding the stereospecific Faworsky rearrangement of 21:21-dibromo-21-ethoxyoxalyl-4-pregnen-11-α-ol-3:20-dione (XIII) to methyl cis-4:17(20)-pregnadien-11-α-ol-3-one-21-oate (XIV). This rearrangement can now be rationalised in terms of the above mechanism. Representing the dibromoketone by the figure (XIIIa), the conformation which allows minimum electrostatic repulsion between the carbonyl group and the two bromine atoms, and minimum steric

interactions, can be represented by figure (XIIIb). Elimination of hydrogen bromide gives the cyclopropanone in which the remaining bromine atom $Br_{(b)}$ and the large group R_L are cis disposed. Hence, in the final product R_L will be cis disposed to the carbalkoxyl group (XIV).

EXPERIMENTAL

Attempted preparation of 1:8-dichlorooctane (C7)

(a) 1:8 Dimethoxyoctane (5:3g: 0.03M) was added at 0° to a mixture of acetyl chloride (6g: 0.076M) and stannous chloride[71] (0.02g). After standing at room temperature for 12 hours the mixture was poured into water, and left for 30 minutes. The mixture was extracted with ether and the organic extracts combined and washed successively with saturated sodium hydrogen carbonate solution and brine. After drying over anhydrous magnesium sulphate, solvent removal gave solourless oil (5g) b.p. 98°/15m.m. which was shown to be 1:8-dimethoxyoctane.

(b) Treatment of 1:8-dimethoxyoctane with gaseous hydrogen chloride at 0° resulted in complete recovery of starting material.

(c) Refluxing concentrated hydrochloric acid in the presence of a catalytic amount of zinc chloride also failed to yield 1:8-dichlorooctane.

Demethylation of 1:8-dimethoxyoctane

(a) 1:8-Dimethoxyoctane (5g) was refluxed for 12 hours with aqueous hydrobromic acid (50ml: 50% w/v). The cooled reaction mixture was poured into ice-water (100ml) which was thoroughly extracted with ether. The combined ether extracts were washed with sodium hydrogen carbonate solution and brine and dried over magnesium sulphate. Solvent removal gave a dark brown oil which still showed strong absorption in the infrared spectrum at 1110 cm^{-1}, characteristic of the methoxyl group.

The above product was treated with a further amount of hydrobromic acid and the product (5g) showed no absorption at 1110 cm^{-1}. b.p. 115-119°/1m.m. n_D^{22} 1.4982. ν_{max} (thin film) 1200,1240, 724 cm^{-1}.

(b) 1:8-Dimethoxyoctane (5g) was dissolved in a solution of hydrogen bromide in glacial acetic acid (50ml: 50% w/v) and gently refluxed for 12 hours. The reaction mixture was poured into water (300ml) and the aqueous mixture extracted with ether. The combined organic extracts were washed with sodium hydrogen carbonate solution and brine and dried over anhydrous magnesium sulphate. Removal of solvent gave a dark brown oil (5g). The infra red spectrum showed that complete demethylation had occurred (no peak at 1110cm^{-1}) a band at 1745 cm^{-1} suggested that the reaction product contained acetoxy octanes.

This product was refluxed for 6 hours with acetic acid (50ml) and anhydrous potassium acetate (8g). On cooling, water (100ml) was added and the mixture extracted with ether. The combined ethereal extracts were washed with sodium hydrogen carbonate solution, brine and dried over magnesium sulphate. Removal of solvent gave an oil which was hydrolysed by refluxing with aqueous ethanolic potassium hydroxide for 3 hours. Most of the ethanol was removed and ether extraction gave the sweet-smelling 1:8-dihydroxyoctane which solidified. Recrystallisation from ethyl acetate as needles m.p. 59° (lit[74] 55-58°). ν_{max} (nujol mull) 3350, 1050, 1042,980, 735 cm^{-1}.

Hydrolysis of 1:8-dibromo octane

1:8-Dibromooctane (3g) was dissolved in aqueous ethanolic potassium hydroxide (2g) and refluxed for 4 hours. Most

of the ethanol was removed and the residue extracted with ether. After washing and drying the solvent was removed to give an oil which did not solidify. The infrared spectrum of this oil showed some ethoxyl absorption (1110cm^{-1}). Distillation gave octane 1:8-diol but in only 50% yield.

Octane-1:8-diol (c6)

1:8-Dimethoxyoctane (100g) was refluxed overnight with a solution of hydrogen bromide in glacial acetic acid (250ml: 50% w/v). On cooling the mixture was added to water (1 litre) and thoroughly extracted with ether. The combined organic extracts were washed with water, saturated bicarbonate and brine and finally dried over magnesium sulphate. Removal of solvent gave an oil which was refluxed for 3 hours with acetic acid (500ml) and anhydrous potassium acetate (150g). On cooling the precipitated potassium bromide was removed and the solution concentrated at the water pump. Water (300ml) was added and the mixture extracted with ether. The ethereal extracts were washed with bicarbonate and brine and dried over anhydrous magnesium sulphate. Evaporation gave a brown oil.

This oil was refluxed for 3 hours with potassium hydroxide (60g) in 60% ethanol (500ml). On cooling the mixture was concentrated and acidified with 6N hydrochloric acid. Ether extraction gave a dark brown oil (65g) which solidified. The product was purified by distillation b.p.118-122°/0.05m.m. (59g. 70%) (lit[74] b.p. 138-142°/3.5m.m.).

1:8-Dichloro-octane (C7)

Octane-1:8-diol (47g) was stirred at 0° with pure pyridine (15ml) and redistilled thionyl chloride (158g) added at such a rate that the temperature did not exceed 10°. The

reaction mixture was then allowed to reach room temperature slowly and finally heated on a steam bath for 2 hours with stirring. The cooled mixture was poured into ice water (500ml). The product was extracted with light petroleum and the combined extracts successively washed with 6N sulphuric acid, saturated sodium bicarbonate and brine. After drying over anhydrous magnesium sulphate the solvent was removed and the residue, a dark red oil distilled b.p. 117-119°/12m.m. n_D^{23} 1.4578. (51g: 89%). (lit[74] 118°/14m.m. n_D^{25} 1.4572).

1-Chloro-8-iodooctane[74] (C8)

Sodium iodide (42g: 0.28M) in acetone (200ml) was added dropwise with stirring to a refluxing solution of 1:8-dichlorooctane (51g: 0.27M) in acetone (100ml). After a 4-hour reflux the precipitated sodium chloride was filtered off and the acetone solution taken to small bulk under vacuum. Water (100ml) was added and the mixture extracted with light petroleum ether. The combined extracts were washed with water and dried over magnesium sulphate. Removal of solvent gave a pale yellow oil (64.5g) which was fractionated through a 15cm. Vigreux column.
The following fractions were obtained:-

	T	p	n_D^{21}	g
(i)	78-81	0.2 m.m.	1.4642	17.2
(ii)	90-100	"	1.5005	34
(iii)	100-105	"	1.5171	
(iv)	Residue		1.5521	10.5

Fractions (ii) and (iii) were recombined and further fractionated.

	T	p	n_D^{23}
(i)	90-95	0.2 m.m.	1.4772
(ii)	95-99	"	1.4974
(iii)	100-102	"	1.5112

The final fraction (22g: 30%) was assumed to be almost pure product(lit value[74] $101^{\circ}/2.5$m.m. n_D^{25} 1.5113).

Subsequent vapour phase chromatography has shown this compound to contain two impurities to the extent of abour 15%. The conditions employed for the chromatography were 5% Apiezon at 120°.

10-Chlorodec-1-yne (C9)

1-Chloro-8-iodooctane (20g: 0.073M) was added to a suspension of sodium acetylide, prepared from sodium (2.2g: 0.1M) in the usual way, in liquid ammonia (300ml) at -33°. The mixture was stirred for 6 hours, acetylene being bubbled through the reaction mixture during the first two hours. Solid ammonium chloride (6g) was added slowly followed by dry ether (50ml). The ammonia was allowed to evaporate off overnight and then water (150ml) was added. The ether layer was separated and the aqueous mixture was extracted with ether. The extracts were washed with 2N sulphuric acid, saturated bicarbonate solution and brine and finally dried over magnesium sulphate. Removal of the solvent through a Dufton column gave a reddish brown oil which was distilled b.p. $112\text{-}116^{\circ}/14$m.m. (8.25g: 60%). ν_{max} (thin film) 3300, 2100, 730 cm^{-1}.

The mercury salt crystallised as needles from ethanol m.p. 51.5°.

Despite repeated fractionation the analysis figures were consistently low for carbon content. This suggested that the impurities were probably more highly halogenated compounds.
(Found:- C,67.8; H 9.5; $C_{10}H_{17}O$ requires C 69.5; H 9.9%)

10-Bromodec-1-yne

1:8-Dibromooctane (9.5g: 0.035M) in ether (50ml) was added to a suspension of sodium acetylide (prepared from 0.8g sodium) in liquid ammonia (200ml). After stirring at -30° for 6 hours solid ammonium chloride (4g) was added and then ether (50ml). The ammonia was allowed to evaporate off overnight: water (100ml) was added and the mixture then extracted with ether. The combined extracts were washed with 2N sulphuric acid, saturated sodium bicarbonate and brine and dried over magnesium sulphate. Removal of the ether through a Dufton column gave a brown oil. ν_{max} (thin film) 3300, 2100 cm^{-1}.

The product distilled continuously over the range of 76-114°/1 m.m. and could not be successfully fractionated.

10-Acetoxydec-1-yne (C10, R=Ac)

10-Chlorodec-1-yne (5g) was refluxed for 5 hours with a solution of fused potassium acetate (4.5g) and potassium iodide (2g) in acetic acid (20 ml). The mixture was then poured into water (50 ml) and the product extracted with ether. The organic extracts were washed with saturated sodium hydrogen carbonate solution and brine and dried over anhydrous magnesium sulphate. Removal of the ether gave a light brown oil (5g) which was fractionated.

The middle fraction b.p. 80-90°/0.5 m.m. was collected and redistilled b.p. 75°/0.2 m.m. n_D^{21} 1.4574.

(Found:- C, 69.2; H, 9.87 $C_{12}H_{20}O_2$ requires C,73.43; H, 10.87%)

Despite subsequent refraetionation the carbon analysis remained low.

Vapour phase chromatography (5% Apiezon grease at 130°) showed that the material was more than 90% pure. ν_{max} (thin film) 3300, 2100, 1725 cm^{-1}.

Undec-10-ynoic acid[75] (C12)

Undec-10-Enoic acid (98g) was dissolved in light petroleum ether (250ml) and a solution of bromine (27.5ml) in petroleum ether (35 ml) added slowly with stirring and cooling. Stirring was stopped after the addition and 30 minutes later a yellow precipitate formed. This was filtered off and the filtrate concentrated to give a further crop of solid. Total yield (156g) was mixed with a concentrated solution of potassium hydroxide (250g in 150 ml. water) in a 3l flask and heated at 150°-160° for 8 hours. The cooled mixture was added to water (Il) and acidified with concentrated sulphuric acid. The product was extracted with ether and thoroughly washed with brine. The ethereal extract was dried over anhydrous magnesium sulphate and the solvent then removed. The residual oil (68g) solidified: the product was purified by distillation. b.p. 135-142°/1.5m.m. (60g: 62%) m.p. 40° (lit[75] 177-182°/ 15 m.m.; m.p. 42°).

Methyl undec-10-ynoate (C13)

Undec-10-ynoic acid (60g) was dissolved in methanol (5ooml) containing concentrated sulphuric acid (3ml) and allowed to stand overnight at room temperature. Most of the methanol was removed before pouring into water (200 ml). Ether

extraction gave a sweet-smelling oil (60g) which was distilled b.p. 99°/0.5m.m. n_D^{24} 1.4460 (lit[75] b.p. 121°/5m.m.)

1:1-Diphenylundec-1-ene-10-yne[76] (C14)

Methyl undec-10-ynoate (43g) was dissolved in anhydrous ether (250ml) and added dropwise at room temperature to a stirred solution of phenyl magnesium bromide (from 19.2g magnesium and 121.5g bromobenzene) in ether (250ml). The solution was refluxed with stirring for 2 hours and then left at room temperature for 16 hours. Ice (500g) was added and then 2N sulphuric acid until the mixture was acidic. The ether layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed with saturated sodium carbonate, water and brine and dried over magnesium sulphate. Removal of the ether gave a viscous oil which was heated under nitrogen at 220° for 1 hour with anhydrous potassium hydrogen sulphate. The product (40g) was distilled b.p. 152°/2 x 10^{-3}m.m., m.p.33° n_D^{20} 1.5630. (lit[76] 152°/0.02m.m., m.p. n_D^{21} 1.5620).

Dec-9-ynoic acid[76] (C15)

To a warm (50°) well-stirred solution of 1:1 diphenyl undec-1-ene-10-yne (13g) in acetic acid (150ml) was added over 2 hours a solution of chromium trioxide (8.5g) in water (10ml). After stirring at room temperature for 16 hours most of the acetic acid was removed from the reaction mixture. The residue was heated on the steam bath with 2N sulphuric acid (200ml) for 1 hour. The cooled solution was saturated with brine and extracted with ether. After washing with brine the combined extracts were dried over magnesium sulphate and then the solvent removed. The residue (4g) was distilled b.p. 90°/0.1m.m. to give dec-9-ynoic acid (3g:40%) (lit[76] 88°/0.1m.m.)

10-Hydroxydec-1-yne (C10, R=H)

Dec-9-ynoic acid (2g) in dry ether (25ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (0.5g) in dry ether (150ml). The mixture was refluxed overnight and the excess lithium aluminium hydride decomposed with ethyl acetate. Water (100ml) was slowly added and then the mixture acidified with 2N hydrochloric acid. The ether layer was separated and the aqueous layer extracted with ether. The combined extracts were washed with saturated bicarbonate solution and brine and finally dried over magnesium sulphate. Removal of solvent gave a semi-solid residue (1.3g, 60%). This was distilled to give the alcohol (0.75g) b.p. $74^{o}/0.1$m.m., n_D^{25} 1.4575.
ν_{max} (thin film) 3400, 3300, 2150 cm^{-1}.
Mercury salt (ethanol) m.p. $143-145^{o}$.
α-Naphthylurethane m.p. $73-74^{o}$ needles from petrol.
($C_{21}H_{25}NO_2$ requires C, 77.98, H,7.79, N 4.33. Found: C,77.79, H 7.81, N 4.54%).

(b) 1:1-Diphenylundec-1-ene-10-yne (20g) was dissolved in chloroform and cooled in a Drikold-chloroform bath. Ozone was passed through the solution for two hours. The cold solution was then added dropwise with stirring to a cooled solution of sodium borohydride (8g) in 50% aqueous ethanol (50ml). After being stirred at room temperature for 3 hours the mixture was heated on a steam bath for 1 hour, then cooled and acidified with dilute hydrochloric acid. The product was isolated with ether and the extracts dried over magnesium sulphate. Removal of the ether gave a yellow oil (21g) which was fractionated.
1) b.p. $74-80^{o}/0.2$m.m. (5g. 50%)
2) b.p. $114^{o}-120^{o}/0.2$m.m. 10g.

The lower boiling fraction was shown to be 10-hydroxydec-1-yne be means of its mecury salt m.p.143-144 and α-naphthylurethane, m.p.73-74°. The higher boiling fraction was benzhydrol.

10-Acetoxydec-1-yne (C10 R=Ac)

10-Hydroxydec-1-yne (0.5g) was dissolved in acetic anhydride (5ml) containing pyridine (1ml) and the mixture refluxed for 4 hours. On cooling, water (20ml) was added and the mixture extracted with ether. The ether extract was washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution and brine. After drying over magnesium sulphate the solvent was removed. The residual oil was shown to be identical with that previously prepared by infrared spectrum and gas liquid chromatography.

Reaction of Lithium methyl with undec-10-ynoic acid.

To lithium sand[77] (0.95g: 0.135M) in dry ether was added methyl iodide (0.5ml) and the mixture heated until the reaction just began. Methyl iodide (18.4g: 0.15M) in ether (100ml) was added at such a rate that the solution boiled gently. After the addition the mixture was refluxed for 1 hour.

After cooling, the solution was filtered under nitrogen and added dropwise to a solution of undec-10-ynoic acid (3g) under nitrogen. A white precipitate was formed. The mixture was refluxed for 1 hour and after cooling dilute acid (20ml) was added; the ether layer was separated and the aqueous layer extracted with ether. The combined ether layers were washed with bicarbonate and dried. Removal of the ether gave an oil (0.1g).

Acidification of the bicarbonate washings followed by ether extraction gave an oil which solidified (2.8g). This was shown to be unchanged undec-10-ynoic acid.

A similar result was obtained using tetrahydrofuran as solvent.

11-Oxododec-1-yne (C16)

Undec-10-ynoic acid (5g) was converted to undec-10-ynoyl chloride in 95% yield using oxalyl chloride (6g) in dry benzene (20ml).

To an ethereal solution of methyl magnesium bromide from magnesium (1.32g) and methyl iodide (8.5g) was added, under nitrogen, cadmium chloride (6g) at 0^{o} [78]. The mixture was stirred under reflux for 1 hour, and the ether then replaced by dry benzene. Undec-10-ynoyl chloride (5g) in dry benzene (50ml) was added to the cooled mixture and the whole heated under reflux for 1 hour during which time a brown precipitate formed. After addition of water (50ml) the benzene layer was separated and the aqueous layer extracted with ether. The combined organic solutions were washed with saturated sodium bicarbonate solution, and brine and finally dried over magnesium sulphate. Removal of solvent gave a dark brown oil (5.1g).

Attempted distillation of this oil resulted in almost complete decomposition. From the minute amount which did distil b.p.75-85^{o}/0.05m.m. a crystalline semi-carbazone m.p. 99-100^{o} was obtained.
($C_{13}H_{23}N_3O$ requires C, 65.78; H,9.77; N,17.71.
Found: C,65.42; H,9.84; N,17.81%)
The crude product also formed the same semi-carbazone m.p. 99-100^{o}.

The product was partially purified by elution from Grade V alumina with petrol.

ν_{max} (thin film) 3300, 2150, 1710 cm^{-1}.

Treatment of 11-oxododec-1-yne with trifluoroperacetic anhydride[79]

Trifluoroacetic anhydride (3.2g:.015M) was added dropwise to a cooled suspension of hydrogen peroxide (Iml 90%) in methylene chloride (10ml). This mixture was then added to a suspension of sodium monohydrogen phosphate (10g) in methylene chloride containing 11-oxododec-1-yne (1.8g 0.01M). The mixture was refluxed for one hour, filtered and extracted with ether. The extract was dried and the ether removed.

A sample of the product was subjected to vapour phase chromatography at 130° on 5% apezon: no peak which could correspond to 10-acetoxydec-1-yne was observed.

1:1-Dibromo-10-hydroxy-2-oxodecane. (C17, R=H)

10-Hydroxydec-1-yne (690mg) was added to a suspension of N-bromosuccinimide (2.4g: 3 equivs) and sodium acetate trihydrate (1.8g: 3 equivs) in 50% aqueous acetic acid (50ml), and shaken at room temperature for 3 hours. The reaction mixture was poured into water (50ml) and the whole thoroughly extracted with ether. The organic extract was washed with water, saturated bicarbonate solution, saturated sodium metabisulphite solution and brine and then dried over anhydrous magnesium sulphate. Removal of the ether gave a pale yellow oil (1.09g).

The oil decomposed on distillation. It formed a red bis-dinitrophenylhydrazone m.p. 174-6° (chloroform/methanol) ($C_{22}H_{26}N_8O_9$ requires C, 48.36; H, 4.76, Found: C, 48.57; H. 4,82%)

λ_{max} (ethanol) 397 mμ 444 mμ.

ν_{max} of ketone. 3400 1710 cm^{-1}.

1:1-Dibromo-10-acetoxy-2-oxodecane. (C17, R=Ac)

Repitition of the above procedure using 10-acetoxydec-1-yne instead of 10-hydroxydec-1-yne gave a pale yellow oil which would not distil. The 1.R. spectrum showed peaks at 1735 and 1710 cm^{-1}.

Bis-dinitrophenylhydrazone m.p. 151° (ethanol)
λ_{max} 397, 444 mμ.
($C_{24}H_{28}N_8O_{10}$ requires C, 48.98 H, 4.80
Found C, 48.87 H, 4.58%).

10-Hydroxydec-2-enoic acid (C1)

(a) 10-Acetoxy-1:1-dibromo-2-oxodecane (100mg) in ethanol (5ml) was added at 0° to a solution of potassium hydroxide (50mg. 4 equivs) in ethanol (10ml). The mixture was heated on a steam bath, with stirring, for 2 hours. The potassium bromide was filtered off and 4N sodium hydroxide (2ml) added. The clear solution was refluxed for 2 hours. Most of the ethanol was removed and the neutral products removed with ether. The aqueous solution was acidified with dilute hydrochloric acid and the product extracted with ether. The ether extract was washed with water and brine and dried over magnesium sulphate. The ether was removed and the residual semi-solid product (30mg), was chromatographed on silica gel (10g). The fraction (8mg) which was eluted with a mixture of benzene-ether (4:1) solidified m.p. 64-66°. The solid was sublimed 60°/10 ^{4}m.m. to give a white solid m.p. 71-72°. which showed no depression on mixing with an authentic sample of cis-10-hydroxydec-2-enoic acid.

The 1.R. spectrum of the solid before and after sublimation was identical with that of authentic cis-10-hydroxydec-2-enoic acid.
ν_{max} (Nujol mull) 3400, 1705, 1650 cm^{-1}.

(b) 1:1-Dibromo-10-hydroxy-2-oxodecane (1g) in methanol (10ml) was added at 0° to a solution of sodium (0.25g: 0.35 equivs) in methanol (20ml). The mixture was heated on the steam bath for 2 hours: water (5ml) was added and the heating continued for 2 hours. Most of the methanol was removed and the neutral material removed with ether. The aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were washed with water and dried over magnesium sulphate. Removal of solvent gave a brown oil (371mg) which partially solidified.

The reaction product (50mg) gave pure cis-10-hydroxy-dec-2-enoic acid (15mg 20%) on sublimation at $60^{\circ}/10^{-3}$m.m. The residue was not identified.

After chromatography on silica a sample was recrystallised from petroleum-ether m.p. 70-71°.

Chromatography on a thin-plate of silica showed the crude reaction product to contain at least three components. The conditions used, chloroform-methanol (3:1), did not separate a mixture containing authentic cis and trans 10-hydroxydec-2-enoic acids.

(c) Repitition of the rearrangement of 1:1 dibromo-10-hydroxy-2-oxodecane with sodium methoxide (3 equics) in 1:2 dimethoxyethane gave the same result as that given above.

Attempted isomerisation of cis 10-hydroxy-dec-2-enoic acid (C59)

cis-10-Hydroxydec-2 enoic acid (10mg) was dissolved in benzene (2ml) containing iodine (2mg) and refluxed for 3 hours. The iodine was washed out with sodium thiosulphate solution and the benzene solution dried. Removal of the

benzene gave the starting material (8mg) m.p. 71°, which showed no depression on admixture with authentic cis 10-hydroxydec-2-enoic acid.

Esterification of crude product from Faworsky rearrangement.

The crude product (50mg) was dissolved in ether and treated with diazomethane. After 15 minutes the solution was washed with bicarbonate and dried. Solvent removal gave a pale yellow oil (45mg).

Thin plate chromatography on Kieselguhr with chloroform containing 5% methanol showed 3 main spots, one of which moved at the same rate as a mixture of authentic cis and trans methyl 10-hydroxydec-2-enoate.

Gas phase chromatography on 10% polyethylene glycol adipate at 154° showed the product to contain some methyl 10-hydroxydec-2-enoate and also a large proportion of a compound with a much longer retention time. Use of 10% Apiezon or 10% polyethylene glycol adipate failed to separate cis and trans methyl 10-hydroxydec-2-enoate.

1:1-Dibromo-2-oxohexane (C38)

(a) Hex 1-yne (10g) in acetic acid (20ml) was added dropwise with stirring to a cooled suspension of N-bromosuccinimide (65.5g: 3 equivs) and sodium acetate trihydrate (49g:3 equivs) in 50% aqueous acetic acid (600ml). After 4 hours the mixture was poured into water (1l) and extracted with ether. The ether extracts were thoroughly washed with water and then with saturated sodium hydrogen carbonate and sodium metabisulphite solutions. The dried extract was then evaporated to give a heavy oil which was distilled (22g: 70%) b.p. 88-90°/20m.m. N_D^{25} 1.4995.
(Found: C,28.17 H,4.08; $C_6H_{10}OBr_2$ requires C 27.92,H.3.88%)
ν_{max} (thin film) 1705 cm^{-1}.

Bis-2:4 dinitrophenylhydrazone:- m.p.215° (needles-methanol)
λ_{max} 397 ε 33,000.

(Found: C,45.39, H 3.83, N 23.66; $C_{18}H_{18}N_8O_8$ requires C,45.57, H 3.82, N 23.62%)

Dioxime m.p. 125° (benzene)

(Found: C,50.02, H 8.18, N 19.45; $C_6H_{12}N_2O_2$ requires C,49.98, H 8.39, H 19.43%)

Bis-semicarbazone m.p. 235-236°

(Found: C,42.34, H 6.87, N 36.98; $C_8H_{16}N_6O_2$ requires C,42.09, H 7.07, N 36.82%)

(b) Using N:N-dibromodimethylhydantoin ("Bromodan") in place of N-bromosuccinimide under similar conditions a yield of 68% of the required α:α-dibromoketone was obtained.

1:1-Dichloro-2-oxohexane

Hex-1-yne was treated with 2 equivalents of hypochlorous acid derived from either N-chlorosuccinimide or N:N dichlorodimethylhydantoin ("Hydan") under the conditions described above.60% of the hex-1-yne was recovered unchanged.

1:1-Dibromoacetophenone (C43)

Phenylacetylene (5g) was added dropwise to a cooled suspension of "Bromodan" (21g: 3 equivs) and sodium acetate trihydrate (20g: 3 equivs) in 50% aqueous acetic acid (300ml). After stirring for 4 hours, the mixture was poured into water (1l) and extracted with ether. Washing with water, saturated sodium hydrogen carbonate, and sodium metabisulphite solutions was followed by drying over anhydrous magnesium sulphate. Solvent removal gave an oil (8.4g: 62%) b.p.175-178°/20m.m.(lit[103] 175-6/23m.m.)
ν_{max} (thin film) 1705 cm^{-1}.

Dioxime m.p. 162-164° (lit[67] 165-166°)
(Found: C 58.78, H 4.93, N 16.96; $C_8H_8N_2O_2$ requires: C 58.53, H 4.91, N 17.07%).

1:1-Diethoxyacetophenone. (C44)

1:1-Dibromoacetophenone (2.78g: 0.01M) was added to a solution of sodium (0.66g: 03M) in ethanol (50ml) and refluxed for 2 hours. Most of the solvent was removed at the pump and water (20ml) was added. Ether extraction gave an oil (1.45g: 70%) which was distilled; b.p. 114°/20m.m. (lit[106] 110°/15m.m.)
ν_{max} (thin film) 1700, 1020-1100 cm^{-1}.

Phenylglyoxal (C45)

1:1-Diethoxyacetophenone (1g) was dissolved in acetic acid (5ml) and shaken with 6N hydrochloric acid (5ml) for six hours. Ether extraction gave an oil (0.5g: 80%) which solidified and crystallised from aqueous ethanol as needles m.p. 86-88° (lit[107] 91° monohydrate)
ν_{max} (Nujol mull) 174o, 1690 cm^{-1}.

Faworsky rearrangement of 1:1-dibromo-2-oxohexane (C38)

(a) 1:1-Dibromo-2-oxohexane (6.5g) was added to a cooled solution of potassium hydroxide (4g: 3 equivs) in ethanol such that the temperature did not exceed 5°. The solution was refluxed for 3 hours and then most of the ethanol removed. Neutral material was removed with ether. Following acidification with 6N sulphuric acid the product was extracted with ether. The extracts were washed and dried and the solvent removed. Distillation gave a foul smelling oil (1.6g: 58%) b.p.116°-120°/20m.m. n_D^{20} 1.4380 (lit for trans hex-2-enoic acid: b.p.[101] 118°/19m.m. n_D^{17} 1.4407). ν_{max} (thin film) 1705, 1650 cm^{-1}.

When the product was esterified with diazomethane and subjected to vapour phase chromatography on 10% polyethylene glycol adipate at 72° the major peak did not correspond to that of authentic methyl trans-hex-2-enoate.

(b) 1:1 Dibromo-2-oxohexane (15g) in methanol (20ml) was added dropwise at 0°C to a stirred solution of sodium (2.7g: 2 equivs) in methanol (50ml). The reaction mixture was refluxed for 4 hours and then most of the methanol was removed. Water (10ml) was added and ether extraction gave a sweet smelling oil (5.6g) which showed only weak absorption at 1650 cm^{-1} in the infrared spectrum.
Distillation gave four fractions:-

	T	p	n_D^{21}
(i)	70	2om.m.	1.4275
(ii)	72	"	1.4280
(iii)	74-76	"	1.4270
(iv)	76	"	1.4210

The ultraviolet spectrum of the final fraction showed it to contain least conjugated double bond absorption at 214 mu. This fraction was chromatographed on grade III alumina from which it was eluted in light petroleum ether (b.p.40-60). Distillation gave a colourless oil b.p. 84°/30m.m. n_D^{21} 1.4215. ν_{max} (thin film) 1735, 1090 cm^{-1}.

The vapour phase chromatogram on 10% Peg A at 72° showed that this compound was identical with the major product of the reaction.

Methyl 3-methoxyhexanoate (C39) was prepared by treating trans methyl hex-2-enoate with sodium methoxide in methanol[102] and was shown by infrared spectrum and by gas chromatography on 10% Peg A and 5% Apiezon to be identical with the above product.

Methyl cis-hex-2-enoate (C40)

1:1 Dibromo-2-oxohexane (6g) in methanol (10ml) was added at 0° to a stirred solution of sodium (1.6g: 3 equivs) in methanol (50ml). After one hour most of the methanol was removed at room temperature and then water (10ml) added. The product was extracted with ether and the extract washed with saturated sodium hydrogen carbonate solution and brine and dried. Careful removal of the ether gave a sweet smelling colourless oil (3g). This oil showed strong absorption in the infrared at 1650 and 820 cm^{-1}.

The oil was chromatographed on silica and gave two main fractions:-

(1) Eluted with petrol (b.p.40-60°): a volatile bromine containing mixture (1g) ν_{max} 1100, 790 cm^{-1}. This compound was not identified.

(2) Eluted with benzene: colourless sweet smelling oil (2g: 60%), b.p. 50°/20m.m. n_D^{20} 1.4380.

(Found C, 65.24, H 9.73; $C_7H_{12}O_2$ requires C 65.59, H 9.44%)
ν_{max} (thin film) 1715, 1645, 820 cm^{-1}.
U.V. spectrum: end absorption 213 mμ (9,000)

Methyl trans-hex-2-enoate (C41)

Methyl-cis-hex-2-enoate was chromatographed on grade I alumina with benzene as eluent to give, quantitatively, trans methyl hex-2-enoate. b.p. 67°/20m.m. (lit[108] 64°/22m.m.)
ν_{max} (thin film) 1715, 1650, 980 cm^{-1}.
U.V. spectrum: end absorption 213 mμ (9,000).

This was identical with an authentic sample[101].

1:1-Dibromo-2-oxo-octane (C50)

Oct-1-yne (5.5g) was added dropwise with cooling to a stirred suspension of N-bromosuccinimide (26g: 3 equivs) and sodium

acetate trihydrate (24g: 3 equivs) in 50% aqueous acetic acid (300ml). After 4 hours water (1l) was added and the whole extracted with ether. After most of the acetic acid had been washed out, the extract was shaken with saturated sodium hydrogen carbonate and sodium metabisulphite solutions. Drying and removal of the solvent gave the product (8.9g: 64%) b.p. 70-74°/0.2m.m. n_D^{25} 1.4950 (lit[70] 80-82°/0.4m.m. n_D^{21} 1.4950).

Methyl cis-oct-2-enoate. (C51)

1:1 Dibromo-2-oxooctane (5g) was added at 0° to a solution of sodium (1.2g: 3 equivs) in methanol. After stirring at room temperature for 1 hour water (10ml) was added and the product extracted with ether. Drying and removal of solvent gave a colourless oil (2.9g). This oil was chromatographed on silica to give two fractions:-

1. Eluted with petrol (b.p. 40-60°)
   Bromine containing by-products ν_{max} (thin film) 1100, 790 cm^{-1}.
2. cis Methyl oct-2-enoate (1.8g: 67%)
   Eluted with benzene
   b.p. 68-72°/20m.m. n_D^{22} 1.4395
   ν_{max} (thin film) 1715, 1645, 820 cm^{-1}.

Methyl trans oct-2-enoate (C52)

cis Methyl oct-2-enoate was quantitatively converted to trans methyl oct-2-enoate by eluting from grade I alumina with benzene b.p. 100°/20m.m. (lit[109] 97°/17m.m.)
ν_{max} (thin film) 1715, 1650, 980 cm^{-1}.

Bis-2:4 dinitrophenylhydrazone derived from hex-1-yne

Hex-1-yne (20mg) in acetic acid (1ml) was added to a mixture of N:N dibromo dimethylhydantoin (100mg: 3 equivs) and sodium

acetate trihydrate (35mg: 3 equivs) in 50% aqueous acetic acid (5ml). The mixture was shaken at room temperature for 2 hours and then poured into water (10ml). The product was extracted with ether. The extract was thoroughly washed with water and sodium metabisulphite solution. Removal of solvent gave a pale yellow oil which was dissolved in ethanol (5ml). To this solution was added Bradys reagent containing 150mg. 2:4 dinitrophenylhydrazine and the mixture heated on a steam bath for 30 minutes. The red bis-2:4 dinitrophenylhydrazone (75mg: 62%) was filtered off. This crystallised as needles from Methanol/chloroform mixture. m.p. 215-217°.

($C_{18}H_{18}N_8O_8$ requires C 45.57; H 3.82 ; N 23.62 .
found C 45.39; H 3.83 ; N 23.66%)

U.V. spectrum 397 (ε 33,000) 444 mu.

Bis-oxime derived from hex-1-yne

Crude 1:1 dibromo-2-oxohexane prepared as above from hex-1-yne (20mg) was dissolved in pyridine (10ml) and hydroxylamine hydrochloride (55mg: 3 equivs) added. The mixture was heated on the steam bath for 2 hours and then poured into water (20ml). The product was extracted with ether and the ether extracts washed with dilute hydrochloric acid and then dried over magnesium sulphate. Removal of solvent gave an oil (21mg: 60%) which solidified and recrystallised from benzene m.p. 125°.

($C_6H_{12}N_2O_2$ requires C,49.98; H,8.39; H,19.43.
found C 50.02; H,8.18; N,19.45%)

Derivatives from acetylenes.

The above procedures were repeated with the following compounds, giving the bis-2:4 dinitrophenylhydrazones or dioximes as quoted.

(i) Oct-1-yne

Bis-2:4 dinitrophenylhydrazone (ethanol) m.p.179-180°
($C_{20}H_{22}N_8O_8$ requires C 47.8; H 4.4; N 22.3;
found C 47.7; H 4.3; N 22.4%

(ii) Propargyl alcohol

Bis-2:4 dinitrophenylhydrazone (ethanol) m.p. 213-217°
($C_{15}H_{12}N_8O_9$ requires C 40.19; H 2.68; N 25.00;
found C 40.33; H 2.42; N 25.10%)
U.V. $_{max}$ 397, 444

(iii) Phenylacetylene

Dioxime (benzene) m.p. 162-164° (lit[67] value 165-166°)
($C_8H_8N_2O_2$ requires C 58.53; H 4.91; N 17.07;
found C 58.78; H 4.93; N 16.96%)

(iv) Ethynylcyclohexanol

Dioxime (benzene) m.p. 141-142°
($C_8H_{14}N_2O_3$ requires C51.60; H 7.58; N 15.04;
found C51.83; H 7131; N 14.79%)

(v) 10-Hydroxydec-1-yne

Bis-2:4 dinitrophenylhydrazone (ethanol) m.p. 174-166.
($C_{22}H_{26}N_8O_9$ requires C 48.36; H 4.76;
found C 48.57; H 4.82%)

$_{max}$ 397, 444

(vi) 10-Acetoxydec-1-yne

Bis 2:4 dinitrophenylhydrazone (ethanol) 150-151°
($C_{24}H_{28}N_8O_{10}$ requires C 48.98; H 4.80;
found C 48.87; H 4.58%)

(vii) Undec-10-ynoic acid

Dioxime m.p. 129-130°
($C_{11}H_{20}N_2O_4$ requires C54.08; H 8.25; N 11.47;
found C54.09; H 7.94; H 11.57%)

$HO(CH_2)_7CH{=}CHCOOH$. (C1,B23).

↓

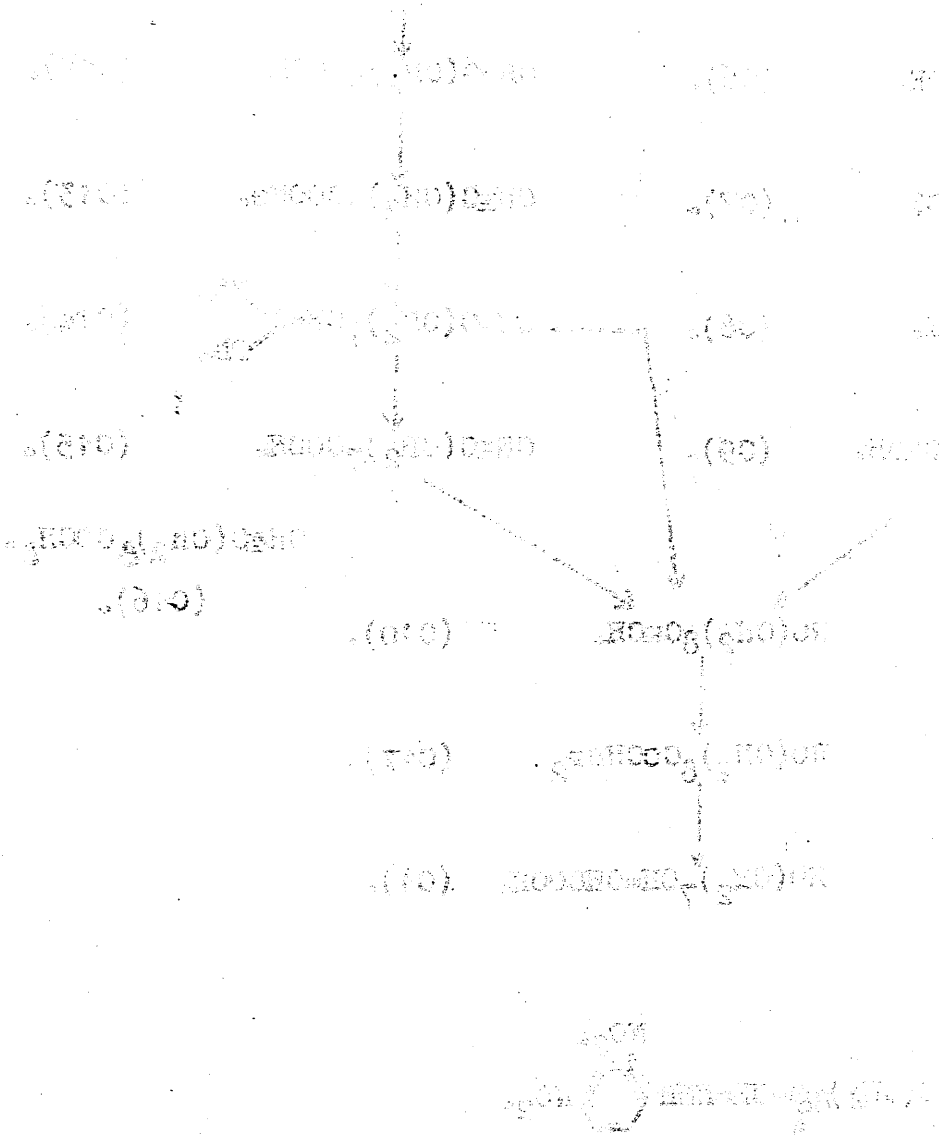
$HO(CH_2)_9COOH$. (C2).

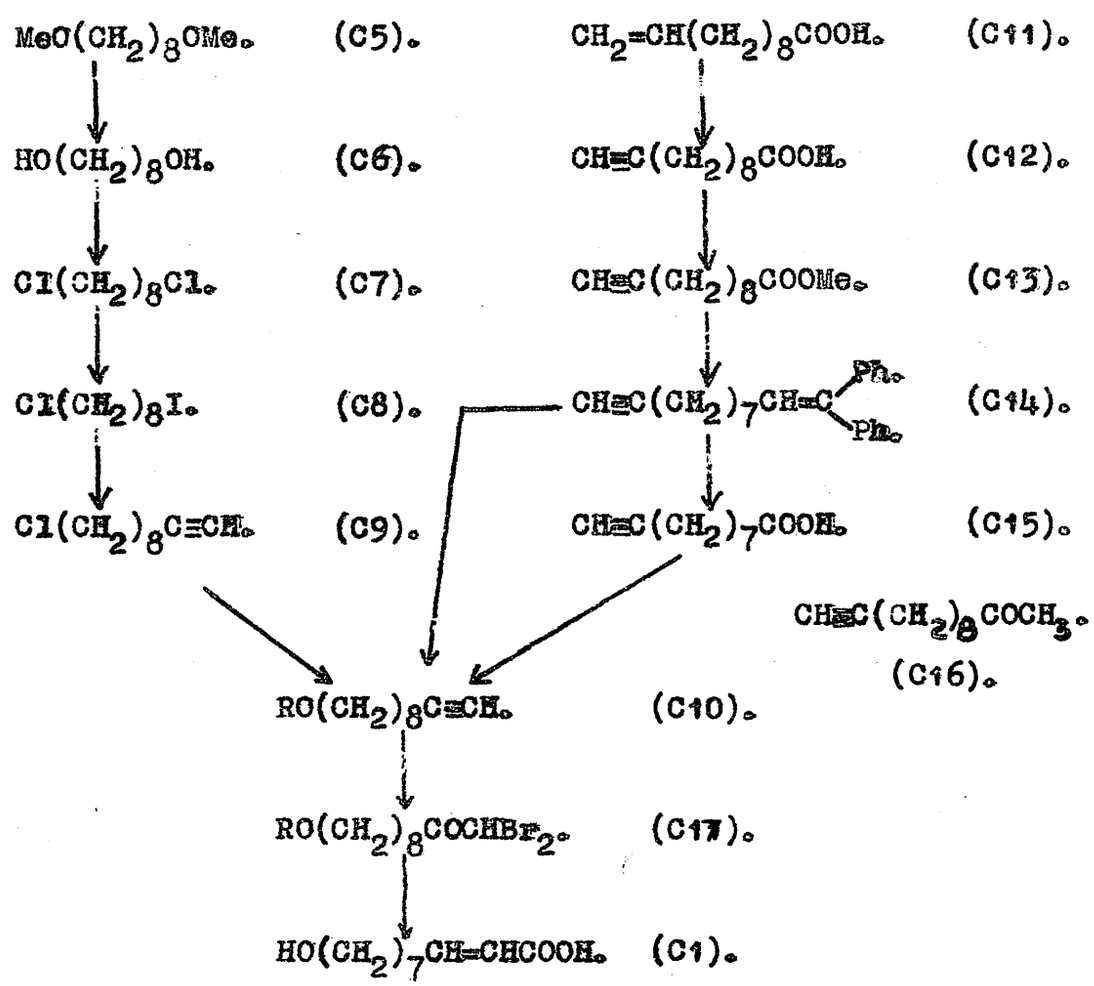
↓

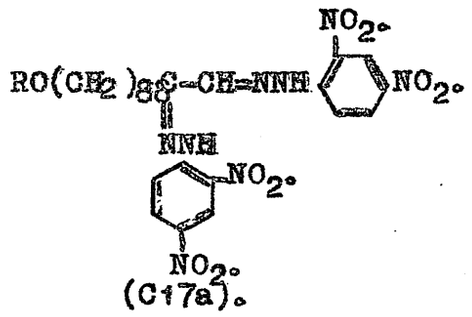
$HO(CH_2)_{10}OH$. (C3).

↓

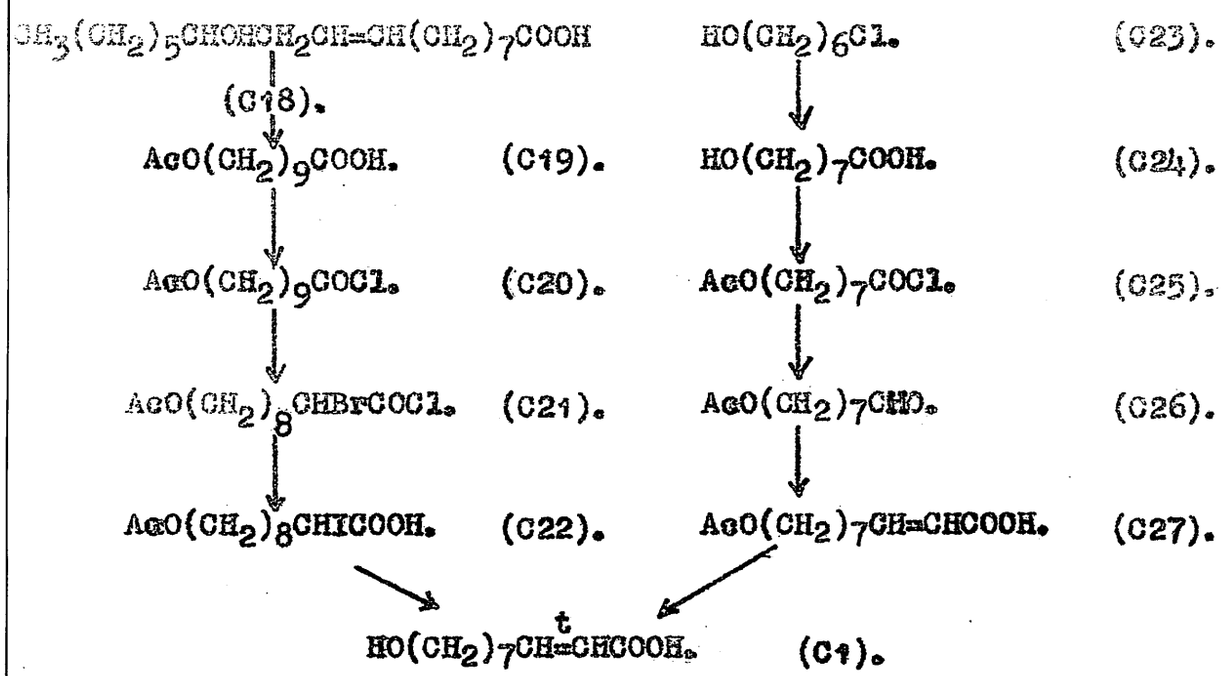
$HOOC(CH_2)_8COOH$. (C4).

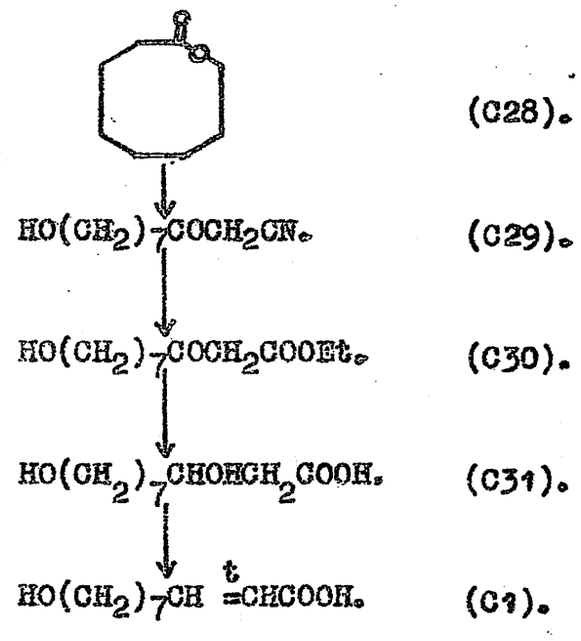


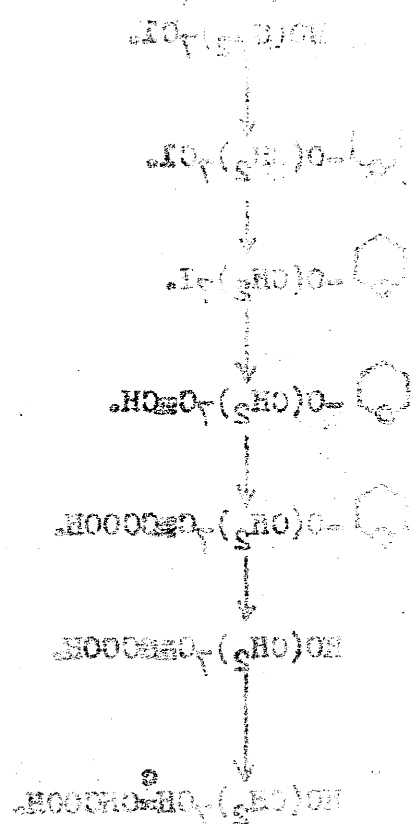

MeO(CH2)8OMe. (C5).
HO(CH2)8OH. (C6).
Cl(CH2)8Cl. (C7).
Cl(CH2)8I. (C8).
Cl(CH2)8C≡CH. (C9).
CH2=CH(CH2)8COOH. (C11).
CH≡C(CH2)8COOH. (C12).
CH≡C(CH2)8COOMe. (C13).
CH≡C(CH2)7CH=C Ph. Ph. (C14).
CH≡C(CH2)7COOH. (C15).
CH≡C(CH2)8COCH3. (C16).
RO(CH2)8C≡CH. (C10).
RO(CH2)8COCHBr2. (C17).
HO(CH2)7CH=CHCOOH. (C1).


NO2.
RO(CH2)8C-CH=NNH
NO2.
NNH
NO2.
NO2.
(C17a).

3C


$CH_3(CH_2)_5CHOHCH_2CH=CH(CH_2)_7COOH$ (C18).
$AcO(CH_2)_9COOH$. (C19).
$AcO(CH_2)_9COCl$. (C20).
$AcO(CH_2)_8CHBrCOCl$. (C21).
$AcO(CH_2)_8CHICOOH$. (C22).
$HO(CH_2)_6Cl$. (C23).
$HO(CH_2)_7COOH$. (C24).
$AcO(CH_2)_7COCl$. (C25).
$AcO(CH_2)_7CHO$. (C26).
$AcO(CH_2)_7CH=CHCOOH$. (C27).
$HO(CH_2)_7CH=^{t}CHCOOH$. (C1).


(C28).
$HO(CH_2)_7COCH_2CN$. (C29).
$HO(CH_2)_7COCH_2COOEt$. (C30).
$HO(CH_2)_7CHOHCH_2COOH$. (C31).
$HO(CH_2)_7CH=^{t}CHCOOH$. (C1).



(C53).

(C54).

(C55).

(C56).

(C57).

(C58).

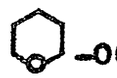
(C59).

$HO(CH_2)_7Cl$. (C53).

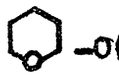
↓


$-O(CH_2)_7Cl$. (C54).

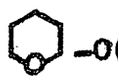
↓


$-O(CH_2)_7I$. (C55).

↓


$-O(CH_2)_7C{\equiv}CH$. (C56).

↓

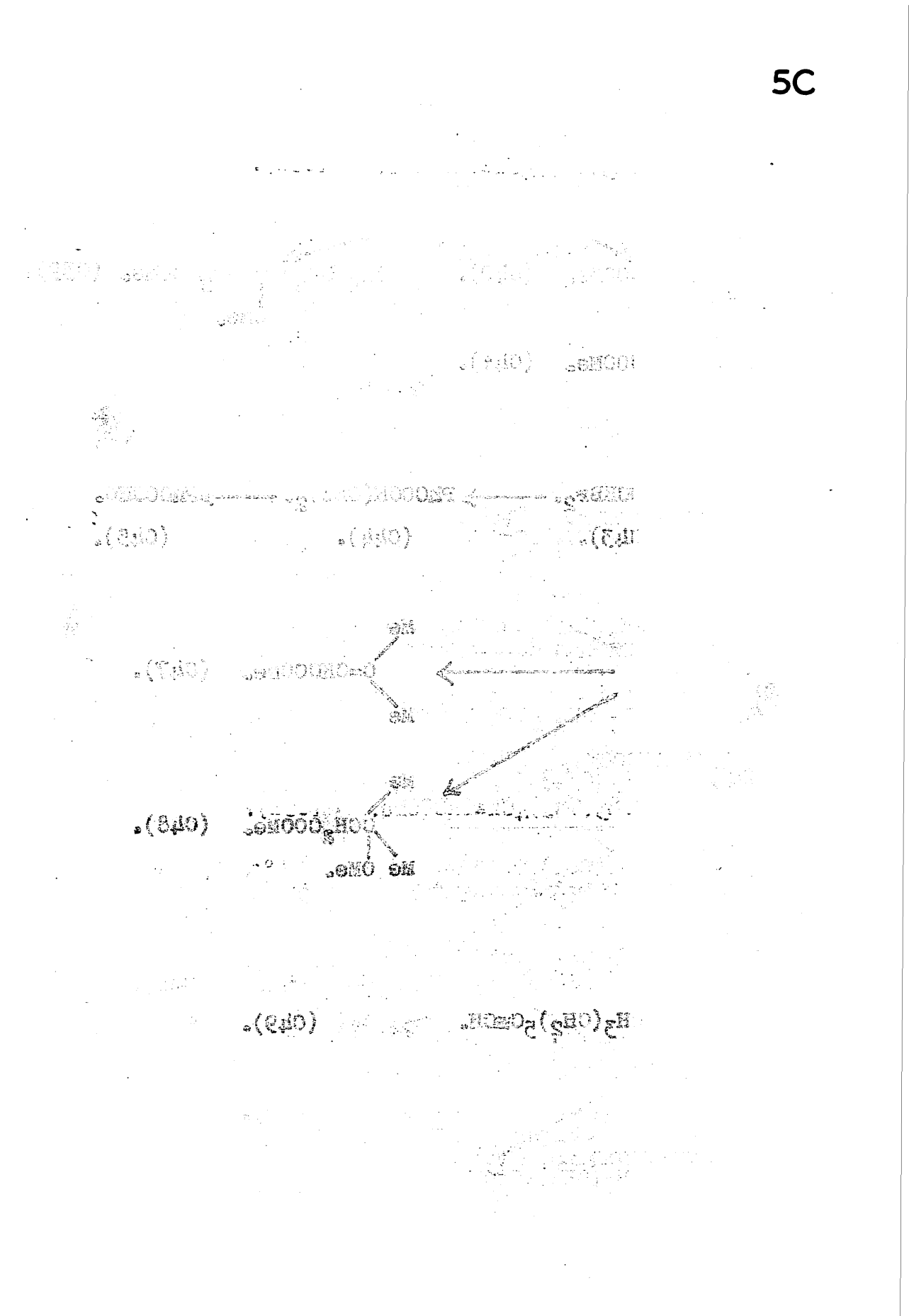

$-O(CH_2)_7C{\equiv}CCOOH$. (C57).

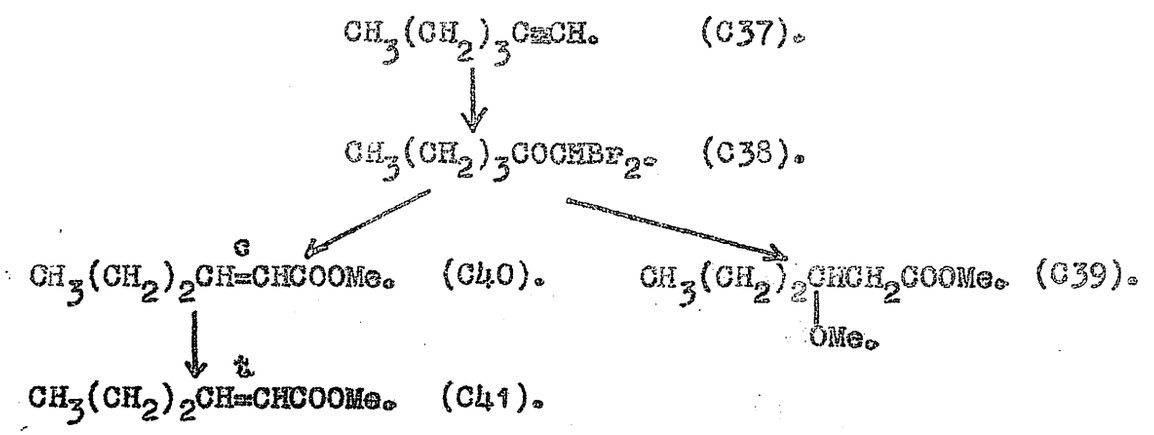
↓

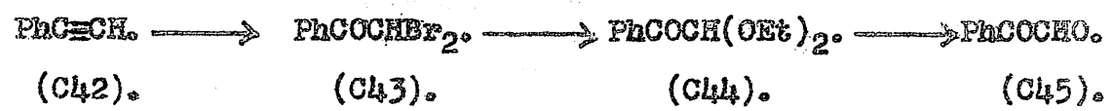
$HO(CH_2)_7C{\equiv}CCOOH$. (C58).

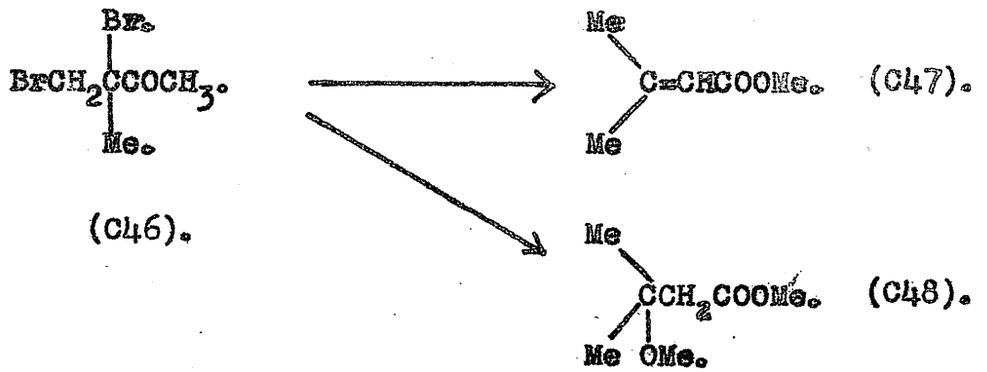
↓

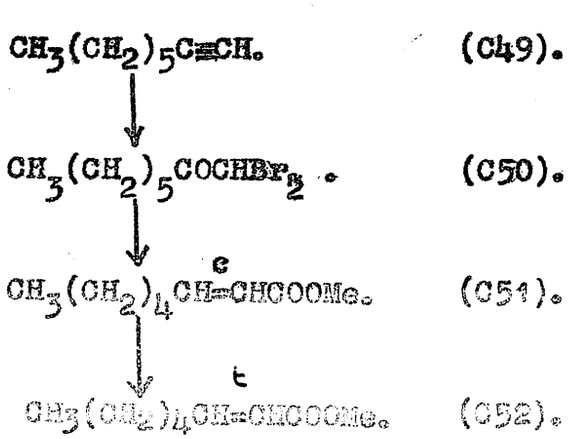
$HO(CH_2)_7CH{=}CHCOOH$. (C59).

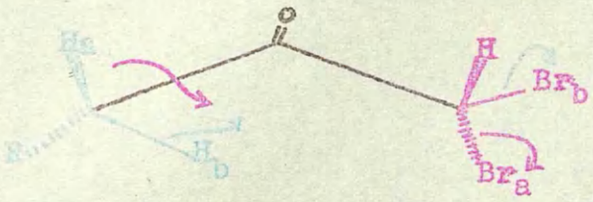



$CH_3(CH_2)_3C{\equiv}CH$. (C37).
$CH_3(CH_2)_3COCHBr_2$. (C38).
$CH_3(CH_2)_2CH{=}CHCOOMe$. (C40).
$CH_3(CH_2)_2CHCH_2COOMe$. (C39).
OMe.
$CH_3(CH_2)_2CH{=}CHCOOMe$. (C41).

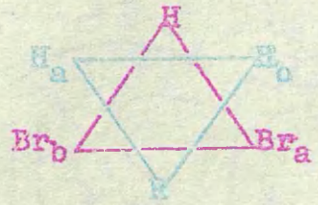

$PhC{\equiv}CH$. → $PhCOCHBr_2$. → $PhCOCH(OEt)_2$. → PhCOCHO.
(C42). (C43). (C44). (C45).


$BrCH_2CCOCH_3$.
Br.
Me.
(C46).
C=CHCOOMe. (C47).
CCH_2COOMe. (C48).
Me OMe.

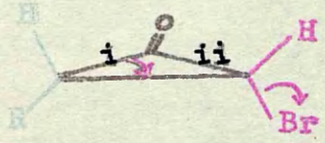

$CH_3(CH_2)_5C{\equiv}CH$. (C49).
$CH_3(CH_2)_5COCHBr_2$. (C50).
$CH_3(CH_2)_4CH{=}CHCOOMe$. (C51).
$CH_3(CH_2)_4CH{=}CHCOOMe$. (C52).



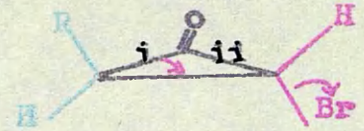
(XII).



(XIIa)



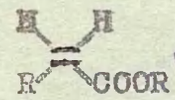
(IX).



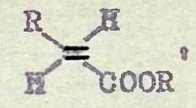
(XI).

(IXa).

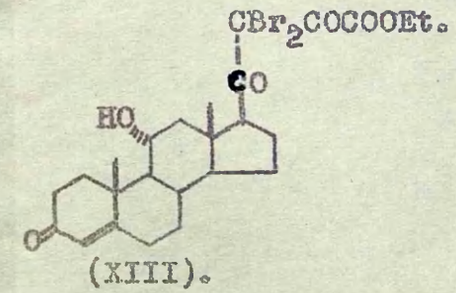
(XIa).



(VIII).



(X).



(XIII).

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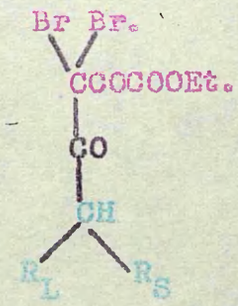
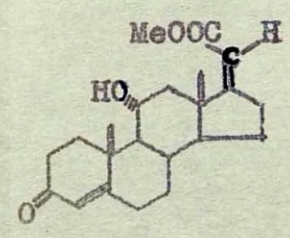
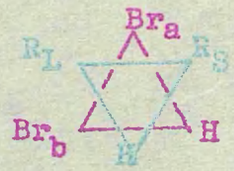


(XIIIa).



(XIV).



(XIIIb).

PART FOUR.

SYNTHESES OF 1:7-DIHYDROXYPYRROLIZIDINES.

INTRODUCTION

Among the families Compositae, Leguminosae, and Boraginaceae, the genus Senecio provides a large number of alkaloids which contain the pyrrolizidine nucleus (D1). Such alkaloids have been called "Senecio" or"pyrrolizidine" alkaloids and the detailed chemistry of them has been reviewed.[110,111].

The alkaloids are best isolated by extraction and partition chromatography[112]. Hydrolysis of the pure natural product provides a basic fragment, the necine, and an acidic fragment, the necic acid. The gross structure of the alkaloid falls into one of three groups:-

(1) Monoesters of necines with a monocarboxylic necic acid;
(2) diester of necines with two different monocarboxylic necic acids;
(3) Cyclic esters of necines with dicarboxylic necic acids.

The necic acids are branched chain aliphatic acids containing from five to ten carbon atoms. The necines contain either seven or eight carbon atoms and those so far isolated, with two exceptions,[113,114] contain at least one hydroxyl group.

Three of the most common necines are (+) heliotridine[115] (D2), (+) retronecine[116] (D3) and (-) platynecine[117] (D4). The first two had the same molecular formula, $C_8H_{13}NO_2$[118], which differed from the third by having two hydrogen atoms less. The former contained a tertiary nitrogen atom, two hydroxyl groups and depending on the conditions absorbed one or two molecules of hydrogen on catalytic reduction. The reduction was accompanied by hydrogenolysis (+) heliotridine giving (-) oxyheliotridine (D5), and (+) retronecine giving (-) retronecanol (D6). Both of these reduction products on

dehydration and further reduction gave (-) heliotridane (D7) (-) Platynecine (D4) was also converted into this pyrrolizidine[119] showing that the three natural products (D2), (D3) and (D4) had the same carbon skeleton. Exhaustive methylation and reduction[120] of (-) heliotridane (D7) gave (-)-dihydro-des-N methylheliotridane (D11), the structure of which was subsequently confirmed by synthesis.[121] This fact along with a synthesis of dl 1-methylpyrrolizidine allowed Menshikov[122] to deduce that (-)-heliotridane was an optical isomer of 1-methylpyrrolizidine (D7).

(+) Retronecine (D3) was converted to (-) platynecine (D4) and a study of the chemical properties of the two hydroxyl groups showed[123] that one was a primary group and could therefore only be accommodated as a hydroxymethyl group on $C_{(1)}$ and that the other was secondary. The ease of formation of anhydroplatynecine[119] (D14) from platynecine (D4) and the stability of the anhydro-derivative indicated that the secondary hydroxyl group was in position 6 or 7. That it was in the 7 position was confirmed when Leonard[124] synthesised (-)1-methyl-7-ketopyrrolizidine and showed it to be identical to (-) retronecanone (D13) which Adams and Hamlin[123] had obtained from retronecanol (D6).

Desoxyretronecine (D8) was converted to isoheliotridine (D9) of which the hydrochloride was ozonised.[125] The product was shown to be the methyl keto acid (D10) so fixing the double bond in retronecine (D3) and heliotridine (D2) in the 1:2 position.

Platynecine (D4) readily gave the very stable anhydroplatynecine (D14) and consideration of the possible stereochemistry of this led Leonard and Felley[126] to the conclusion that the hydrogen atoms on $C_{(1)}$ and on $C_{(8)}$ were

cis-disposed. The relative stereochemistry of the hydrogen atom on $C_{(7)}$ was resolved when it was found that platynecine readily gave the anhydro derivative on treatment with toluene-p-sulphonyl chloride[127] and that it readily formed a cyclic sulphite[128] (D15) which could be reconverted into the parent compound. (D4). These facts indicated that the hydrogen atoms on $C_{(1)}$ and $C_{(7)}$, and hence on $C_{(1)}$ $C_{(8)}$ and $C_{(7)}$, were cis disposed.

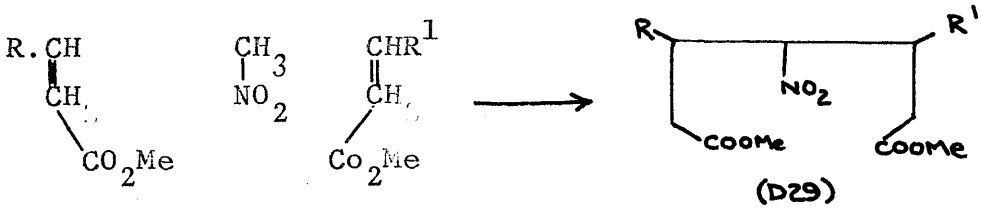
The absolute configurations of the necines were elucidated by Warren and Klemperer[129] who, by a series of Hofmann degradations and subsequent reductions, correlated (-) heliotridane (D7) with (+) 3-methylheptane (D17) which was known to have the (S) configuration[130]. This showed the configuration at position 1 in (-) heliotridane (07) and in the related (-) platynecine (D4) to be S. It followed from the structure of platynecine and (+) retronecine (D3) that the configuration at the seven and eight positions must be R. That the one position was indeed of the S configuration was confirmed when Adams and Fles correlated (S) (-) methylsuccinic acid (D19) to synthetic (-) retronecanone (D13), via (+) 2-methyl-4-aminobutyric acid (D18), from which it had been synthesised[124]. The same workers[132] converted desoxyretronecine (D9) by ozonolysis and a Grignard reaction to the optically active carbinol (D20) which was also obtained from (S) (-) proline (D21). This established the configuration at C_8 as being R.

Hence the structures (D2) (D3) and (D4) represent the absolute stereochemistry of (+) heliotridine, (+) retronecine, and (-) platynecine.

Robinson[133] has proposed a biogenetic scheme for the pyrrolizidine alkaloids in which 3-hydroxyglutamic acid

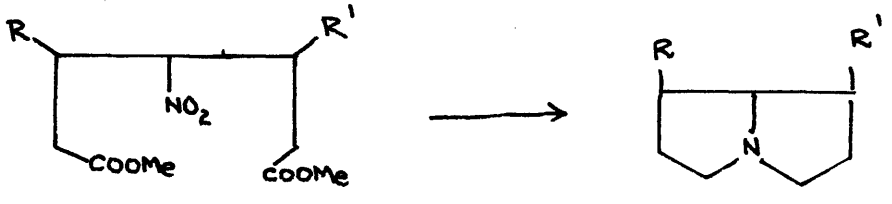
(D22) yields the aldehyde (D23). Two molecules of this aldehyde condense with ammonia to give the imine (D24) which readily undergoes intramolecular condensation with subsequent dehydration and reduction to give either heliotridine (D2) or retronecine (D3). Some experimental evidence was provided for this scheme when Leonard and Blum[134] converted γ:γ'-imino-bis-butyraldehyde (D25), at pH 7, into 1-aldehydopyrrolizidine (D26) and thence into laburnine (D27) and trachelanthimidine (D28).

Numerous syntheses of pyrrolizidine[135,141] of 1-methyl pyrrolizidine[122,124,142-145], and of other alkyl pyrrolizidines[146,147] have been reported. Of these syntheses that of Leonard and Felley[146] in which substituted acrylic esters were condensed with nitromethane was the one of most general applicability:-



(D29)

The γ-nitropimelic ester on hydrogenation over copper chromite gave a substituted pyrrolizidine (D30).



(D29.) (D30.)

This route did not lend itself to the preparation of hydroxylated pyrrolizidines owing to the inaccessibility of the necessary hydroxy-acrylates and crotonates.

Other routes, however, have led to the stereospecific syntheses of the following monohydroxylated pyrrolizidines:-

1 α - hydroxymethyl-(8α)-pyrrolizidine (trachelanthimidine)[148]

1 β - hydroxymethyl-(8β)-pyrrolizidine (laburnine),[134] and of

1 β - hydroxymethyl-(8α)-pyrrolizidine (isoretronecanol)[134,149-151].

Prior to the beginning of the present work no accounts of the synthesis of 1-hydroxymethyl-7-hydroxypyrrolizidines had been published.

DISCUSSION

N-Carbethoxyalanine ethyl ester condenses with diethyl fumarate to give the substituted pyrrolid-3-one[152] (D31) which on decarboxylation with hydrochloric acid gives the acid (D32); on esterification with methanol or ethanol, this acid gives the methyl ester (D34) and the ethyl ester (D33) respectively of 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetic acid (D32).

When the ethyl ester (D33) was refluxed with concentrated hydrochloric acid in an attempt to remove the N-carbethoxyl group, only the C-carbethoxyl group reacted, and the product obtained gave, on esterification with methanol, the crystalline methyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate (D34). However, refluxing with hydrobromic acid and subsequent esterification with methanol containing hydrogen bromide gave 2-methylcarbomethoxy-3-oxopyrrolidinum bromide (D35) in 50% yield.

Two routes to retronecine (D3) from this compound were projected. The first route involved the condensation of the hydrobromide (D35) with methoxalyl chloride to give the N-methoxalylpyrrolid-3-one (D36). Catalytic reduction of the ketone group and subsequent lactonisation with the carbomethoxymethyl group on $C_{(2)}$ would establish the relative stereochemistry at $C_{(7)}$ and $C_{(8)}$ in the pyrrolizidine which would result from the next step. Internal Dieckmann condensation of this lactone was expected to give 1-carbomethoxy-7-hydroxy-2:3-dioxopyrrolizidine (D38) which on selective catalytic reduction[152] dehydration and chemical reduction with lithium aluminium hydride, would yield retronecine (D3).

The second approach required the condensation of methyl bromoacetate with the hydrobromide (D35) to give the N-carbomethoxymethyl derivative (D40), which by a similar sequence of reactions (D41), (D42), (D43) could yield retronecine.

2-Carbomethoxymethyl-3-oxopyrrolidinium bromide (D35) was condensed with methoxalyl chloride to give methyl 1-methoxalyl-3-oxopyrrolidin-2-yl acetate (D36). However, at this stage in the synthesis it was made known by Geissman[153] that he had just completed a synthesis of retronecine[154] by a route which was essentially that which we intended to follow. Consequently, this route was not pursued any further.

Geissman and Waiss[154] condensed the hydrochloride of 3-pyrrolidinol-2-acetic acid lactone (D44) with ethyl bromoacetate to give the N-carbethoxyethyl pyrrolidone (D45). Reaction of this lactone with sodium ethoxide followed by catalytic reduction gave 1-carbethoxy-2:7-dihydroxypyrrolizidine (D46), which was dehydrated and then reduced with lithium aluminium hydride to give (±) retronecine (D3). Resolution of this racemate gave the (+) isomer which was identical with natural (+) retronecine.

In the present work synthetic routes to anhydroplatynecine (D14) were also investigated.

1:2:4-Trihydroxybutane was dehydrated by distilling it from toluene-p-sulphonic acid, to give 3-hydroxytetrahydrofuran.[155] Oxidation of this alcohol with chromium trioxide gave 3-oxotetrahydrofuran (D47) in 30% yield.

It was hoped at this stage to introduce carbethoxymethyl groups in the 2 and 4 positions of 3-oxotetrahydrofuran (D47), but the reaction between this ketone and the

ethyl hemiacetal of glyoxylic ester under the following conditions:-

(i) refluxing in the presence of n-butylamine[156]

(ii) refluxing in the presence of sodium methoxide;

(iii) heating at 200° for 2 hours,[157]

and the reaction with glyoxylic acid, which had been generated in situ,[158] failed to give any desired product.

When an attempt was made to prepare the morpholine enamine of 3-oxotetrahydrofuran, the product, (a mixture of two components), showed anomalous infrared absorption in the carbonyl region and the idea of introducing the carbethoxymethyl group by the action of ethyl bromoacetate on the enamine was abandoned.

Had the desired 2:4 dicarbethoxymethyl-3-oxotetrahydrofuran (D48) been obtained it was proposed to convert it to the corresponding 3-amino compound (D49) which could well yield the bis-lactam (D50). Lithium aluminium hydride reduction of this lactam was expected to give anhydroplatynecine (D14).

Alternative routes to 2:4 dicarbomethoxymethyl-3-oxotetrahydrofuran (D48) were investigated.

Addition of dimethyl malate to methyl acrylate would give the ether (D51) which in the presence of sodium could cyclise to any one of the four products (D52, D53, D54, D55). However, Clark-Lewis and Mortimer[152] showed that the similar compound (D56) obtained by condensing N-carbethoxyalanine ethyl ester and diethyl fumarate, although capable of giving rise to four condensation products, only yielded the furanid-3-one (D33). Hence, it seemed reasonable to hope that the ether (D51) would give 4 -carbomethoxy-2-carbomethoxymethyl -3-oxotetrahydrofuran (D55). Such a product on condensation

with methyl bromoacetate and decarboxylation would give the desired furanid-3-one (D49).

All attempts to add dimethyl malate across the double bond of methyl acrylate or of acrylonitrile failed, the products isolated from such attempts being fumaric acid or dimethyl fumarate. This failure to cyanoethylate a hydroxy ester has been observed with methyl lactate[159] and certain other hydroxy[160] esters.

Condensation of ethylene cyanohydrin with dimethyl fumarate or with dimethyl maleate was expected to give the ether (D57). This ether is closely related to the one described above (D51) and in a similar fashion would be expected to yield 4-cyano-2 carbomethoxymethyl-3-oxo-tetrahydrofuran (D58) on cyclisation. This compound could also be converted into 2:4-dicarbomethoxymethyl-3-oxotetra-hydrofuran (D48) by treatment with methyl bromoacetate and subsequent hydrolysis, decarboxylation and esterification

Once again the initial condensation could not be achieved, despite numerous variations in conditions, and this approach to anhydroplatynecine was abandoned.

During the course of this work a synthesis of (±) platynecine (D4) was reported[161]. Ethyl 2-methoxymethyl-prolinate (D59) was condensed with ethyl acrylate to give (D60) which was cyclised in base to 6-carbethoxy-1-methoxymethyl-7-oxo-pyrrolizidine (D61). Hydrolysis, decarboxylation and catalytic reduction gave (±) platynecine (D4).

EXPERIMENTAL

N-Carbethoxy-B-alanine ethyl ester[162]

B-Alanine (178g: 2 moles) in water (250ml) was made alkaline to phenolphthalein with 10% sodium hydroxide solution. Ethyl chloroformate (234g: 2.15M) and 10% sodium hydroxide solution were added dropwise from separate funnels with stirring, at 0^{o} such that the reaction mixutre just remained basic. The solution was taken to pH 1 with concentrated hydrochloric acid and thoroughly extracted with chloroform. Drying and evaporation gave a colourless oil which solidified.

This oil was dissolved in absolute ethanol (500ml) and the solution was saturated with hydrogen chloride and left overnight. Removal of the ethanol gave a colourless oil which was distilled to give N-carbethoxy-B-alanine ethyl ester (280g: 79%) b.p. $93\text{-}97^{o}/0.4$mm, n_{D}^{20} 1.4410 (lit[162] $150\text{-}54^{o}/30$m.m, n_{D}^{20} 1.4408).

Ethyl 1-ethoxycarboxyl-3-oxopyrrolidin-2-yl acetate[152](D33)

N-Carbethoxy-B-alanine ethyl ester (76g: 0.4M9, and diethyl fumarate (38.8g: 0.4M) were added successively to a stirred suspension of sodium wire (9.2g: 0.4M) in dry benzene. The mixture was gently heated until the sodium had dissolved and then stirred for a further 30 minutes. On cooling the brown solution was poured into ice-water (600ml) and neutral material removed with ether. Acidification of the aqueous layer with concentrated sulphuric acid (13ml) was followed by saturation with brine and extraction with ethyl acetate. The organic extracts were washed with brine and with sodium hydrogen carbonate solution. Drying, followed by evaporation gave an oil (106g) which was then dissolved in

10N-hydrochloric acid (300ml). On the next day the solution was evaporated under reduced pressure; ethanol (400ml) was added and the solution evaporated once more.

The acidic residue was dissolved in ethanol (300ml) which had been saturated with hydrogen chloride and the solution refluxed for five hours. Evaporation and then distillation of the residue gave the expected ester (40g: 43%) b.p. 124-127°/0.3m.m, (lit[152] 122-128°/0.3m.m). ν_{max} (thin film) 1750, 1730, 1695 cm^{-1}.

Methyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate (D34)

When the acidic residue obtained in the above experiment after the initial condensation and treatment with concentrated hydrochloric acid was esterified with methanol instead of ethanol the product was a solid which crystallised from petroleum ether. m.p. 62-64°. Sublimation at 70°/0.2m.m. gave sharp-melting solid m.p. 66°.
(Found C, 52.21; H 6.70; N 6.21;
$C_{10}H_{15}NO_5$ requires C, 52.39; H 6.60; N 6.11%)
2:4 Dinitrophenylhydrazone (ethanol) m.p. 153-156°
(Found C, 47.24; H. 4.80; N, 17.30; $C_{16}H_{19}N_5O_8$ requires C, 46.94; H, 4.68; N, 17.11%)
ν_{max} (Nujol mull): 1750, 1710, 1690 cm^{-1}.

Reaction of ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate with concentrated hydrochloric acid.

Ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate (5.7g) was refluxed in concentrated hydrochloric acid (50ml) for 3 hours. The solution was taken to dryness at the pump and methanol (100ml) added and the solution was once more evaporated. This procedure was repeated several times.

The residue was dissolved in methanol (100ml) and the mixture saturated with hydrogen chloride. After 18 hours the solvent was removed at the pump.

The product (5g) solidified. This was eluted from alumina (grade III) with benzene-chloroform (1:1) and sublimed at $70^{o}/0.2$m.m., m.p. $66-67^{o}$.

Admixture with the compound (D34) obtained above gave no melting point depression.

Methyl 3-oxopyrrolidin-2-yl acetate hydrobromide (D35)

Ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate (25g) was refluxed with 48% aqueous hydrogen bromide (190ml) for 5 hours. The solution was taken to dryness at the pump and methanol (150ml) added and the mixture evaporated again. This was repeated three times. The residual oil was dissolved in methanol and the solution saturated with hydrogen bromide. Next day the solvent was removed; the residual oil was dissolved in methanol (5ml) and ether added. The solid which separated (10g: 50%) crystallised from methanol m.p. $159-162^{o}$(d).

Found: C, 35.46; H, 5.25; N, 5.65; $C_7H_{12}NO_3Br$ requires C, 35.31; H, 5.09; N, 5.89%)

ν_{max} (Nujol mull) 2500 2700, 1750, 1710cm^{-1}.

Some methyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate (5g) was recovered from the mother liquors.

Methyl 1-methoxalyl-3-oxopyrrolidin-2-yl acetate (D36)

Methyl 3-oxopyrrolidin-2-yl-acetate hydrobromide (1.2g) was heated on the steam bath with methoxalyl chloride[163] (1g: 1.6 equivs) for 2 hours. Dry benzene (10ml) was added and the solution washed with saturated sodium hydrogen carbonate

solution dried and evaporated. The residual oil (0.8g:66%) was purified by molecular distillation 130°/0.1m.m. (Found, C, 49.58; H 5.72; $C_{10}H_{13}NO_6$ requires C 49.38; H, 5.39%) ν_{max} (thin film):- 1650, 1710, 1730, 1750cm^{-1}.

3-Hydroxytetrahydrofuran[155]

1:2:4 Trihydroxybutane (106g) was distilled through a 15cm Vigreux column from toluene p-sulphonic acid (1g) in a flask heated to 180° and under a reduced pressure of 20m.m. The fraction of boiling point 84-88°/20m.m. was collected and redistilled to give 3-hydroxytetrahydrofuran (70g:80%) b.p. 84°/14m.m, n_D^{25} 1.4497. (lit[155] b.p. 93-95°/26m.m, n_D^{25} 1.4497).

3-Oxotetrahydrofuran (D47)

A solution of chromium trioxide (66g) concentrated sulphuric acid (60g) and water (100ml) was added dropwise with stirring to a cooled solution of 3-hydroxy-tetrahydrofuran (66g) in water (50ml). After having been stirred overnight the green solution was saturated with sodium chloride and constantly extracted with ether for 24 hours. Drying and evaporation gave the furan (20g: 32%) b.p.75°/60m.m. n_D^{20} 1.4350 (lit[164] b.p. 139°, n_D^{20} 1.4384). ν_{max} (thin film):- 1750 cm^{-1}. 2:4-Dinitrophenylhydrazone m.p. 158° (lit 155°). (Found: C 44.93; H 4.00; N 20.95; $C_{10}H_{10}N_4O_5$ requires: C 45.11; H 3.79; N 21.05%)

Ethyl 1-ethoxy-1-hydroxyacetate

A solution of diethyltartrate (100g: 0.5M) in benzene (500ml) at -10° was treated with lead tetraacetate (220g: 0.52M) over a period of two hours. After stirring for 12 hours the lead salts were removed from the reaction mixture and the benzene removed at the pump. Ethanol (450ml) was added to the residue

which was then fractionated through a 30cm. Vigreux column. The distillate b.p. 50-58°/15m.m. was redistilled to give the desired ester (132g: 50%) b.p. 55-60°/20m.m. n_D^{20} 1.4160. (lit[165] b.p. 54-55°/16m.m.)

Condensation of 3-oxotetrahydrofuran with the ethyl demiacetal of ethyl glyoxylate.

(a) n_Butylamine[156] (0.2g) was added dropwise to a refluxing solution of 3-oxotetrahydrofuran (1g: 0.012M) and ethyl 1-ethoxy-1-hydroxyacetate (1.6g: 0.014M) in dry benzene (20ml) and the mixture refluxed for three hours. The cooled mixture was washed with dilute hydrochloric acid, brine and dried. Evaporation gave a brown oil (650mg) from which ketonic derivatives could not be obtained. Attempted distillation resulted in almost complete decomposition; only a minute amount of an oil b.p. 104°/0.1m.m. was obtained. ν_{max} (thin film) 3400, 1750, 1730, 1650 cm^{-1}.

(b) The above experiment was repeated using sodium ethoxide in ethanol as the base. The resultant oil was similar and could not be purified.

(c) 3-Oxotetrahydrofuran (1:1g: 0.013M) and 1-ethoxy-1-hydroxyacetate (1.3g: 0.01M) were heated in a sealed tube at 200° for 2 hours[157]. The product, a dark brown gum, was completely intractable.

(d) A mixture of 3-oxotetrahydrofuran (1:1g: 0.013M) and 1-ethoxy-1-hydroxyacetate (2.6g: 0.02M) gave a similar result when heated at 200° for 2 hours.

Attempted condensation of 3-oxotetrahydrofuran with glyoxylic acid[158]

To a cooled solution of sodium periodate (4.28g) in concentrated sulphuric acid (0.4ml) and water (10ml),

tartaric acid (3g: 0.02M) in water (6ml) was added. After 5 minutes the cooling bath was removed and the mixture shaken at room temperature for 25 minutes.

3-oxotetrahydrofuran (1.72g: 0.02M) sodium hydroxide (3g) and 30% aqueous ethanol (70ml) were added in order to the above solution. After 14 hours the solution was heated to 60° for 10 minutes. Constant ether extraction followed by washing of the extract with thiosulphate gave on evaporation of the ether, a minute amount of an oil (10mg).

Attempted preparation of the morpholine enamine of 3-oxotetrahydrofuran.

3-Oxotetrahydrofuran (1.4g: 0.012M) and morpholine (1.4g: 0.012M) were refluxed in benzene (10ml) containing toluene-p-sulphonic acid (0.05g) with constant removal of water, for six hours. The cooled solution was washed with sodium hydrogen carbonate solution, dried and evaporated. Fractionation of the residual oil (2.2g) gave two main fractions (i) and (ii) and some residue.

(i) b.p. 75°/0.1m.m.
ν_{max} 1710, 1650, 1610, complex 850-1100 cm^{-1}.

(ii) b.p. 120°/0.1m.m.
ν_{max} (thin film) 1750, 1700, 1620, 1600 complex 850-1100 cm^{-1}.

Attempted condensation of dimethyl malate and methyl acrylate.

(a) Dimethyl malate (5g: 0.031M) was added to atomised sodium (0.71g: 0.031M) in dry benzene (50ml) and heated until most of the sodium had dissolved. Methyl acrylate (2.7g: 0.031M) was added to the brown mixture which was then stirred overnight at room temperature. Methanol (5ml) was

added and then water (10ml). Ether extraction removed the neutral products. Acidifcation of the aqueous layer was followed by ether extraction.

The neutral fraction gave unchanged methyl acrylate (2g) which was identified by b.p. (85^{o}) and infrared spectrum.

The acidic fraction gave two components:-

(i) benzene-insoluble solid (3g) which sublimed at 100^{o}/0.1m.m. m.p.140-146^{o}.

(Found: C, 46.18; H, 4.57; $C_4H_4O_4$ requires C,41.29; H,3.45% $C_4H_2O_3$ requires C, 47.96; H, 1.41%)

(ii) A benzene soluble gum which was intractable. This gum gave a positive ferric chloride test (wine-coloured).

(b) A similar result was obtained when the reaction was carried out in tetrahydrofuran.

(c) Methyl acrylate (2.5g: 0.029M) was added at 0^{o} to a stirred solution of sodium (0.7g: 0.029M) in dimethyl malate (25g: 0.15M). After stirring at room temperature for 3 days, water (20ml) was added; a solid precipitated and was filtered off. The organic material was taken up in ether, washed with dilute hydrochloric acid and the extract dried. Removal of solvent gave an oil (17g).

(i) The precipitated solid crystallised from petroleum ether, m.p. 103^{o} (Found: C 49.94, H 5.26; $C_6H_8O_4$ requires C 50.00, H 5.60%) (lit[166] m.p. dimethyl fumarate: 102^{o})

ν_{max} (Nujol mull) 1710, 1690, 980, 870, 780 cm^{-1}.

(ii) The oil consisted mainly of methyl malate with a trace of methyl acrylate.

(d) When the condensation was carried out using only catalytic amounts of sodium, no reaction took place and the dimethyl malate and methyl acrylate were recovered unchanged.

(e) Similar negative results were obtained when dimethyl malate was treated with acrylonitrile under the conditions described in sections (i) and (iv)

Attempted condensation of dimethyl fumarate with ethylene cyanohydrin

(a) Ethylene cyanohydrin (2.3g: 0.033M) was added to atomic sodium (0.68g: 0.03M) in dry tetrahydrofuran (50ml) and the mixture stirred under reflux until the sodium had dissolved. Diethyl fumarate (5.1g: 0.03M) was added and the mixture was stirred overnight, and then concentrated. Ethanol (5ml) was added and then water (20ml). Neutral product was removed with ether and then the aqueous layer was acidified and extracted with ether.

The neutral product (2.0g), b.p. $100^{o}/14$m.m., was shown by comparative infrared spectroscopy to be diethyl fumarate. (lit[166] b.p. $99^{o}/14$m.m.).

The acidic product (2.1g) crystallised from water m.p. $286-290^{o}$ and admixture with fumaric acid gave no melting point depression.

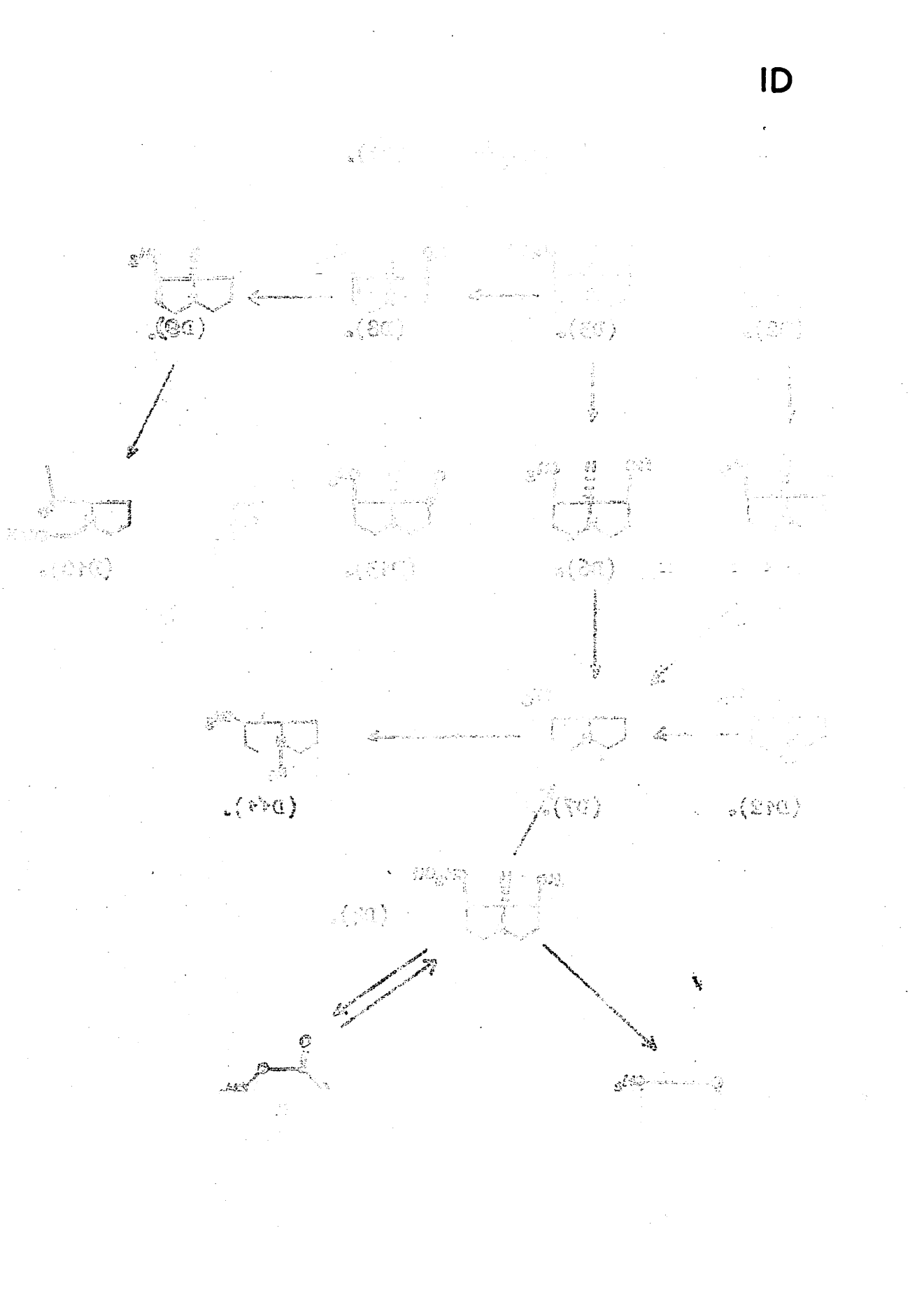
(b) When an attempt was made to carry out the condensation using a large excess of ethylene cyanohydin as solvent, the dissolution of sodium in this reagent resulted in an explosion which was probably due to polymerisation of the cyanohydrin.

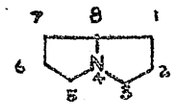
(c) Using no solvent and only a catalytic amount of sodium there was no reaction between diethyl fumarate and ethylene cyanohydrin, under similar conditions to those reported in (i).

(d) Ethylene cyanohydrin (10g: 0.14M) diethyl fumarate (2.4g: 0.014M) and triethylamine (1.4g: 0.014M) were heated

at 110° for five hours. Distillation of the product gave a mixture of ethylene cyanohydrin and diethyl fumarate. b.p. 100-120°/14m.m.

(e) When the above series of reactions was repeated using diethyl maleate instead of diethyl fumarate similar negative results were obtained.





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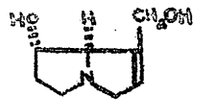

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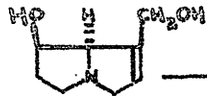
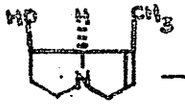


(D3)。



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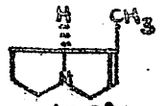
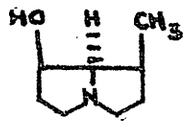


(D9)。

(D5)。



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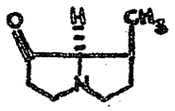
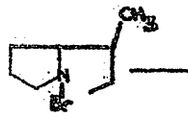


(D13)。

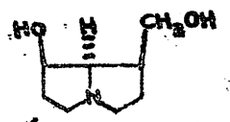
(D10)。



(D12)。

(D7)。

(D11)。



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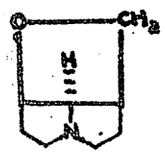

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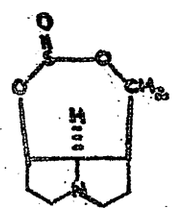


(D15)。

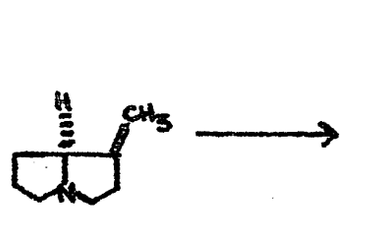
(D17).

(D16).

(D17).

(D18).

(D13).



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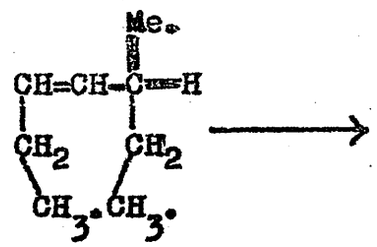
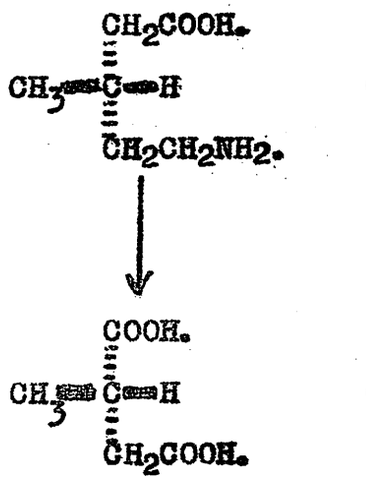


(D16).

(D17).



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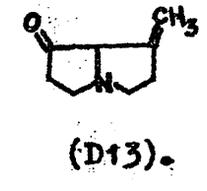
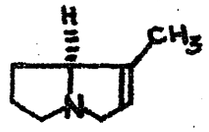


(D13).

(D19).



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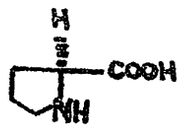

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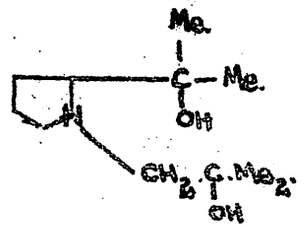
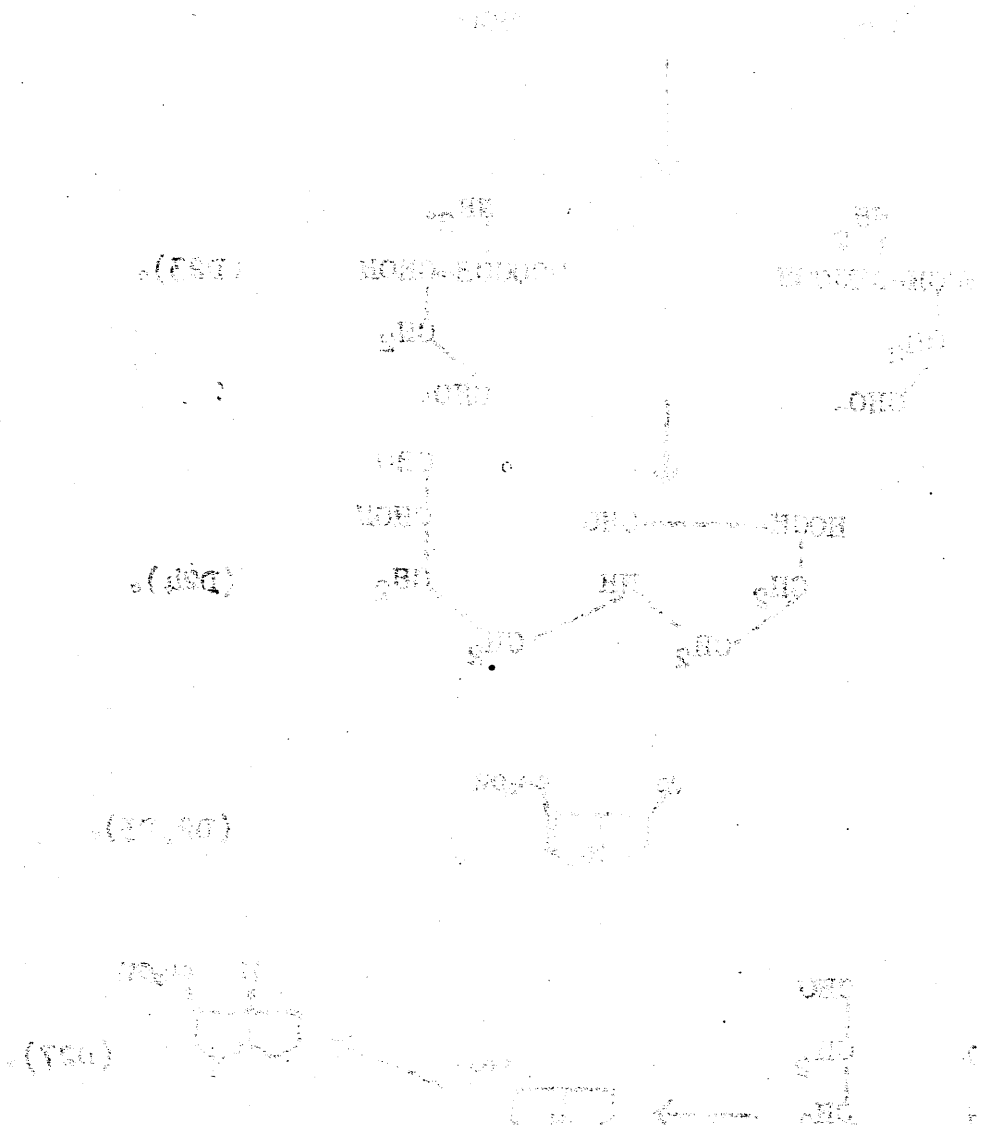
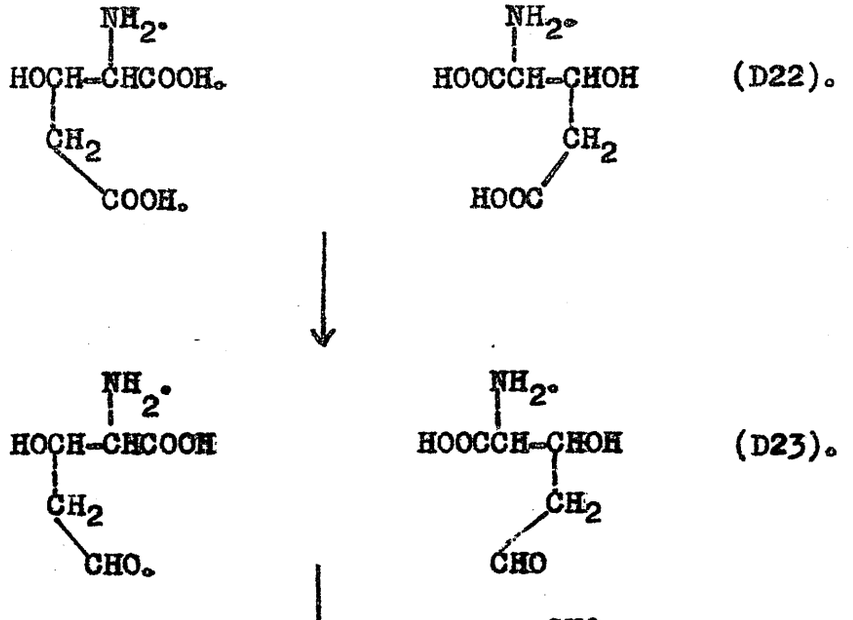


(D20).

3D



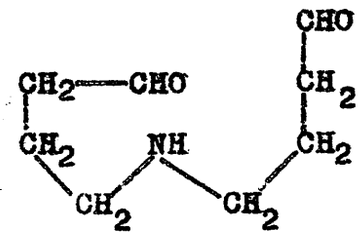


(D22)。

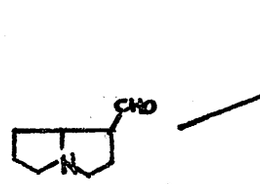
(D23)。

(D24)。

(D2,D3)。



(D25)。



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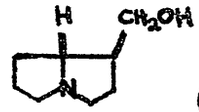

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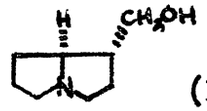

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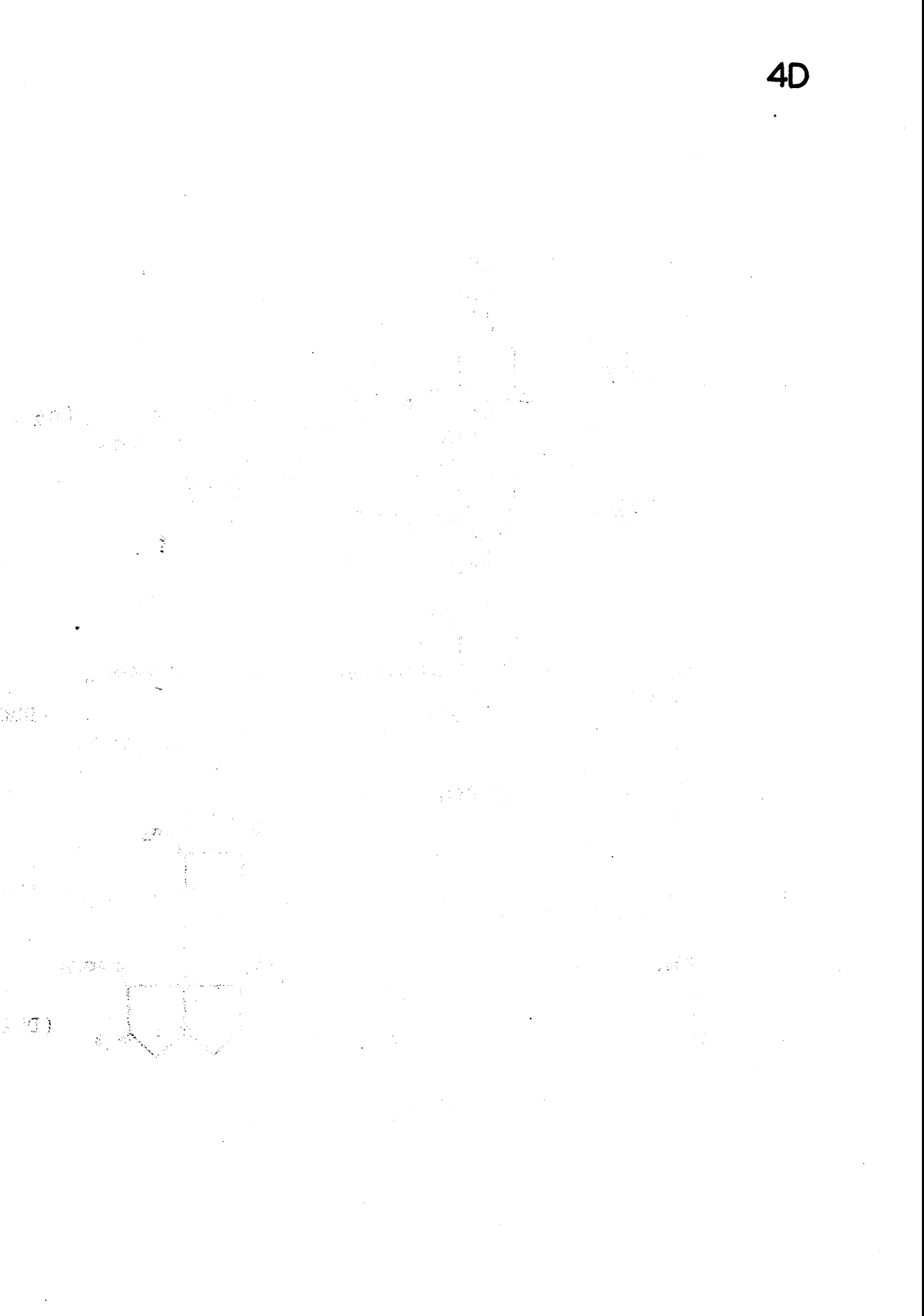
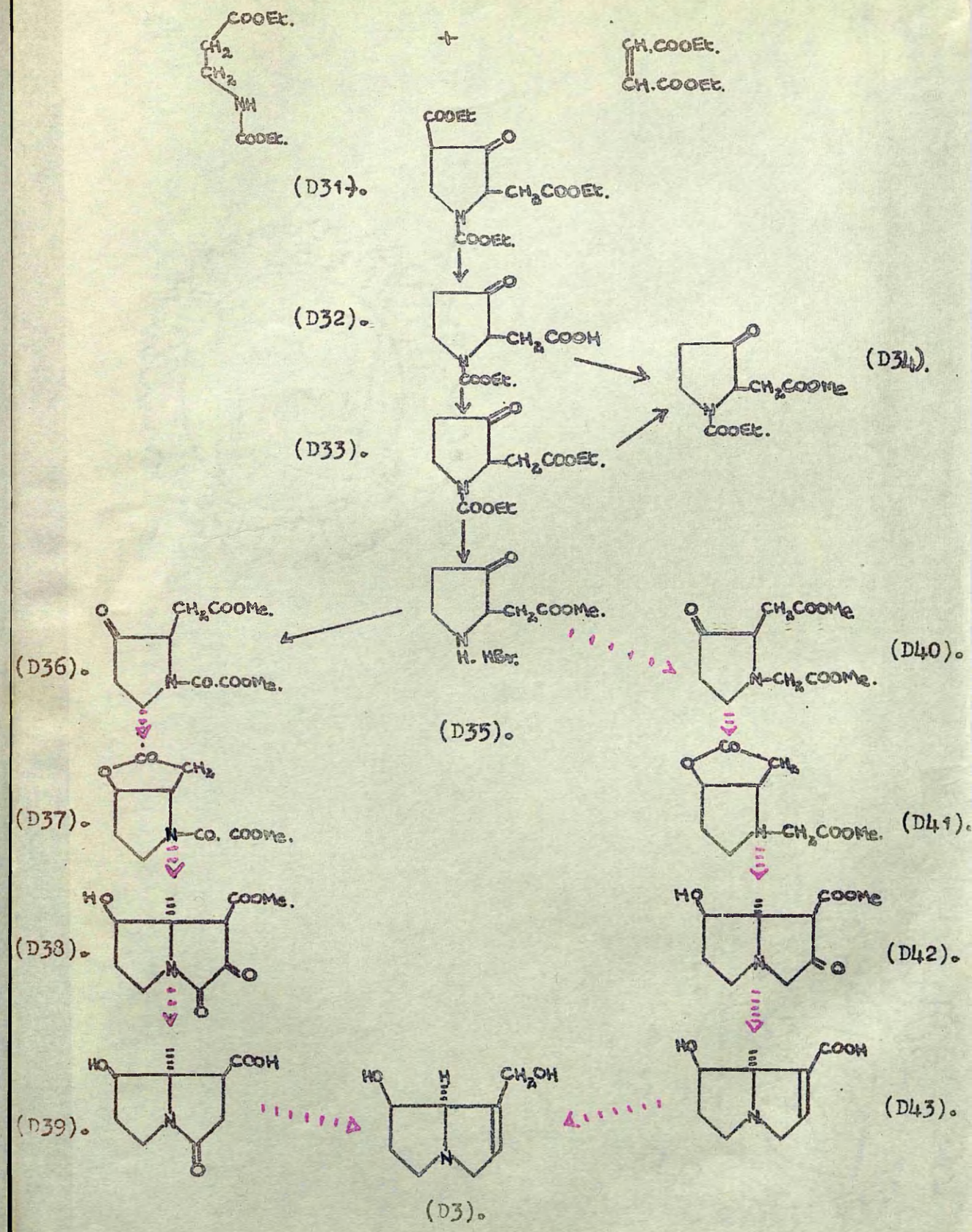
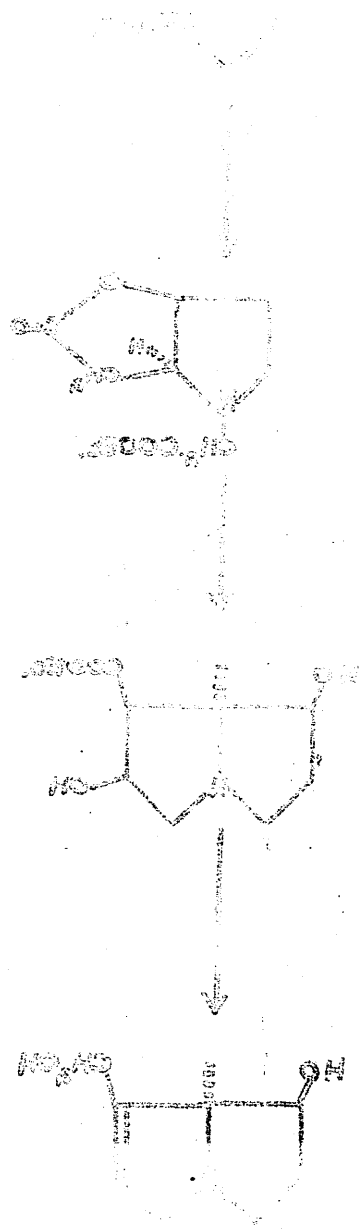
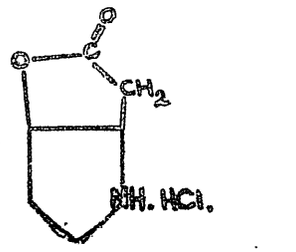
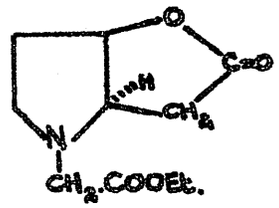



COOEt.
CH2
CH2
NH
COOEt.
+
CH.COOEt.
CH.COOEt.
(D31).
COOEt
O
CH2COOEt.
N
COOEt.
(D32).
CH2COOH
(D34).
CH2COOMe
(D33).
CH2COOEt.
(D35).
CH2COOMe.
H. HBr.
(D36).
N—CO.COOMe.
(D40).
N—CH2COOMe.
(D37).
CO
CH2
N—CO. COOMe.
(D41).
(D38).
HO
COOMe.
(D42).
(D39).
COOH
(D43).
HO
H
CH2OH
N
(D3).





(D44).



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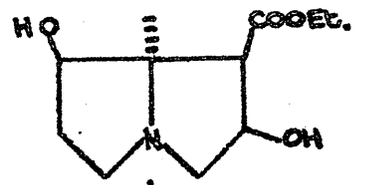

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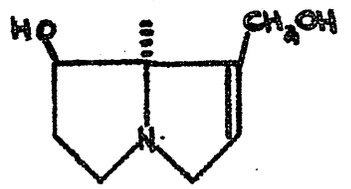

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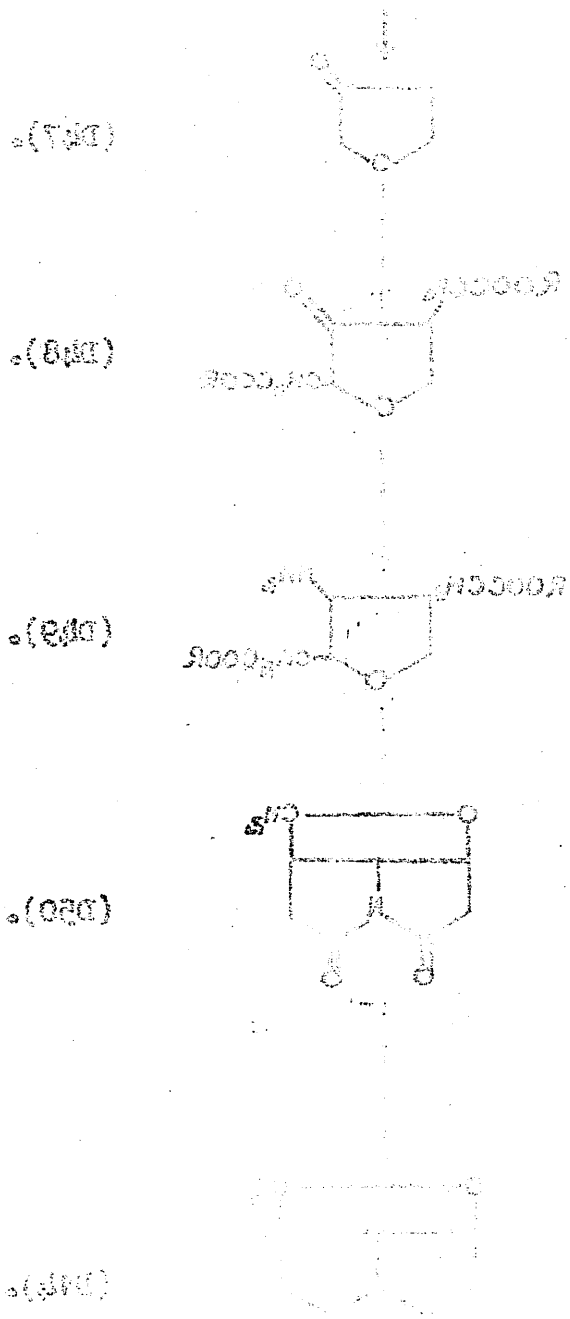
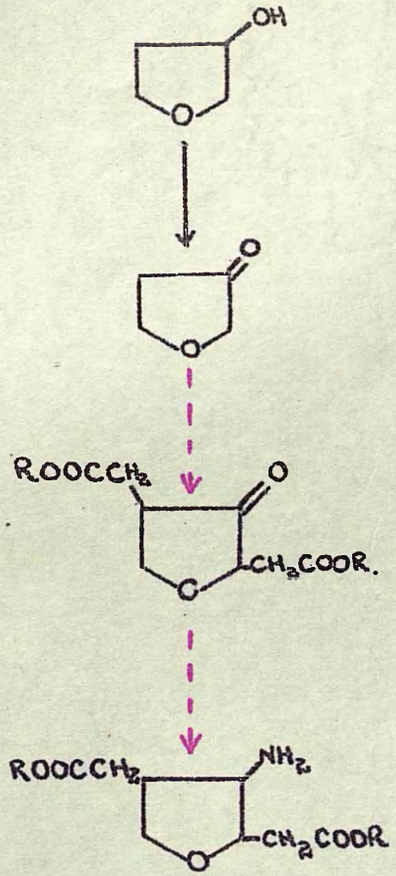
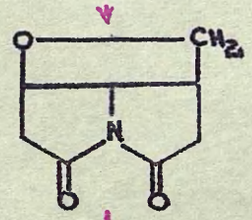




(D47).

(D48).

(D49).



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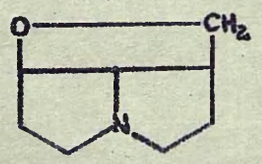

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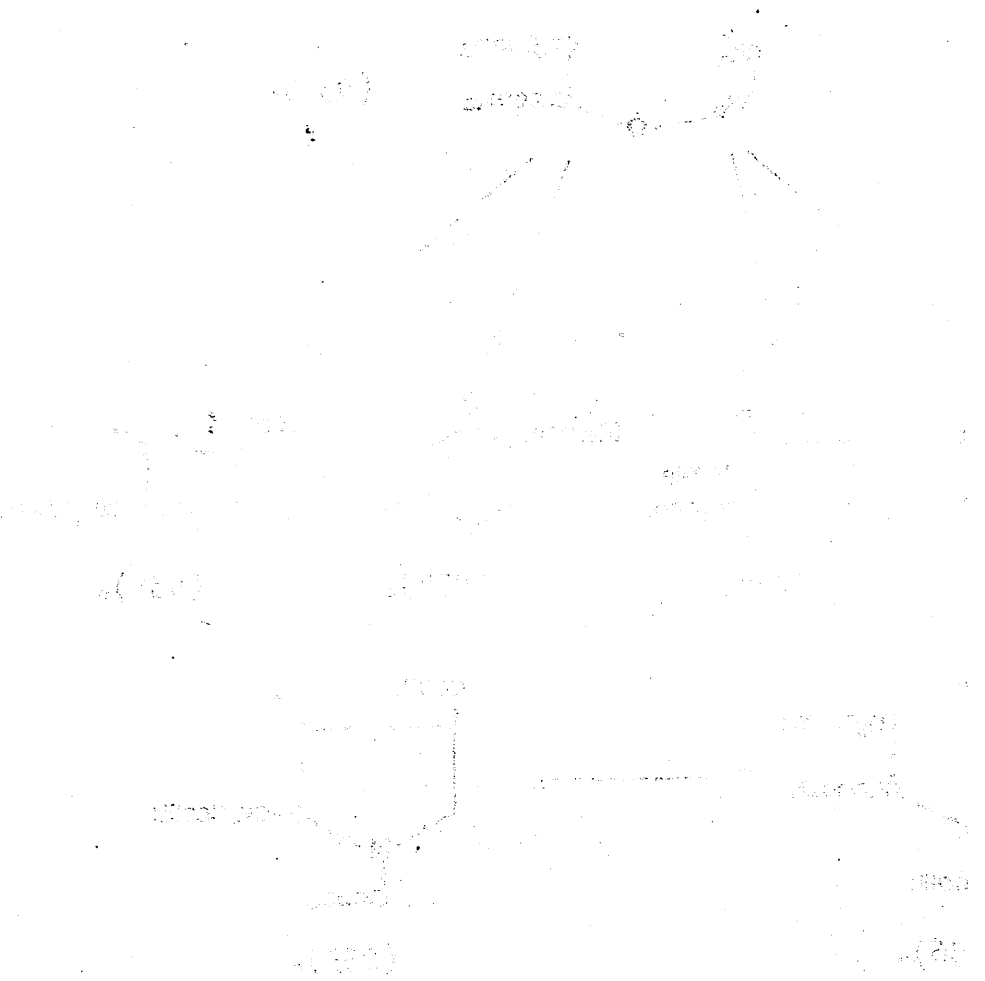

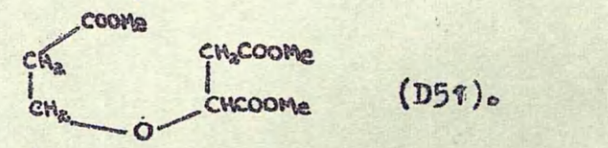

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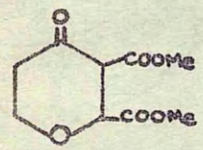

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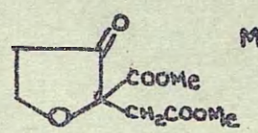
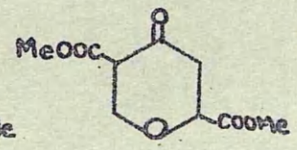


(D53).



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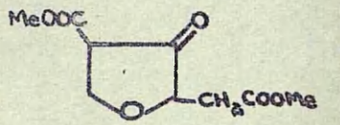

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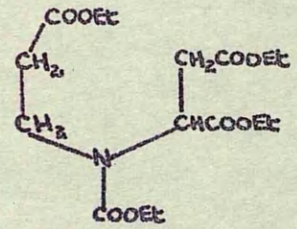
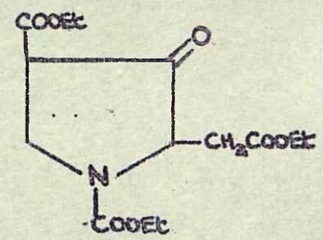
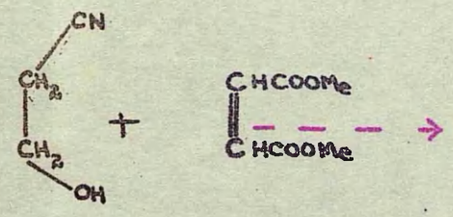


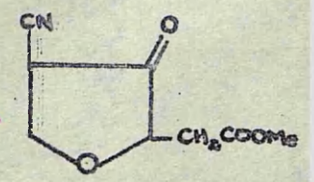
(D56).



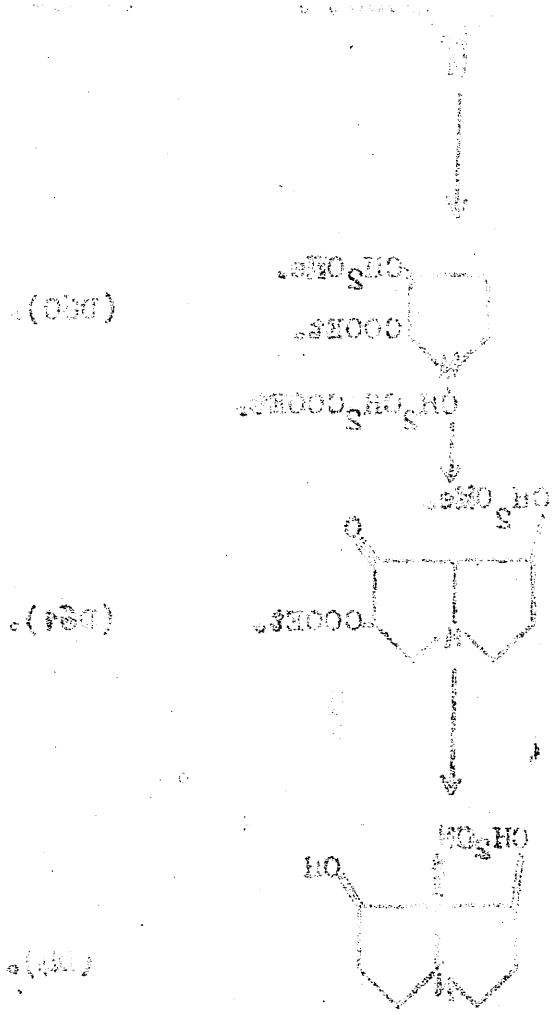
(D33).

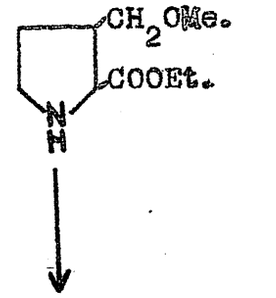


(D57).

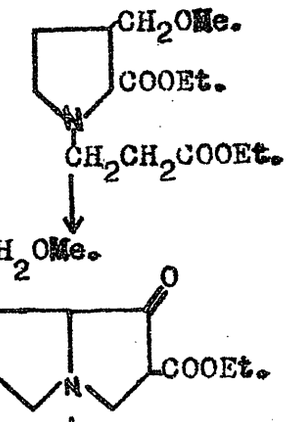


(D58).



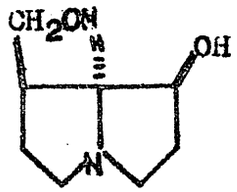


(D59).



(D60).

(D61).



(D4).

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