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SYNTHETIC INVESTIGATION ON THE BUILDING OF RING A OF STEROIDS

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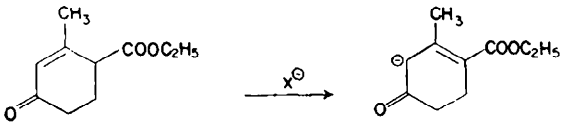
Abstract—Methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va) has been prepared by the reduction of 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (III) with lithium and ammonia followed by hydrolysis of the enol ether, esterification and migration of the double bond. Alkylation of Va has led to the substitution at the expected 8-position. Methyl 4-keto-7-methoxy-1,2,3,4-tetrahydronaphthoate (X), an intermediate in the preparation of III, has been converted into methyl 3-methyl-3-cyano-4-keto-7-methoxy-1,2,3,4-tetrahydronaphthoate (XIII).

FOR the attachment of ring A to the tricyclic intermediates in the B, C, D route for the synthesis of steroids, it has often been found expedient to protect the more reactive methylene group adjacent to the carbonyl function by a methylanilinomethylene group.[1] Model experiments using a suitably substituted bicyclic ring system, for the development of a new method dispensing with the necessity of a protecting group, have been described in the present communication.

It has been established that 3-methyl-4-ethoxycarbonylcyclohex-2-ene-1-one (I, Hagemann ester) is exclusively alkylated at the 2-position[2] in the absence of a protecting group on the keto methylene. The essential feature of this compound is the presence of a vinylogous β-keto ester function which facilitates the formation of the carbanion (II) in the presence of a base. It appeared to us that a decalin derivative, such as Va, carrying the Hagemann ester system distributed in its two rings would be



I II

ideal for the purpose of this study.

7-Methoxy-1,2,3,4-tetrahydronaphthoic acid (III), the starting material for preparation of the bicyclic unsaturated keto ester (Va), was first synthesized by Fieser and Holmes[3] and later by Hey and Nagdy.[4] This has now been prepared in an improved yield by modification (*vide* Experimental) of the method adopted by the latter workers. The acid (III) was reduced by Birch's method[5] as modified by Wilds

[1] [a] A. R. Pinder and R. Robinson, *J. Chem. Soc.* 1224 (1952); [b] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **73**, 2403 (1951); **74**, 4223 (1952); [c] L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *Ibid.* **76**, 5014 (1954); [d] L. B. Barkley, W. S. Knowles, H. Raffelson and Q. E. Thompson, *Ibid.* **78**, 4111 (1956); [e] D. K. Banerjee, S. Chatterjee and S. P. Bhattacharya, *Ibid.* **77**, 408 (1955).

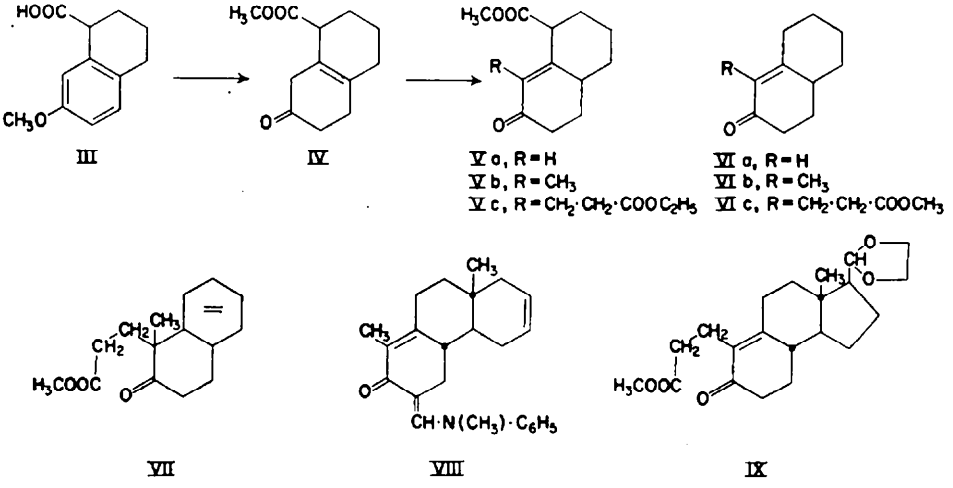
[2] L. I. Smith and G. F. Ronalt, *J. Amer. Chem. Soc.* **65**, 631 (1943); G. Stork and A. Burgstahler, *Ibid.* **73**, 3544 (1951); H. H. Inhoffen and E. Prinz, *Chem. Ber.* **87**, 684 (1954); E. Adlerova, L. Norak and M. Protiva, *Coll. Czech. Chem. Comm.* **23**, 681 (1958).

[3] L. F. Fieser and H. L. Holmes, *J. Amer. Chem. Soc.* **58**, 2319 (1936).

[4] D. H. Hey and K. A. Nagdy, *J. Chem. Soc.* 1894 (1953).

[5] A. J. Birch, *Quart. Rev.* **4**, 69 (1950).

and Nelson.[6] No attempt was made to isolate the intermediate dihydro derivative which was hydrolysed with 5 per cent sulphuric acid in chloroform solution, and the resulting product was esterified with diazomethane. The colourless liquid, thus obtained, did not show any ultra-violet absorption maximum characteristic of the Hagemann ester system[7] and was assigned the structure IV. This was justified by its conversion to the α,β-unsaturated keto ester (Va) by treatment with methanolic hydrogen chloride. The compound (Va) showed ultra-violet absorption maximum at 236 mμ (log ϵ 4·07) with a small hump at 280 mμ, the latter probably indicating the presence of a trace of methyl 7-methoxy-1,2,3,4-tetrahydronaphthoate. Treatment of IV with methanol containing a few drops of hydrochloric acid according to Wild's procedure[8] furnished Δ^{1-9}-octalone-2 (VIa) as the major product. Two different cosolvents, 1,2-dimethoxyethane and dioxane, were used for this reduction, the former giving a better yield.

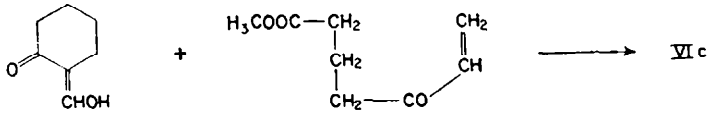


Methylation of Va was carried out with sodium hydride and methyl iodide in benzene, and the product showed the expected bathochromic shift in the ultra-violet absorption maximum. The final proof of the structure of methyl 7-keto-8-methyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vb) was obtained by its conversion to 1-methyl-Δ^{1-9}-octalone-2 (VIb) by treatment with aqueous alkali.

In view of Barkley *et al.*[1d] work showing that, whereas Woodward's[1b] addition of acrylonitrile to the tricyclic unsaturated ketone (VIII) yielded predominantly a product with an unfavourable stereochemistry, methylation of the tricyclic unsaturated keto ester (IX) furnished stereoselectively the product with the desired configuration, alkylation of Va with ethyl β-chloropropionate was also studied. It was found that by using potassium t-butoxide in t-butanol in place of sodium hydride in benzene, methyl 7-keto-8-β-ethoxycarbonylethyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vc) could be obtained in a better yield. The structure (Vc) assigned to the aforementioned condensation product was proved by degrading it to 1-β-methoxycarbonylethyl-Δ^{1-9}-octalone-2 (VIc) by treatment with aqueous methanolic potassium hydroxide

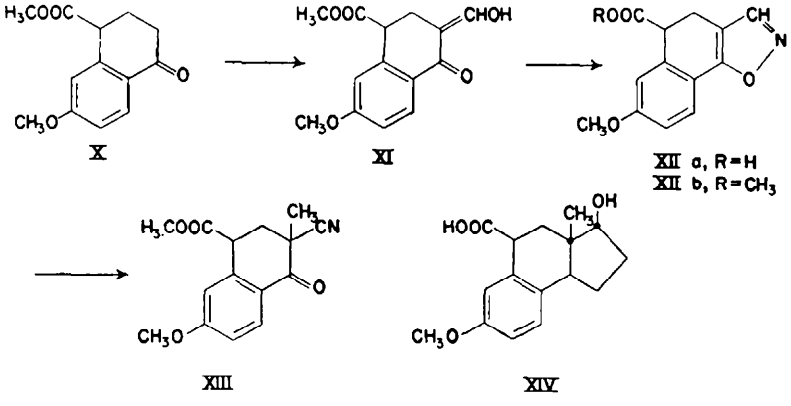
[6] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5360 (1953).
[7] R. M. Acheson and R. Robinson, *J. Chem. Soc.* 1130 (1952).
[8] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5366 (1953).

followed by esterification with diazomethane and by direct comparison of the semicarbazone of VIc with that of an authentic specimen prepared by the condensation of 2-hydroxymethylenecyclohexanone with methyl 5-keto-6-heptenoate[1d] in the presence of potassium t-butoxide in t-butanol followed by successive treatment with alkali and diazomethane. The yield was poorer when the above condensation was carried out with cyclohexanone.



Methylation of VIc following the procedure of Barkley *et al.*[1d] furnished a mixture of a 1-methyl-1-β-methoxycarbonylethyloctalone-2 (VII) and the starting material which could be separated on an acid washed alumina column. The structure of the former was deduced from the absence of the characteristic ultra-violet absorption maximum of an α,β-unsaturated ketone.

The methyl ester (X) of 4-keto-7-methoxy-1,2,3,4-tetrahydronaphthoic acid, an intermediate in the preparation of 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (III) by the method of Hey and Nagdy,[4] was converted into methyl 3-methyl-3-cyano-4-keto-7-methoxynaphthoate (XIII) via the hydroxymethylene derivative (XI) and the isoxazoles (XIIa and XIIb) following the procedure of Johnson *et al.*[9] Our future programme consists in the stereospecific conversion of the keto cyano ester (XIII) by the method of Banerjee *et al.*[10] into the benzohydrindane derivative (XIV), which in the context of present investigation may be regarded as an important intermediate for the synthesis of testosterone.



EXPERIMENTAL*

7-Methoxy-1,2,3,4-tetrahydronaphthoic acid (III)

m-*Methoxybenzyl alcohol.* Previously prepared from *m*-methoxybenzaldehyde by electrolytic reduction by Rapson and Robinson[11] in 56% yield and by catalytic hydrogenation by Woodward[12]

* All melting and boiling points are uncorrected, and all ultra-violet measurements were taken in 95% ethanol and with Beckmann Quartz Ultraviolet Spectrophotometer, Model DU.

[9] W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Amer. Chem. Soc.* **69**, 2942 (1947).
[10] D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *J. Amer. Chem. Soc.* **78**, 3769 (1956).
[11] W. S. Rapson and R. Robinson, *J. Chem. Soc.* 1537 (1935).
[12] R. B. Woodward, *J. Amer. Chem. Soc.* **62**, 1481 (1940).

in quantitative yield. This has now been prepared by crossed Cannizzaro reaction[13] in 92·5% yield. To a stirred solution of 37·05 g of *m*-methoxybenzaldehyde and 31 cc 40% formalin in 54·5 cc of methanol at 65° was added a small portion of a solution of 45·7 g KOH in 32·6 cc water. The temp was initially maintained by external heating until the reaction started which was indicated by the rise in temperature. The exothermic reaction was then maintained at 70° by controlling the rate of addition of the alkali. After stirring for 40 min the solution was refluxed for 25 min. After cooling and dilution with water the product was extracted with ether. The extract was washed with water, the ether removed, and the residue fractionated to yield 34·75 g *m*-methoxybenzyl alcohol, b.p. 98–105° (0·8 mm); recorded b.p. 125° (12 mm)[11] and 150° (25 mm).[13]

m-*Methoxybenzyl chloride.* Prepared from *m*-methoxybenzyl alcohol by the method of Cornforth and Robinson[14] in 94% yield. When phosphorus trichloride was used the yield was lower (69%), and no action was observed with dry hydrogen chloride in benzene.

m-*Methoxyphenylacetonitrile.* Prepared from *m*-methoxybenzyl chloride by the method of Rapson and Robinson[11] except that ethanol was replaced by acetone as solvent, and a higher yield (93·5%) was obtained. Hey and Nagdy[4] prepared this compound from *m*-methoxybenzaldehyde by the hippuric acid method in 23% yield. Overall yield in our case from the same starting material was 71%.

Ethyl m-*methoxyphenylcyanoacetate.* Previously prepared by the condensation of *m*-methoxyphenylacetonitrile with diethyl carbonate in the presence of sodium dust in ether by Hey and Nagdy[4] following the procedure of Niederl and Roth.[15] Considerable improvement in the yield of this product has now been achieved by introducing the following modification. To a cooled and stirred mixture of 3·9 g sodium hydride, 50 cc benzene and 19·2 cc diethyl carbonate under 1 atm nitrogen, was added a solution of 23 g *m*-methoxyphenylacetonitrile in 15 cc benzene at such a rate that the reaction was never too vigorous. The reaction mixture was allowed to stand overnight, and the solid cake formed decomposed with iced HCl under nitrogen with cooling. The organic layer was separated and washed with water. After removal of the solvent the residue was fractionated *in vacuo* to yield 6·4 g unchanged *m*-methoxyphenylacetonitrile and 21·5 g (87% on the basis of recovered material) ethyl *m*-methoxyphenylcyanoacetate, b.p. 156–157° (1·5 mm); recorded[4] 120–125° (5×10^{-3} mm).

Diethyl α-(m-*methoxyphenyl*)-α-*cyanoglutarate*

To a solution of sodium ethoxide, prepared from 0·05 g sodium in 10 cc ethanol, was added 21·3 g ethyl *m*-methoxyphenylcyanoacetate. To this mixture was then added with swirling 11 cc methyl acrylate at such a rate that the temp was maintained at 50–55°. After standing for 2 hr a few drops of acetic acid were added and the product worked up after dilution with water in the usual manner to yield 1·5 g unchanged material and 26·8 g (84%) diethyl α-(*m*-methoxyphenyl)-α-cyanoglutarate, b.p. 185–188° (1·7 mm). Floyd and Miller[16] also observed similar ester exchange during the addition of methyl acrylate to alkylmalonic esters. (Found: C, 63·9; H, 6·9. Calc. for $C_{17}H_{21}NO_6$: C, 63·9; H, 6·6%).

α-(m-*Methoxyphenyl*)*glutaric acid.* Prepared by refluxing for 24 hr a mixture of 26·6 g diethyl α-(*m*-methoxyphenyl)-α-cyanoglutarate, 100 cc conc HCl and 100 cc water. The ethereal extract on evaporation furnished 18·44 g (90%) α-(*m*-methoxyphenyl)glutaric acid, m.p. 120–121°. On crystallization from dil HCl the product melted at 120·5–121°. Hey and Nagdy[4] prepared the same compound, m.p. 121–122°, by the hydrolysis of ethyl α,γ-dicyano-α-*m*-methoxyphenylbutyrate in 72% yield. (Found: C, 60·5; H, 6·0. Calc. for $C_{13}H_{14}O_5$: C, 60·5; H, 5·9%).

7-*Methoxy*-4-*keto*-1,2,3,4-*tetrahydronaphthoic acid.* Previously prepared by Hey and Nagdy[4] from the aforementioned glutaric acid by cyclodehydration with hydrogen fluoride in 86% yield. This has now been prepared by a different method but in a lower yield. To a stirred cold solution of 10 g α-(*m*-methoxyphenyl)glutaric acid in 30 cc benzene was added 20 g finely powdered phosphorous pentachloride. After cooling in an ice-bath, the acid chloride was treated with a chilled solution of 11 cc stannic chloride in 75 cc benzene. After standing for 15 min the product was poured into ice. The organic layer was separated and washed thoroughly with water. After removal of the

[13] D. Davidson and M. T. Bogert, *J. Amer. Chem. Soc.* **57**, 905 (1935).
[14] J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 686 (1942).
[15] J. Niederl, R. J. Roth and A. A. Plentl, *J. Amer. Chem. Soc.* **59**, 1901 (1937); J. Niederl and R. J. Roth, *Ibid.* **60**, 2140 (1938).
[16] D. E. Floyd and S. E. Miller, *J. Org. Chem.* **16**, 883 (1951).

solvent the solid residue was crystallized from dilute acetic acid to furnish 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoic acid, m.p. 151–153°; recorded[4] 155°, in 76% yield.

7-Methoxy-1,2,3,4-tetrahydronaphthoic acid (III). This was obtained by Hey and Nagdy[4] by reduction of the aforementioned keto acid by the Clemmensen method in 53% yield. An improved yield was obtained when the reduction was carried out by Huang-Minlon's[17] method. A mixture of 1·95 g of the above keto acid, 2·55 g KOH in 25 ml diethylene glycol and 2·5 ml 50% hydrazine hydrate was heated for 2 hr at 135° (inner temp). The temp of the mixture was raised to 195–200° by allowing the vapours to escape and maintained at that point for 2 hr. The cooled solution was diluted and treated with 4·5 ml dimethyl sulphate at 70–75° with shaking. Potassium hydroxide (5 g) was then added and the mixture heated for 1 hr on the steam bath. The cooled solution was filtered into an excess HCl and 1·7 g (93%) of the crude acid, m.p. 130–132°, obtained. After purification by short-path distillation and crystallization from ether–pet ether (40–60°) the product melted at 137–138°; recorded[4] 137–138°.

Methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va)*

To a solution of 5 g 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (III) in 40 ml dry 1,2-dimethoxyethane was added 1·5 l. anhydrous liquid ammonia. To the above stirred mixture was then added within 5 min, 5 g metallic lithium, cut into small pieces. After stirring for 10 min, 150 ml ethanol was added fairly rapidly when the blue colour was discharged. The ammonia was allowed to evaporate and the mixture neutralized with cooling and stirring by dropwise addition of conc H_2SO_4. Chloroform (40 ml) and then enough conc H_2SO_4 to make the solution 5% by volume was slowly added, and the mixture stirred at room temp for 18 hr. The chloroform layer was separated and the aqueous layer thoroughly extracted with chloroform. The combined chloroform layer after washing with water was dried. The brown syrupy residue, obtained after removal of the solvent, was treated with an ethereal solution of diazomethane, prepared from 5 g nitrosomethylurea. After 5 min the excess diazomethane was destroyed by addition of glacial acetic acid. The ethereal solution was successively washed with water, cold KOH solution and water. Removal of the solvent and distillation of the residue *in vacuo* furnished 4·4 g of an oil, b.p. 90–150° (2 mm). On refractionation a sample of (IV) for analysis was collected at 140° (2 mm); n_D^{23} 1·5072; d_4^{22} 1·130. (Found: C, 69·4; H, 8·3; mol refractivity, 54·8. Calc. for $C_{13}H_{16}O_3$: C, 69·2; H, 7·7%; mol refractivity, 54·4).

The β,γ-unsaturated keto ester (IV, 21·8 g) was refluxed for 4 hr with methanolic hydrogen chloride (11 g hydrogen chloride in 600 ml methanol). The methanol and the hydrogen chloride were removed under suction, and the residue distilled to give 12·2 g methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va), b.p. 145–150° (1·5–2 mm); n_D^{23} 1·5140. (Found: C, 69·7; H, 7·7. Calc. for $C_{13}H_{18}O_3$: C, 69·2; H, 7·7%).

The *semicarbazone* of Va crystallized from alcohol, m.p. 199–200° (dec); λ_{max} 269 mμ, log ε 4·48. (Found: N, 15·7. Calc. for $C_{14}H_{19}N_3O_3$: N, 15·9%).

A reduction of 2 g of the acid (III) in 25 cc dimethoxyethane and 500 cc anhydrous ammonia with 2·1 g lithium metal gave 1·9 g (IV), which was refluxed with 25 cc dry methanol and 0·6 cc conc HCl for 4 hr. The removal of methanol under diminished pressure and evaporative distillation of the residue gave 1·18 g $\Delta^{1\text{-}9}$-octalone-2 (VIa); b.p. 120–130° (1·5 mm); λ_{max} 238 mμ, log ε 3·95. The semicarbazone melted at 205° (dec); recorded 214,[16] 215,[18] 208.[19] (Found: N, 20·00. Calc. for $C_{11}H_{17}N_3O$: N, 20·3%).

Methyl 7-keto-8-methyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vb)

To a stirred mixture of 0·58 g sodium hydride and 100 ml benzene was added a solution of 5 g methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va) in 50 ml benzene under 1 atm nitrogen. After stirring for 24 hr, 35 g methyl iodide was added and the stirring continued for a further 24 hr. The mixture was finally refluxed for 7 hr. To the cooled reaction mixture ice-cold water was added under nitrogen and the mixture extracted with ether–benzene. The extract was washed with water, the solvent removed and the residue distilled to furnish 3·5 g Vb, b.p. 128–130° (0·9 mm); n_D^{25}

* Wild and Nelson's procedure (*loc. cit.*) was made available to us through the courtesies of Dr. W. S. Johnson and Dr. A. L. Wilds before its publication.

[17] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[18] A. J. Birch, *J. Chem. Soc.* 434 (1944).
[19] E. C. Du Feu, F. J. McQuillin and Robert Robinson, *J. Chem. Soc.* 53 (1937).

1·5098; λ_{max} 246–247 mμ, log ε 3·73. (Found: C, 70·8; H, 8·1. Calc. for $C_{13}H_{18}O_3$: C, 70·3; H, 8·1%).

The *semicarbazone* crystallized from alcohol, m.p. 213–215° (dec); λ_{max} 271 mμ, log ε 4·45. (Found: N, 15·4. Calc. for $C_{14}H_{21}N_3O_3$: N, 15·1%).

Conversion of methyl 7-keto-8-methyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vb) *to 1-methyl-Δ^{1-9}-octalone-2* (VIb)

To a solution of 0·8 g of the keto ester (Vb) in 8·5 ml ethanol was added a solution of 0·9 g KOH in 1·5 ml water, and the mixture was refluxed for 7 hr under nitrogen. The cooled solution was diluted with water and extracted with benzene. The extract was washed with dilute alkali and then with water. After removal of the solvent the residue on distillation furnished 0·25 g of the methyl-octalone (VIb), b.p. 95–100° (2·5 mm); λ_{max} 248 mμ, log ε 4·1; recorded[1e] λ_{max} 249, log ε 4·1. The *semicarbazone* melted at 210–212° (dec); recorded[1e] 212° (dec). Admixture with an authentic specimen did not depress the melting point.

Methyl 7-keto-8-β-ethoxycarbonylethyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vc)

To a cold solution of potassium t-butoxide in t-butanol, from 1·2 g of potassium and 45 ml t-butanol, was added a solution of 6 g of the keto ester (Va) in 12·5 ml t-butanol. After standing at the room temp for 3 hr, 4·65 g ethyl β-chloropropionate was added with cooling in ice. The mixture was refluxed for 18 hr. To the cooled reaction mixture was added 2 ml glacial acetic acid, and then most of the t-butanol was removed under suction. After addition of water the product was extracted with ether. The ether extract was washed with 2% cold KOH solution and water. After removal of the ether and fractionation of the residue 5·6 g of the keto diester (Vc), b.p. 130–145° ($1·4 \times 10^{-2}$ mm); λ_{max} 245 mμ, log ε 4·1, was obtained. (Found: C, 66·3; H, 7·8. Calc. for $C_{17}H_{24}O_5$: C, 66·2; H, 7·8%). The *semicarbazone* crystallized from ethanol, m.p. 157–159°; λ_{max} 272 mμ, log ε 4·5. (Found: N, 11·9. Calc. for $C_{18}H_{27}N_3O_5$: N, 11·5%).

Conversion of methyl 7-keto-8-β-ethoxycarbonylethyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vc) *to 1-β-methoxycarbonylethyl-Δ^{1-9}-octalone-2* (VIc)

A mixture of 13·3 g of the unsaturated keto diester (Vc) and a solution of 6 g KOH in 10 ml water and 60 ml methanol was refluxed for 3 hr. The acidic material isolated in the usual way was esterified with diazomethane. On fractionation 7·6 g of the unsaturated keto ester (VIc), b.p. 138–140° (0·8 mm); λ_{max} 247–249 mμ, log ε 4·2, was obtained. (Found: C, 71·4; H, 8·7. Calc. for $C_{14}H_{20}O_3$: C, 71·2; H, 8·5%). The *semicarbazone* crystallized from dilute alcohol, m.p. 158–160°; λ_{max} 271–272 mμ, log ε 4·5. The aforementioned melting point was not depressed on admixture with an authentic specimen, m.p. 160–163°. (Found: N, 14·7. Calc. for $C_{15}H_{23}N_3O_3$: N, 14·3%).

Preparation of the authentic specimen of 1-β-methoxycarbonyl-Δ^{1-9}-octalone-2 (VIc)

(a) To a solution of potassium t-butoxide, prepared from 0·5 g potassium and 30 ml t-butanol, was added a mixture freshly distilled 10 g 2-hydroxymethylenecyclohexanone and 17·7 g methyl 3-keto-Δ^1-heptenoate[1d] in 10 ml t-butanol. After standing overnight, the reaction mixture was acidified with dil acetic acid and extracted with ether. The extract was washed with water and the ether removed. The residue was stirred with a solution of 28 g KOH in 2 l. dioxan–water (1 : 1) mixture. After acidification the product was worked up by extraction with ether in the usual way and esterified with diazomethane. Distillation *in vacuo* furnished 6·2 g of the unsaturated keto ester (VIc), b.p. 150° (1 mm); λ_{max} 247–249 mμ, log ε 4·2. (Found: C, 70·9; H, 8·6. Calc. for $C_{14}H_{20}O_3$: C, 71·2; H, 8·5%). The *semicarbazone* melted at 160–162°.

(b) When an experiment was carried out with 40 g cyclohexanone, 0·5 g potassium in 75 ml t-butanol and 30 g methyl 3-keto-Δ^1-heptenoate following the aforementioned procedure except that the ring closure and esterification were carried out with aqueous sodium hydroxide[1d] and methanolic hydrogen chloride respectively, 2·8 g of the unsaturated keto ester (VIc) was obtained.

1-Methyl-1-β-methoxycarbonylethyloctalone-2 (VII)

To a solution of 7·7 g of the unsaturated keto ester (VIc) in 80 ml t-butanol at 45° was added all at once a solution of potassium t-butoxide, prepared from 2 g potassium and 60 ml t-butanol, and

then within few minutes a solution of 15 ml methyl iodide in 10 ml t-butanol. The mixture was refluxed for 2½ hr, cooled and then treated with dil acetic acid. The product was extracted with ether, and the extract washed with water, cold dil KOH solution and water. Removal of the solvent and distillation of the residue furnished 7·5 g of a product boiling at 160–165° (2 mm). A solution of 3·4 mg of this product per litre of 95% ethanol showed an optical density of 0·333 at 245 mμ. It was then chromatographed on a column of acid washed alumina (300 g). Elution with pet ether (40–60°)–benzene (9 : 1) mixture followed by distillation furnished 3·23 g 1-methyl-1-β-methoxycarbonylethyloctalone-2 (VII), b.p. 155–160° (1 mm), which did not show any ultra-violet absorption maximum characteristic of α,β-unsaturated ketone. Elution with 1 : 1 mixture of pet ether (40–60°) and benzene followed by distillation gave 2·55 g of the unchanged unsaturated keto ester (VIc). (Found: C, 72·2; H, 8·6. Calc. for $C_{14}H_{22}O_3$: C, 72·0; H, 8·8%).

Methyl 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoate (X)

A mixture of 4·3 g 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoic acid, 75 cc dry methanol and 5 cc of conc H_2SO_4 was refluxed for 16 hr. This was cooled and poured into ice and water. The separated oil was taken up in ether and the aqueous layer extracted four times with ether–benzene mixture. The combined extract was washed with water, sodium bicarbonate solution and water. The solvent was removed and the residue distilled to furnish 4·4 g (96%) methyl 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoate (X), b.p. 180–185° (2 mm), as a colourless mobile liquid. (Found: C, 66·8; H, 6·1. Calc. for $C_{13}H_{14}O_4$: C, 66·7; H, 6·0%).

6-*Methoxy-4-methoxycarbonyl-3,4-dihydronaphtha-(2,1d)-isoxazole* (XIIb)

To an ice-cold stirred suspension of freshly prepared sodium methoxide (from 2·3 g sodium and 4 cc dry methanol) in 25 cc dry benzene under nitrogen, was added first 14 cc ethyl formate and then, after 15 min, 11 g of the keto ester (X), in 25 cc dry benzene. After standing at room temp for 15 hr, the reaction mixture was cooled and treated with ice and water, the aqueous layer was separated and the benzene solution thoroughly extracted with ice cold 2% NaOH solution. The combined aqueous solution, after extraction with ether was acidified with iced HCl, and the precipitated oil worked up in the usual manner to give 11·5 g of the crude hydroxymethylene derivative (XI) as a gum, which gave intense violet colour with alcoholic ferric chloride solution.

A solution of the aforementioned crude hydroxymethylene derivative in 200 cc glacial acetic acid was treated with 3·5 g dry powdered hydroxylamine hydrochloride as described by Johnson *et al.*[9] to yield 11·65 g of a reddish gummy isoxazole, which was found to be a mixture of XIIa and XIIb. This was taken up in a mixture of 120 cc glacial acetic acid and 24 cc conc HCl and refluxed for 30 min. The solid obtained, on removal of the volatile materials under diminished pressure, was treated with sodium bicarbonate solution and filtered. The filtrate on acidification gave 10·3 g (89%) white crystalline 6-*methoxy-4-carboxy-3,4-dihydronaphtha-(2,1d)isoxazole* (XIIa), m.p. 188–190°; recrystallized from methanol, m.p. 190°. (Found: C, 64·0; H, 4·9. Calc. for $C_{13}H_{11}O_4N$: C, 63·70; H, 4·5%).

The above acid (XIIa, 10·3 g) in 50 cc methanol was esterified with diazomethane to yield 10 g (91%) of the isoxazole ester (XIIb), m.p. 77–78°. (Found: N, 5·6. Calc. for $C_{14}H_{13}O_4N$: N, 5·4%).

Methyl 7-methoxy-4-keto-3-methyl-3-cyano-1,2,3,4-tetrahydronaphthoate (XIII)

A solution of potassium t-butoxide (from 1·7 g potassium and 42·5 cc dry t-butanol) under nitrogen was treated with 10 g 6-methoxy-4-carbomethoxy-3,4-dihydronaphtha-(2,1d)-isoxazole (XIIb) in 40 cc t-butanol and 14 cc methyl iodide as described by Johnson *et al.*[9] to give 9·5 g (90%) methyl 7-methoxy-4-keto-3-methyl-3-cyano-1,2,3,4-tetrahydronaphthoate (XIII), which on crystallization from aqueous methanol melted at 110°. (Found: C, 65·8; H, 5·8. Calc. for $C_{15}H_{15}O_4N$: C, 65·9; H, 5·5%).